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EFFECTS OF EXERCISE TRAINING ON FIBER TYPE COMPOSITION AND ENZYMATIC ACTIVITY IN PATIENTS WITH CHRONIC HEART FAILURE: A SYSTEMATIC REVIEW

TRABAJO FIN DE GRADO

Título en castellano:
Efectos del entrenamiento físico sobre la composición de las fibras musculares y actividad enzimática en pacientes con insuficiencia cardíaca: Revisión sistemática

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INTRODUCTION

Cardiovascular disease (CVD) is an umbrella term for a group of related disorders that affect the heart and blood vessels. It is a major public health concern, claiming approximately 17.9 million lives worldwide annually. Furthermore, the prevalence of CVD is projected to increase globally due to the aging of the population and advances in disease management (Roth et al., 2020).

Coronary artery disease (CAD) is the most prevalent disorder among CVD (Malakar et al., 2019). A hallmark feature of CAD is the presence of cholesterol plaques within the inner lining of coronary blood vessels. The build-up of plaques results in the narrowing of coronary arteries, eventually reducing blood supply to the cardiac muscle. Inadequate tissue perfusion weakens the heart, compromising its pumping capacity and leading to a chronic debilitating condition of heart failure. CAD remains the leading cause of chronic heart failure (CHF), beyond hypertension, valvular disease, and congenital disorders (Mosterd & Hoes, 2007).

Estimates suggest that 64.3 million people globally are affected by CHF (James et al., 2018). CHF remains predominantly the disease of the elderly, with the prevalence of CHF less than 1% in those aged < 55 years, increasing exponentially from there on until surpassing 10% in the eighth decade of life (Bosch et al., 2019). The prognosis of CHF has improved significantly in the past decades, but hospitalization rates remain high, and the quality of life of these patients is greatly reduced (Del Buono et al., 2019). Moreover, according to some estimates, hospital admissions attributed to CHF may increase by as much as 50% by the year 2030, possibly due to the associated comorbidities (Udelson & Stevenson, 2016). Left ventricular ejection fraction (LVEF) has been traditionally used as a criterion in diagnosing and treating CHF. The classification of patients with CHF according to ejection fraction allows discerning between patients with reduced (HFrEF; LVEF below 40%) and preserved LVEF (HFpEF; LVEF above 50%). Recently, the term mildly reduced LVEF has been introduced to refer to those patients with LVEF 40-49% (McDonagh et al., 2021). However, since the studies in the present review were published before the new classification emerged, only the terms HFrEF and HFpEF were used.

The inability of the heart to pump sufficient blood to the periphery means that the metabolic needs of the body cannot be met. Cardinal symptoms of the disease include marked exercise intolerance, shortness of breath, and fatigue (Clark et al., 1996; Sullivan & Hawthorne, 1995), which are often present at rest and during submaximal efforts (e.g., activities of daily living) but become even more apparent on the assessment of exercise capacity during symptom-limited cardiopulmonary exercise testing (CPET). Exercise capacity refers to the magnitude of physical exertion an individual can sustain and is often expressed in units of the metabolic equivalent of task or peak oxygen uptake (VO_2 peak). By itself, VO_2 peak represents the highest rate of oxygen consumption during physical exercise and reflects the integrative response of multiple systems in the body, including cardiovascular, respiratory, and skeletal muscle. Thus, a failure of any single one of these systems would attenuate oxygen uptake response (Del Buono et al., 2019; Sullivan & Hawthorne, 1995). Unsurprisingly, patients with CHF have lower VO_2 peak than age-matched healthy controls (Myers et al., 2002). The attainment of VO_2 peak during CPET is an independent predictor of morbidity and mortality in individuals with CHF (Del Buono et al., 2019). Moreover, patients with VO_2 peak below 14 $ml \cdot kg^{-1} \cdot min^{-1}$ are considered for cardiac transplantation (Mancini et al., 1991).

For decades, the overarching theory to explain poor exercise capacity in patients with CHF highlighted the role of cardiovascular limitations, whereby reduced cardiac output would lead to skeletal muscle hypoperfusion and oxygen deprivation (Piepoli & Coats, 2013). Nonetheless, this model failed to account for the lack of improvement in exercise capacity and VO_2 peak following administration of positive inotropic agents, nor did it offer any explanation of heterogeneity in exercise response among patients with similar reductions in left ventricular function (Clark et al., 1996; Coats et al., 1994). In fact, a lack of correlation between exercise capacity and left ventricular impairment has been reported (Franciosa et al., 1981). Moreover, numerous observations from heart

transplant recipients demonstrated that albeit meaningful increases in VO_2 peak six months after the surgery, these patients still failed to reach age-predicted values (Notarius et al., 1998). Consequently, the "muscle hypothesis" of chronic CHF emerged (Coats et al., 1994). The theory was further supported by the observations of muscle atrophy, metabolic abnormalities, and an unfavorable shift toward highly fatigable muscle fiber phenotype in the biopsy samples of CHF patients (Middlekauff, 2010; Nicoletti et al., 2003).

In humans, the contractile and metabolic properties of the skeletal muscle fiber depend upon the relative expression of three myosin heavy chain (MyHC) proteins: MyHC I, MyHC IIA, and MyHC IIX. Pure muscle fiber types express a single MyHC isoform and are classified into slow-twitch oxidative type I fibers, fast-twitch oxidative type IIA and fast-twitch glycolytic type IIX fibers. The presence of hybrid fibers that coexpress multiple MyHC isoforms (MyHC I, IIA/IIX, and I/II/IIX) leads to a total of six different MyHC isoforms. The skeletal muscle fiber population thus exhibits a spectrum of pure and hybrid fiber types, whereby the percent contribution of either type is malleable by changes in activity patterns (Bottinelli & Reggiani, 2000).

Biopsy samples from vastus lateralis and lateral gastrocnemius muscles of healthy individuals reveal a similar distribution of the type I and IIA isoforms (Murach et al., 2019). Type I muscle fibers possess a greater capillary-to-fiber ratio, higher mitochondrial density, and higher availability of oxidative enzymes compared to fast-twitch fiber types. These intrinsic characteristics confer type I muscle fibers fatigue resistance, making them suitable for prolonged low-intensity activities. Type IIA fibers, often referred to as intermediate, share features of type I and type IIX fibers but manifest either oxidative or glycolytic phenotypic traits in response to functional demands (Gollnick et al., 1972). In patients with CHF, the distribution of MyHC isoforms was skewed toward the fast-twitch glycolytic phenotype (Drexler et al., 1992; Mancini et al., 1989; Sullivan et al., 1990) and correlated with impaired exercise capacity (Middlekauff, 2010). A faster contraction rate and fewer capillaries to deliver oxygen in these fibers call for immediately available anaerobic fuel sources such as intramuscular phosphocreatine and glycogen stores. Limited availability of both substrates means that longer efforts cannot be sustained, and the accumulation of metabolites, such as inorganic phosphate and hydrogen ions, impedes further muscle contraction. Consistent with the reliance on anaerobic metabolism are further observations of faster phosphocreatine depletion and greater muscle acidification in subjects with CHF compared to healthy controls, correlated with impaired exercise capacity in the former group (Drexler et al., 1992; Mancini et al., 1989; Sullivan et al., 1990). Also of note is that these changes persist despite adequate limb perfusion and muscle oxygenation (Sullivan & Hawthorne, 1995).

Abnormal substrate utilization observed in patients with CHF during CPET can also be attributed to reduced mitochondrial content and decreased activity of critical enzymes involved in oxidative phosphorylation (Drexler et al., 1992). Given the complexity of direct measurements of mitochondrial content, laboratories often use biochemical surrogates, such as enzymes involved in oxidative phosphorylation (Bishop et al., 2019; Duscha et al., 2008). In particular, the majority of studies utilized the activity of citrate synthase (CS) as a marker. Comparisons of CS activity in patients with CHF and healthy individuals have consistently revealed significantly lower values in the former group (Brassard et al., 2006; Sullivan et al., 1991). The associations between CS activity and VO_2 peak provide additional evidence to support the notion that mitochondrial enzymes play a critical role in determining exercise capacity. A reduction in succinate dehydrogenase (SDH) activity in the skeletal muscle mitochondria in patients with CHF was also reported and correlated with the VO_2 peak (Sullivan et al., 1990). The diminished activity of enzymes involved in the transport of fatty acids and the β-oxidation contribute to further reductions in oxidative metabolism and exercise capacity in these patients (Bekfani et al., 2020; Sullivan et al., 1990).

Altogether, the existing body of evidence indicates that intrinsic skeletal muscle abnormalities are implicated in decreased exercise capacity of CHF patients. Pharmacologic interventions demonstrated limited efficacy in ameliorating exercise capacity (von Haehling et al., 2021);

meanwhile, exercise has emerged as a promising alternative (Del Buono et al., 2019; von Haehling et al., 2021). The clinical benefits of exercise may be partially attributed to its effects on skeletal muscle function. Skeletal muscle possesses remarkable plasticity, and persistent changes in neuromuscular demands, mechanical stress, or both, elicit cellular and metabolic adaptations (Roy et al., 1991). One such stimulus is exercise. The degree of molecular remodeling following exercise depends on the type, intensity, and duration of a given exercise modality (Nader & Esser, 2001; Sakamoto & Goodyear, 2002), and findings from healthy populations have largely substantiated the exercise-induced adaptations. Aerobic exercise-based interventions, in particular, those with moderate-intensity exercise (MIE), reported increases in the percentage of type I fibers (Harber et al., 2012), with concomitant rises in mitochondrial content and enzymes of oxidative metabolism in both type I and type IIA fibers (Henriksson & Reitman, 1976; Howald et al., 1985; Russell et al., 2003). Additionally, a high-intensity interval exercise (HIIE) activated transcription factors involved in mitochondrial biogenesis and upregulated enzymes of oxidative metabolism in healthy young (Gibala et al., 2009; Jacobs et al., 2013; Little et al., 2010) and older individuals (Robinson et al., 2017). Albeit through the distinct molecular pathways, similar improvements in mitochondrial function were also observed following high-volume, low-intensity aerobic (Wahl et al., 2022) and resistance exercise (RE) (Groennebaek & Vissing, 2017). On the other hand, several publications suggested that engaging in resistance and high-intensity sprint exercise could potentially result in a decrease in the proportion of fast-twitch glycolytic type IIX fibers while simultaneously increasing the percentage of type IIA fibers (Esbjörnsson et al., 1993; Jansson et al., 1990). These findings were later extended to older adults (Hikida et al., 2000) and female subjects (Staron et al., 1990). Unlike type IIX, type IIA fibers also possess a substantial oxidative capacity and a contractile velocity greater than type I (Bottinelli & Reggiani, 2000). Therefore, an increase in the proportion of type IIA fibers, without accompanying changes in type I fibers, may still be considered a favorable adaptation to exercise. However, it is important to note that other experimental research challenged the above findings and failed to verify an increase in type IIA fibers following RE (Green et al., 1999). Moreover, the validity of these adaptations in the presence of CHF pathology remains to be investigated.

To date, the research on the impact of exercise on skeletal muscle impairment in patients with CHF is limited and inconsistent, characterized by heterogeneous protocols, a lack of agreement on the most suitable variables to measure exercise-induced adaptations in this population, and small sample sizes (Duscha et al., 2008; Lee et al., 2017). Duscha et al. (2008) previously reported that exercise interventions, irrespective of exercise characteristics, increased oxidative enzyme activity in patients with CHF. However, observations on muscle fiber type distribution yielded inconclusive results, with findings showing a lack of changes in the proportion of oxidative fibers or relative increases that were of questionable clinical significance. The degree of variation between studies could be the result of distinct techniques used to determine MyHC isoforms from the biopsied muscle (Murach et al., 2019) rather than the exercise effects per se. However, previous review articles failed to recognize the method of analysis as a potential confounder.

Prior reviews focused on a broader spectrum of relevant outcomes, including anabolic and catabolic markers and inflammatory pathways that lead to skeletal muscle atrophy (Adams et al., 2017; Duscha et al., 2008; Lee et al., 2017; Zizola & Schulze, 2013). However, the wide range of protocols employed in these studies makes it difficult to draw conclusions for clinical practice. It is also important to note that since the publication of previous reviews, additional relevant studies have been conducted, thus warranting a systematic review of both prior and recent evidence. Therefore, the present review aimed to: 1) gain a comprehensive understanding of the methodologies and characteristics of previous studies; 2) determine the impact of exercise on the relative distribution of MyHC isoforms and oxidative enzyme activity; and 3) examine potential moderator variables (i.e., exercise modality, aerobic exercise method, frequency, and intervention duration) in the effectiveness of exercise effects on the outcomes of interest.

METHODS

The current systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Page et al., 2021). The protocol was prospectively registered on the PROSPERO database (CRD42023422154).

Search strategy and eligibility criteria

Electronic databases of PubMed, Embase, and Web of Science (i.e., Core Collection, Science Citation Index Expanded, and Conference Proceeding Citation Index – Science) were searched for relevant publications up to December 2022. The search strategy was based on free-text terms and thesaurus (e.g., MeSH and Emtree) following the PICOS approach (population, intervention, comparison, outcomes, and study design). Title, abstract, and keywords (where available) were screened for the relevant free-text terms. The screening of conference proceedings and abstracts was carried out on the Web of Science Core Collection. Moreover, systematic reviews, meta-analyses, and reference lists of the included studies in this review were manually checked to find additional studies. Studies published in English, Spanish, and Russian were considered eligible.

In agreement with the PICOS approach, relevant publications were to meet the following criteria: (1) participants: adult patients, regardless of sex, diagnosed with CHF; (2) interventions: a residential or outpatient exercise program, regardless of the setting (i.e., supervised or unsupervised), based on any exercise modality (i.e., aerobic exercise, resistance exercise, or combined aerobic and resistance exercise [i.e., combined exercise]), either alone or in addition to psychosocial and/or educational interventions; additionally, only studies that performed an intervention period longer than or equal to two weeks were included; (3) comparison: comparison group was not an obligatory condition, if present, the comparison group could be based on non-exercise interventions (i.e., usual care) or an exercise modality different from that of the primary intervention, either alone or in addition to psychosocial and/or educational interventions; (4) outcomes: (a) relative distribution of MyHC isoforms obtained from the biopsy sample and assessed by histochemical staining, immunohistochemistry, or gel electrophoresis; and (b) oxidative enzyme activity: CS; SDH; α-ketoglutarate dehydrogenase (KGDH); mitochondrial complex-I; cytochrome c oxidase (COX); carnitine palmitoyltransferase (CPT) complex; 3-hydroxyacyl-CoA dehydrogenase (HAD); and (5) study design: randomized and non-randomized multi-intervention/controlled studies, as well as pre- and post-intervention studies.

A literature search was organized into two phases. In the first phase, titles and abstracts were screened to identify relevant publications. In the following phase, full texts of the selected publications were inspected to confirm the eligibility.

Data extraction and coded information

The following information was extracted from the included studies: (a) study characteristics (journal, publication, country, year, study design [i.e., randomized or non-randomized]); (b) patient characteristics (CHF diagnosis, sex [i.e., males, females, or mixed sample], number and percentage of male participants, age, LVEF, New York Heart Association [NYHA] functional class, etiology, implantable cardioverter device [i.e., yes or no] and cardiorespiratory fitness [e.g., VO_2 peak]); (c) intervention characteristics (setting [i.e., supervised, unsupervised, or mixed], inpatient program [i.e., yes or no], exercise modality [i.e., aerobic, resistance, or combined], aerobic exercise method where applicable [i.e., HIIE, MIE, and low-intensity exercise], intervention length [weeks], training frequency, exercise mode [e.g., cycle ergometer], and other exercise characteristics [e.g., number of sets, repetitions, and intensity]); (d) no-exercise comparison group characteristics; (e) outcomes reported (relative distribution of MyHC isoforms [i.e., MyHC I, MyHC IIA, or MyHC IIX], oxidative enzyme activity [i.e., CS, SDH, KGDH, mitochondrial complex-I, COX, CPT, HAD]); (f) assessment of MyHC isoforms (biopsy site [i.e., vastus lateralis, gastrocnemius, soleus, triceps brachii], sample analysis [i.e., histochemical staining, immunohistochemistry, or gel electrophoresis], and percentage

of MyHC isoforms [i.e., MyHC I, MyHC IIA, or MyHC IIX]); and (g) assessment of oxidative enzyme activity (enzymes measured [CS, SDH, KGDH, mitochondrial complex-I, COX, CPT, HAD], the measurement unit, and measured activity).

Methodological quality assessment

The tool for the assessment of study quality and reporting in exercise (TESTEX) scale, a tool specifically designed for assessing exercise training studies, was used to assess the methodological quality of the included studies (Smart et al., 2015). This tool is a 15-point scale that assesses study quality (eligibility criteria specified; randomization specified; allocation concealment; groups similar at baseline; and assessor blinding) and reporting (outcome measures assessed in 85% of patients; intention-to-treat analysis; between-group statistical comparisons reported; point measures and measures of variability for all reported outcomes; activity monitoring in control groups; relative exercise intensity remained constant; and exercise volume and energy expenditure). Based on the summary scores, methodological quality was judged as "excellent" (12-15 points), "good" (9-11 points), "fair" (6-8 points), or "poor" (<6 points).

RESULTS

Study selection

Figure 1 shows the flowchart based on the PRISMA statement (Page et al., 2021) that visually summarizes the selection process of the articles included in this review. In brief, the initial electronic database search produced 5281 publications, and after removing duplicates, 2472 studies were retained for final screening. After reviewing titles and abstracts, 40 publications met the eligibility criteria, and their full texts (where applicable) were subjected to further analysis. Eleven publications were excluded as the full texts could not be retrieved (Belardinelli et al., 1996; Belardinelli et al., 1993; Erbs et al., 2005; Erbs, Hoellriegel, et al., 2007; Erbs, Hollriegel, et al., 2007; Forman et al., 2000; Gielen et al., 2010; Hambrecht, Fiehn, et al., 1995; Hoellriegel et al., 2005; Hoellriegel et al., 2006; Vanderent et al., 1994). Seven publications were excluded as they did not assess either of the two outcomes of interest (Adamopoulos et al., 1993; Antunes-Correa et al., 2020; Gielen et al., 2012; Hollriegel et al., 2013; Lenk et al., 2012; Linke et al., 2005; Wang et al., 2022). Two papers were excluded based on the sample characteristics (Ades et al., 1996; Braith et al., 2005). Additionally, one paper was excluded as it contained previously published data related to a different intervention (Gordon et al., 1999). Finally, 19 studies were included. In parallel, the reference lists of the previous reviews and included studies were screened, and two more publications were identified for inclusion (Larsen et al., 2002; Pu et al., 2001), resulting in a total of 21 papers being included in this review article.

Study characteristics

Sample characteristics and exercise protocols description are summarized in Table 1.

A total of 21 publications were included in this review. Studies were published between 1995 and 2022. Nine studies (42.85%) were non-randomized (Belardinelli et al., 1995; Gordon et al., 2000; Gordon et al., 1997; Keteyian et al., 2003; Larsen et al., 2002; Munkvik et al., 2010; Tyni-Lenné et al., 1998; Tyni-Lenné et al., 1997; Tyni-Lenné, Jansson, et al., 1999) and 12 (57.14%) randomized (Gielen et al., 2005; Gordon et al., 1996; Groennebaek et al., 2019; Hambrecht et al., 1997; Hambrecht, Niebauer, et al., 1995; Harjola et al., 2006; Kiilavuori et al., 2000; Magnusson et al., 1996; Pu et al., 2001; Tyni-Lenné, Gordon, et al., 1999; Williams et al., 2007; Winzer et al., 2022). Nine studies (42.85%) included one intervention group (IG) and one control group (CG) (Belardinelli et al., 1995; Gielen et al., 2005; Gordon et al., 1997; Hambrecht et al., 1997; Hambrecht, Niebauer, et al., 1995; Harjola et al., 2006; Kiilavuori et al., 2000; Pu et al., 2001; Williams et al., 2007), two studies (9.52%) two IGs (Gordon et al., 1996; Magnusson et al., 1996), three studies (14.28%) two IGs and one CG (Groennebaek et al., 2019; Tyni-Lenné, Gordon, et al., 1999; Winzer et al., 2022), and seven studies (33.33%) solely included one IG (Gordon et al., 2000; Keteyian et al., 2003; Larsen et al., 2002;

Munkvik et al., 2010; Tyni-Lenné et al., 1998; Tyni-Lenné et al., 1997; Tyni-Lenné, Jansson, et al., 1999).

Notably, only one study included patients with HFpEF (Winzer et al., 2022). The mean LVEF in the remainder of the studies, with patients with HFrEF, was 28.8 ± 4% and 31.6 ± 10.9% in IGs and CGs, respectively. For the entirety of 21 selected publications, sample sizes in IGs ranged from 5 to 16 subjects, and their mean age was 60.4 ± 7.1. Sample sizes in CGs ranged from 6 to 15 subjects, and their mean age was 60 ± 8.4. Three studies (14.28%) recruited female participants (Pu et al., 2001; Tyni-Lenné et al., 1997; Tyni-Lenné, Jansson, et al., 1999), seven studies (33.33%) male participants (Gielen et al., 2005; Gordon et al., 1997; Gordon et al., 1996; Hambrecht et al., 1997; Hambrecht, Niebauer, et al., 1995; Larsen et al., 2002; Munkvik et al., 2010), and the remaining studies (52.38%) had a mixed sample, except for one study (Harjola et al., 2006), where this information was not provided.

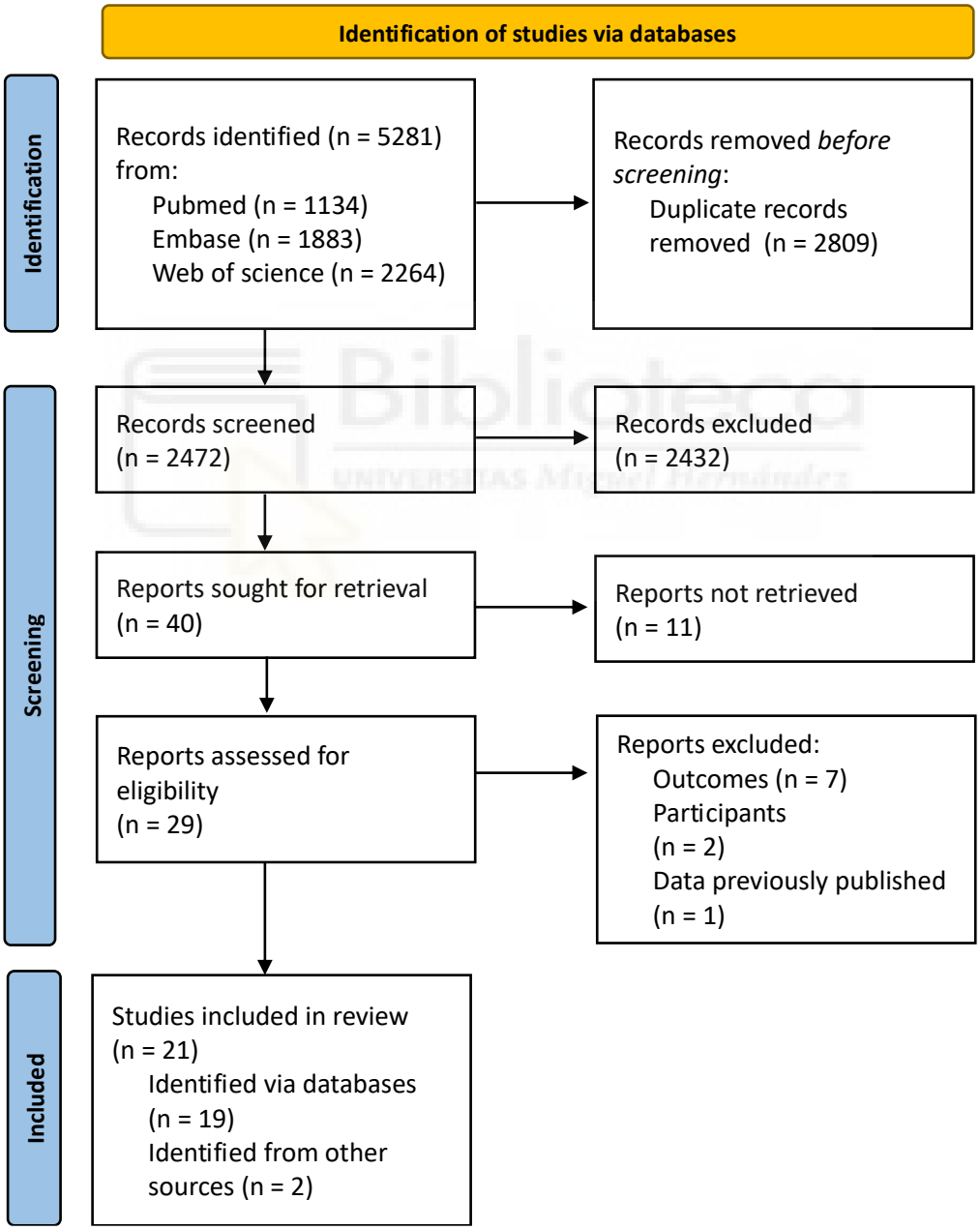

Figure 1. Flowchart of the studies selection process guided by the PRISMA statement.

Aerobic exercise, of low- to moderate-intensity, as the primary intervention, was employed in 14 studies (66.66%) (Belardinelli et al., 1995; Gielen et al., 2005; Gordon et al., 2000; Gordon et al., 1997; Gordon et al., 1996; Hambrecht et al., 1997; Hambrecht, Niebauer, et al., 1995; Harjola et al., 2006; Keteyian et al., 2003; Kiilavuori et al., 2000; Larsen et al., 2002; Tyni-Lenné et al., 1998; Tyni-Lenné et al., 1997; Tyni-Lenné, Jansson, et al., 1999). Three studies (13.0%) (Groennebaek et al., 2019; Pu et al., 2001; Williams et al., 2007) employed RE; also, in the study by Groennebaek et al. (2019), a blood-flow restriction was applied during exercise. Out of those studies where distinct intervention protocols were compared, Winzer et al. (2022) assessed the changes following HIIE and MIE. Magnusson et al. (1996) compared between three distinct protocols (aerobic, resistance, and combined) on a modified ergometer. Tyni-Lenné, Gordon, et al. (1999) compared moderate-intensity cycling to single-leg knee-extensor aerobic exercise on a modified ergometer. On average, interventions lasted for 14.6 weeks, whereby protocols from six to 26 weeks were employed. The duration of eight weeks was applied in nine studies (42.85%) (Belardinelli et al., 1995; Gordon et al., 2000; Gordon et al., 1997; Gordon et al., 1996; Magnusson et al., 1996; Tyni-Lenné et al., 1998; Tyni-Lenné et al., 1997; Tyni-Lenné, Gordon, et al., 1999; Tyni-Lenné, Jansson, et al., 1999), with the frequency of three exercise sessions a week. The latter frequency was also applied in all but three studies (14.28%) (Gielen et al., 2005; Hambrecht et al., 1997; Hambrecht, Niebauer, et al., 1995) where patients exercised daily at home and in one study (Munkvik et al., 2010) where four exercise sessions were spread throughout the week.

In terms of outcomes, 11 studies (52.38%) (Belardinelli et al., 1995; Gordon et al., 2000; Hambrecht et al., 1997; Harjola et al., 2006; Keteyian et al., 2003; Kiilavuori et al., 2000; Larsen et al., 2002; Munkvik et al., 2010; Pu et al., 2001; Tyni-Lenné, Gordon, et al., 1999; Tyni-Lenné, Jansson, et al., 1999) assessed the relative distribution of MyHC isoforms. Out of all of these studies, three of them (14.28%) (Belardinelli et al., 1995; Hambrecht et al., 1997; Pu et al., 2001) did not differentiate between type IIA and type IIX fibers and classified both as type II. 16 studies (76.19%) examined the activity of oxidative enzymes, with CS being assessed in 12 of these studies (57.14%) (Gordon et al., 2000; Gordon et al., 1997; Gordon et al., 1996; Groennebaek et al., 2019; Magnusson et al., 1996; Munkvik et al., 2010; Pu et al., 2001; Tyni-Lenné et al., 1998; Tyni-Lenné et al., 1997; Tyni-Lenné, Gordon, et al., 1999; Williams et al., 2007; Winzer et al., 2022). Very few studies chose distinct markers of oxidative metabolism. Two of them (9.52%) (Gielen et al., 2005; Hambrecht, Niebauer, et al., 1995) assessed COX activity. The activity of NADH was assessed in the study by Winzer et al. (2022), and KGDH was assessed in the study by Kiilavuori et al. (2000). Three studies (14.28%) included enzymes of beta-oxidation among outcomes of interest, with HAD being assessed in two (9.52%) of them (Magnusson et al., 1996; Williams et al., 2007), and only one study (4.76%) evaluating the activity of CPT (Kiilavuori et al., 2000).

Methodological quality assessment

An overview of the methodological quality evaluation of the selected studies utilizing the TESTEX scale can be found in Supplementary material: Table S1. The average rating obtained by the included studies was 6.7 ± 2.3. Eight studies (38.09%) were evaluated as having poor methodological quality (Gielen et al., 2005; Gordon et al., 2000; Gordon et al., 1997; Hambrecht et al., 1997; Keteyian et al., 2003; Larsen et al., 2002; Munkvik et al., 2010; Tyni-Lenné, Jansson, et al., 1999), eight studies (38.09%) as having fair quality (Belardinelli et al., 1995; Gordon et al., 1996; Hambrecht, Niebauer, et al., 1995; Harjola et al., 2006; Kiilavuori et al., 2000; Magnusson et al., 1996; Tyni-Lenné et al., 1998; Tyni-Lenné et al., 1997), and five studies (21.7%) as having good quality (Groennebaek et al., 2019; Pu et al., 2001; Tyni-Lenné, Gordon, et al., 1999; Williams et al., 2007; Winzer et al., 2022). Surprisingly, among the 12 (57.14%) randomized trials (Gielen et al., 2005; Gordon et al., 1996; Groennebaek et al., 2019; Hambrecht et al., 1997; Hambrecht, Niebauer, et al., 1995; Harjola et al., 2006; Kiilavuori et al., 2000; Magnusson et al., 1996; Pu et al., 2001; Tyni-Lenné, Gordon, et al., 1999; Williams et al., 2007; Winzer et al., 2022), only four studies (19.04%) provided a comprehensive account of their randomization procedure (Groennebaek et al., 2019; Tyni-Lenné, Gordon, et al.,

1999; Williams et al., 2007; Winzer et al., 2022). Assessor blinding to patients´ allocation (of MyHC isoforms analysis and/or enzyme assay) was only implemented in three studies (14.28%) (Groennebaek et al., 2019; Pu et al., 2001; Winzer et al., 2022). Two studies (9.52%) (Larsen et al., 2002; Munkvik et al., 2010) failed to confirm the number of patients who successfully completed the protocol and whether adverse events took place throughout the intervention. Intention-to-treat analysis was absent in all 21 studies, and activity monitoring in the control group was performed only in five studies (21.7%) (Belardinelli et al., 1995; Gordon et al., 1996; Hambrecht, Niebauer, et al., 1995; Magnusson et al., 1996; Pu et al., 2001). Eight studies (38.09%) (Belardinelli et al., 1995; Gordon et al., 2000; Harjola et al., 2006; Kiilavuori et al., 2000; Pu et al., 2001; Tyni-Lenné, Gordon, et al., 1999; Williams et al., 2007; Winzer et al., 2022) re-evaluated the participants at some point during the intervention to adjust the load to maintain the relative intensity of the exercise.

Outcome measures

Relevant findings of the studies are summarized in Table 1.

One of the key observations from the present review is the lack of statistically significant changes in fiber type composition in all but three studies (14.28%) (Hambrecht et al., 1997; Keteyian et al., 2003; Tyni-Lenné, Jansson, et al., 1999). Hambrecht et al. (1997) observed significant changes after 26 weeks of MIE, whereby the percentage of type I fibers increased and that of type II fibers decreased. Keteyian et al. (2003) employed a similar aerobic exercise protocol lasting between 14 to 24 weeks and also observed an increase in the relative proportion of type I fibers. However, Tyni-Lenné, Jansson, et al. (1999) previously reported a statistically significant reduction of type I fibers and non-significant increases in both type IIA and IIX fibers following an eight-week intervention period of aerobic exercise. Larsen et al. (2002) corroborated the latter findings and identified a positive trend for type IIX fibers and an opposing trend for type I fibers following 24 weeks of combined exercise, albeit neither of the changes reached statistical significance.

On another note, the positive effects of exercise on oxidative enzyme activity were confirmed in 13 studies (61.9%) (Gielen et al., 2005; Gordon et al., 2000; Gordon et al., 1997; Gordon et al., 1996; Hambrecht, Niebauer, et al., 1995; Magnusson et al., 1996; Munkvik et al., 2010; Pu et al., 2001; Tyni-Lenné et al., 1998; Tyni-Lenné et al., 1997; Tyni-Lenné, Gordon, et al., 1999; Williams et al., 2007; Winzer et al., 2022), with only two exceptions (9.52%) (Groennebaek et al., 2019; Pu et al., 2001), although a trend toward an increase was observed by Pu et al. (2001).

Two studies (9.52%) (Gielen et al., 2005; Hambrecht, Niebauer, et al., 1995) revealed statistically significant increases in COX activity after 26 weeks of MIE. HAD activity increased significantly in aerobic and combined exercise groups in the study by Magnusson et al. (1996). Conversely, Williams et al. (2007) could not confirm statistically significant changes in the measures of HAD activity following RE. Winzer et al. (2022) reported statistically significant increases in NADH activity in a sample of patients randomized to HIIE. Activities of KGDH and CPT complexes were not altered by exercise, according to Kiilavuori et al. (2000).

Analysis of moderator variables

No particular feature of intervention protocols influenced the effects of exercise on muscle fiber type composition, and seemingly similar protocols of aerobic exercise led to significant changes in some (Hambrecht et al., 1997; Keteyian et al., 2003) but not in other studies (Harjola et al., 2006; Kiilavuori et al., 2000). All four studies employed MIE, lasting between 30 (Harjola et al., 2006) and 40 minutes (Hambrecht et al., 1997; Keteyian et al., 2003; Kiilavuori et al., 2000). The duration of interventions showed only slight variations: Keteyian et al. (2003) reported a range of approximately 14 to 24 weeks, Kiilavuori et al. (2000) 24 weeks, and both Hambrecht et al. (1997) and Harjola et al. (2006) 26 weeks.

The magnitude of exercise-induced changes in CS activity varied among the studies, but no single exercise prescription-specific parameter could decisively explain the observed variation.

Magnusson et al. (1996) reported the highest relative increase in CS, up to 71%, in a group of patients randomized to 15 min of continuous single-leg knee-extensor exercise at 75% of the peak work rate for eight weeks, with three exercise sessions per week. On the other hand, the study by Gordon et al. (2000) showed that a similar protocol, at 70% of the peak work rate, led to only a 43% increase in CS activity.

The findings of Munkvik et al. (2010) also suggested that as little as six weeks of exercise could produce significant changes in CS activity. They documented a relative increase of 27 ± 9% following a protocol of MIE on a modified ergometer, with four weekly exercise sessions.

Significant increases were also reported after eight weeks of MIE (Gordon et al., 2000; Gordon et al., 1997; Gordon et al., 1996; Magnusson et al., 1996; Tyni-Lenné et al., 1998; Tyni-Lenné et al., 1997; Tyni-Lenné, Gordon, et al., 1999). Winzer et al. (2022) compared the changes in CS activity following two distinct aerobic exercise protocols and found statistically significant increases compared to a control group in a sample of patients randomized to HIIE but not to MIE. Additionally, a 24-week RE intervention led to statistically significant increases in CS activity in the study by Williams et al. (2007).

Table 1. Study characteristics.

STUDY	SUBJECTS	INTERVENTION	EXERCISE PROTOCOL FOR IG	OUTCOMES
Belardinelli et al. (1995)	27 HFrEF patients classified into IG (n = 18, M = 16, age = 56 ± 7) or CG (n = 9, M = 7, age = 57 ± 6)	8 weeks x 3 sessions / week	Low-intensity exercise @ 40% VO_2 peak for 30 min on a cycle ergometer; adjustments made throughout the intervention to fit individual progress.	% type I / II fibers = N.S.
Gielen et al. (2005)	20 male HFrEF patients randomized to IG (n = 10; age = 55 ± 2) or CG (n = 10, age = 53 ± 3)	2 weeks supervised, followed by 24 weeks of daily exercise @ home	2 weeks: 10 min x 4-6 times daily @ 70% CPET-derived VO_2 max; afterwards, 20 min / day on a cycle ergometer.	COX ↑ 27% increase; from 21.8 ± 10.12 to 27.7 ± 11.07 nmol O_2/mg·min (p = 0.02 vs baseline, p < 0.01 vs control).
Gordon et al. (1996)	14 male HFrEF patients randomized to SL (n = 7, age = 60 ± 7.94) or bilateral (n = 7, age = 57 ± 7.94) knee-extensor exercise	8 weeks x 3 sessions / week	SL group: 15 min @ 35% WR. Bilateral group: 15 min at 65-75% WR. A modified ergometer was used for the exercise, and a bilateral knee-extensor exercise test was used to establish the workload.	In SL group, CS ↑ 23 ± 15.87% (p < 0.05 vs baseline), from 19.4 ± 3.7 to 23 ± 3.44 µmol·g dw^{-1}·min^{-1}. In bilateral group, CS ↑ 35 ± 21.17% (p < 0.01 vs baseline), from 17 ± 4.76 to 23 ± 2 µmol·g dw^{-1}·min^{-1}.
Gordon et al. (1997)	20 male HFrEF patients randomized to IG (n = 13, age = 56 ± 10.82) or CG (n = 7, age = 62 ± 7.94)	8 weeks x 3 sessions / week	Bilateral knee-extensor exercise on a modified ergometer for 15 min @ 65 -75 % WR / sessions in each session.	CS ↑ 28 ± 18.03% (p < 0.01), from 18.9 ± 3.97 to 24.2 ± 3.61 µmol·g dw^{-1}·min^{-1} (p < 0.01).
Gordon et al. (2000)	8 HFrEF patients (M = 4, age = 66 ± 12)	8 weeks x 3 sessions / week	SL knee-extensor exercise for 16-18 min / session @ 50 - 70% WR derived from an incremental SL knee-extensor test.	1. % type I/ IIA/ IIX fibers = N.S. 2. CS ↑ 46%, from 0.31 ± 0.06 to 0.45 ± 0.06 µkat·g^{-1} dm (p < 0.01).
Groennebaek et al. (2019)	36 HFrEF patients randomized to either BFRRE (n = 12, age = 66 ± 7), control (n = 12, age = 63 ± 10) or RIC (n = 12, age = 62 ± 9)	6 weeks x 3 sessions / week	BFFRE: 4 sets of bilateral knee extensions to fatigue, @ 30% 1 RM, w/ 50% arterial occlusion pressure. Rest in-between sets: 30 s between the sets.	CS = N.S.
Hambrecht, Niebauer, et al. (1995)	22 male HFrEF patients randomized to IG (n = 12; age = 50 ± 12) or CG (n = 10, age = 52 ± 8)	26 weeks of daily exercise; first 3 weeks were supervised	MIE @ 70% CPET-derived VO_2 max for at least 40 min/ day.	COX ↑ 41% (p < 0.05 vs control).
Hambrecht et al. (1997)	18 male HFrEF patients randomized to IG (n = 9, age = 50 ± 12) or CG (n = 9, age = 52 ± 8)	26 weeks of daily exercise; first 3 weeks were supervised	MIE @ 70% CPET-derived VO_2 max for at least 40 min/ day.	IG: % type I fibers ↑ from 48 ± 7% to 52 ± 7%; % type II fibers ↓ from 52 ± 7% to 48 ± 6% (p < 0.05). CG: % type I fibers ↓ from 49 ± 5% to 46 ± 7% (p < 0.05).

Table 1. Continued.

STUDY	SUBJECTS	INTERVENTION	EXERCISE PROTOCOL	OUTCOMES
Harjola et al. (2006)	27 HFrEF patients randomized to IG (n = 12, age = 50.2 ± 8) or CG (n = 15, age = 50.3 ± 11.4)	24 weeks x 3 supervised sessions/ week	MIE @ 60% of VO_2 max for 30 min on a cycle ergometer.	% type I/ IIA/ IIX = N.S.
Keteyian et al. (2003)	15 HFrEF patients (M = 10, age = 59.5 ± 4.81)	14- to 24-weeks x 3 sessions/ week	MIE @ 50-60% of HRR for 40 min; intensity ↑ to 80% of HRR after 2 weeks.	% type I fibers ↑ 8 ± 16.27% ($p < 0.08$ vs baseline in male patients).
Kiilavuori et al. (2000)	27 HFrEF patients randomized to IG (n = 12, age = 52 ± 7) or CG (n = 15, age = 52 ± 9)	24 weeks x 3 supervised sessions/ week	MIE @ HR at 50-60% of VO_2 peak for 30 min. The load was adjusted accordingly.	1. % type I/ IIA/ IIX fibers = N.S. 2. KGDH = N.S. CPT = N.S.
Larsen et al. (2002)	15 male HFrEF (age = 68.5 ± 7.5) patients compared to 15 healthy controls	24 weeks x 3 sessions/ week	Combined exercise @ 80% CPET-derived VO_2 max.	% type I/ II fibers = N.S., but a trend towards ↓ in % type I fibers (from 32.1 ± 9.2% to 26.0 ± 8.9%, $p = 0.062$) and an opposite trend in % type IIX fibers (from 5.1 ± 3.4% to 7.3 ± 2.9%, $p = 0.08$).
Magnusson et al. (1996)	11 HFrEF patients randomized to RE (n = 5) or MIE (n = 6), age = 56 ± 9	8 weeks x 3 sessions / week	RE: SL knee extensions @ 80 % of 1 RM; 4 sets x 6-10 reps, 2 min rest in-between. Contralateral leg left untrained. MIE: 15 min continuous SL knee-extensor exercise @ 65-75% WR on a modified ergometer. Contralateral leg performed both RE and MIE protocols (combined).	1. CS ↑ 77% in MIE; ↑ 49% in Combined ($p < 0.01$). 2. HAD ↑ 53% in MIE; ↑ 50% in Combined ($p < 0.05$). 3. RE = N.S.
Munkvik et al. (2010)	11 male HFrEF (age = 68.4 ± 1.5) patients compared to 13 age-matched healthy controls	6 weeks x 4 sessions / week	Randomization to exercise either the dominant or nondominant leg on a modified cycle ergometer; the nonexercised leg was used as a control. 4 sessions/ week: 1 x high-intensity (HI), at the load, which exhausted the subject after 20 min, 2 x low-intensity @ 70% of HI load, 1 x MIE @ 80% of HI.	1. % type I/ IIA/ IIX fibers = N.S. 2. CS ↑ 27 ± 9% ($p < 0.05$ vs baseline).
Pu et al. (2001)	16 female HFrEF patients randomized to RT (n = 9, age = 76.6 ± 6) or CG (n = 7, age = 76.6 ± 6.35)	10 weeks x 3 sessions / week	3 sets per exercise x 8 reps @ 80% 1 RM. Rest in-between sets 60-90 s. Exercises included: seated leg press, leg curl, chest press, knee extension, and triceps extension.	1. CS = N.S. 2. % type I/ II = N.S.
Tyni-Lenné et al. (1997)	16 female HFrEF patients (age = 62.5 ± 10)	8 weeks x 3 supervised sessions / week	15 min of continuous bilateral knee-extensor work @ 65 - 75% WR on a modified ergometer.	CS ↑ from 0.25 ± 0.07 to 0.36 ± 0.07 $\mu kat \cdot g^{-1}$ dm ($p = 0.0001$).
Tyni-Lenné et al. (1998)	24 HFrEF patients (M = 12, age = 60.5 ± 9.84)	8 weeks x 3 supervised sessions / week	15 min of continuous bilateral knee-extensor work @ 65 - 75% WR on a modified ergometer.	CS ↑ 35% and 37% in men and women, respectively ($p < 0.0001$).
Tyni-Lenné, Gordon, et al. (1999)	24 HFrEF patients randomized to cycling (n = 8), SL knee-extensor (n = 8, age = 62 ± 11) IG or CG (n = 8, age = 64 ± 12)	8 weeks x 3 supervised sessions / week	Cycling IG: MIE @ 50-70% WR for 20 min. Knee-extensor IG: 15 min of SL work @ 50-70% WR derived from a modified cycle ergometer SL test. IGs were matched for total oxygen consumption.	1. % type I/ IIA/ IIX fibers = N.S. 2. Cycling IG: CS ↑ 23%; knee-extensor IG: CS ↑ 45%.

Table 1. Continued.

STUDY	SUBJECTS	INTERVENTION	EXERCISE PROTOCOL	OUTCOMES
Tyni-Lenné, Jansson, et al. (1999)	16 female HFrEF patients (age = 62 ± 10)	8 weeks x 3 sessions / week	Bilateral knee-extensor exercise on a modified ergometer 15 min per session @ 65-75% WR.	N.S.↑ in % type IIA (+18%) and type IIX (+5%) fibers. % type I fibers ↓ 12% (p = 0.03 vs baseline).
Williams et al. (2007)	13 HFrEF patients were randomized to RE (n = 7, age = 67 ± 9) or CG (n = 6, age = 74 ± 4)	24 weeks x 3 supervised sessions / week	Circuit: leg cycling (30 s - 2 min), elbow extension/flexion (30 s), stair climbing (30 s - 2 min), arm cycling (30 s - 2 min), knee extension/ flexion (30 s), and shoulder press/pull (30 s).	CS ↑ from 13.06 ± 2.73 to 18.24 ± 4.31 µmol·min^{-1}·kg^{-1} ww (p < 0.01 vs baseline). A trend towards ↑ in HAD (from 12.10 ± 2.65 to 17.16 ± 6.91 µmol·min^{-1}·kg^{-1} ww) without reaching statistical significance.
Winzer et al. (2022)	41 HFpEF patients randomized to MIE (n = 15), HIIE (n = 14) or CG (n = 12); ages between 69 and 77	24 weeks x 3 supervised / week	HIIE: 4 x 4-min intervals @ 80-90% of HRR, interspersed by 3-min active rest @ 20-50% of HRR. MIE: 40 min @ 35-50% HRR + 2 home sessions / wk.	1. HIIT: CS ↑ (p = 0.004 vs control) and mitochondrial complex – I (p = 0.001 vs control). 2. MIE: N.S.

BFRRE = Blood flow-restricted resistance exercise; CG = Control group; COX = Cytochrome C Oxidase activity; CPT = Carnitine palmitoyltransferase complex; CPET = Cardiopulmonary exercise testing; CS = Citrate synthase activity; dw = dry muscle weight; HAD = Hydroxyacyl-CoA dehydrogenase; HIIE = High-intensity interval exercise; HFrEF = Heart failure with reduced ejection fraction; HFpEF = Heart failure with preserved ejection fraction; HR = Heart rate; HRR = Heart rate reserve; IG = Intervention group; KGDH = α-Ketoglutarate dehydrogenase complex; LVEF = Left ventricular ejection fraction; MIE = Moderate-intensity continuous exercise; MyHC = Myosin heavy chain; N.S. = Non-significant; RIC = Remote ischemic conditioning; reps = repetitions; RM = Repetition maximum; RE = Resistance exercise; SL = Single-leg; vs = versus; ww = wet muscle weight; WR = peak work rate. Values are reported as mean ± standard deviation unless otherwise is stated.

DISCUSSION

Histological and metabolic changes in skeletal muscle observed in patients with CHF, including alterations in fiber type composition and decreased activity of oxidative enzymes, are believed to contribute to reduced exercise tolerance in patients with CHF. While exercise is effective in counteracting these alterations in healthy individuals, it remains unclear whether the same benefits can be extrapolated to CHF pathology. Therefore, the primary aim of this systematic review was to examine the impact of exercise on muscle fiber type distribution and oxidative enzyme capacity in CHF.

A comprehensive synthesis of previous research did not firmly establish that exercise interventions modify muscle fiber type composition in patients with CHF, and only three studies reported statistically significant changes. Methodological limitations in these studies and the lack of corroboration from robust research preclude us from drawing definitive conclusions based on their findings. However, exercise did appear to alter oxidative enzyme activity in patients with CHF, increasing the activity of mitochondrial enzymes. These two observations align with previous reviews that reported inconsistent findings on the exercise effect on muscle fiber type composition and confirmed the positive effect on oxidative enzyme activity. Additionally, our examination of potential moderator variables did not identify any characteristics of exercise protocols that could influence the observed outcomes.

Outcome measures

The research into the plasticity of human skeletal muscle has been ongoing for some 50 years, ever since the publication of the first papers on the differences in skeletal muscle phenotypic traits between aerobically trained and sedentary individuals (Gollnick et al., 1972; Holloszy & Coyle, 1984). Further investigation shed light on the molecular mechanisms underlying fiber type transition (Schiaffino, 2010), substantiating the observations that chronic exposure to aerobic exercise increased the proportion of slow-twitch oxidative fibers and activity of mitochondrial enzymes.

Conversely, cases of extreme muscle disuse, such as immobilization, were associated with atrophy of oxidative fibers (Wang & Pessin, 2013) parallel to increased expression of metabolically inefficient glycolytic isoforms (Häggmark et al., 1986; Hortobágyi et al., 2000). These observations suggest comparable skeletal muscle characteristics between immobilized subjects and those diagnosed with CHF. Based on these considerations, skeletal muscle dysfunction in CHF could be explained, at least in some part, by deconditioning (i.e., prolonged physical inactivity leading to the progressive loss of fitness) (Mettauer et al., 2001). However, while exercise restored fiber type composition in healthy populations following extended periods of inactivity (Häggmark et al., 1986; Hortobágyi et al., 2000), the present review could not corroborate these findings in patients with CHF. The lack of clear-cut evidence on positive exercise effects in patients with CHF could imply that outside of deconditioning, the underlying CHF pathology plays an important role in the development of muscle dysfunction. Previous research revealed elevated levels of circulating inflammatory cytokines and activation of atrophy-related pathways in patients with CHF (Duscha et al., 2008; Zizola & Schulze, 2013). Although these mechanisms may not directly contribute to the absence of exercise-induced changes in fiber type distribution, they underscore the presence of CHF-specific muscle pathology.

The failure of studies in this review to identify significant modifications in MyHC distribution could also be attributed to the inherent limitations of biopsy analysis techniques rather than the effects of exercise per se. Transitions between fiber types occur in a stepwise manner, according to a "nearest-neighbor rule" (Pette & Staron, 2000). Therefore, type IIX fibers do not just transition to the opposite extreme but gradually acquire characteristics of oxidative phenotype, giving rise to hybrid isoforms. Consequently, analysis performed in the studies of Belardinelli et al. (1995); Hambrecht et al. (1997); Pu et al. (2001) that only differentiated between type I and II muscle fibers may not have been sufficiently sensitive to capture the fraction of hybrid fibers. Future research should make sure

to employ analysis techniques that provide a better reflection of the expression of both pure and hybrid isoforms across the muscle fibers (Murach et al., 2019).

However, even in the absence of significant alterations in fiber type distribution, exercise has the potential to enhance muscle function in CHF through alternative pathways. Existing evidence indicates that both aerobic and resistance exercise lead to an expansion of muscle capillary network in older sedentary subjects (Coggan et al., 1992; Verdijk et al., 2016), with the magnitude of exercise-derived improvement comparable to that of younger counterparts (Gavin et al., 2007; Murias et al., 2011). Higher capillary density reflects better oxygen supply to the working muscles, along with a larger surface area for exchange between capillaries and muscles. Predictably, higher capillarization is positively correlated with VO_2 peak (Ingjer, 1978; Saltin et al., 1977). Previous research documented reductions in the capillary-to-fiber ratio in patients with CHF (Adams et al., 2017; Georgiadou & Adamopoulos, 2012), with the ratio reportedly being higher in female subjects (Duscha et al., 2001). A recent publication supported the role of exercise in upregulating the expression of angiogenic factors in CHF (Tryfonos et al., 2021). Along the same lines, Williams et al. (2007) examined the changes in capillary-to-fiber ratio and CS activity following 24 weeks of circuit resistance exercise and reported an increase in both variables. These changes coincided with improved exercise capacity in patients randomized to exercise. Additional investigation is warranted to confirm whether exercise uniformly improves capillarization in individuals with CHF and the implication of these changes for their exercise tolerance.

At the same time, elevations in oxidative enzyme activity point to improved oxygen utilization. CS catalyzes the initial reaction of the citric acid cycle, a major metabolic pathway responsible for generating cellular energy. Given its location within the mitochondrial matrix, CS is frequently used as a proxy for measuring mitochondrial content (Larsen et al., 2012). Mitochondria's ability to deliver energy in the form of adenosine triphosphate mirrors skeletal muscle oxidative capacity (Wilson, 1995), and, predictably, mitochondrial function, inferred from the activity of CS or assessed directly in permeabilized cells, is positively associated with VO_2 peak (Hoppeler et al., 1973; Zwaard et al., 2016). The outcomes of interventions about the exercise effects on CS activity consistently demonstrated a positive trend, except for the studies of Groennebaek et al. (2019) and Pu et al. (2001), which will be discussed later.

Collectively these findings suggest that while exercise may not correct for the skeletal muscle composition in CHF, it, nonetheless, elicits morphological and metabolic adaptations that are beneficial to enhancing muscle function in these patients.

Analysis of moderator variables

An effort to identify parameters specific to exercise prescription that could modulate physiological responses yielded inconclusive results. It is important to acknowledge that methodological limitations, such as small sample sizes, heterogeneity of study designs, and questionable accuracy of some of the biopsy sampling and analysis techniques, may have hindered the ability to recognize potential moderating variables. Despite these methodological discrepancies, studies with good methodological quality yielded similar findings regarding CS activity compared to those with fair or poor quality. Out of the five studies with good methodological quality, three reported statistically significant increases in CS activity (Tyni-Lenné, Gordon, et al., 1999; Williams et al., 2007; Winzer et al., 2022). Pu et al. (2001) and Tyni-Lenné, Gordon, et al. (1999) also examined fiber type composition but did not observe any significant changes. It is worth highlighting that all three studies where changes in fiber type composition did, in fact, reach statistical significance were of poor methodological quality (Hambrecht et al., 1997; Keteyian et al., 2003; Tyni-Lenné, Jansson, et al., 1999); suggesting that these findings should be interpreted with caution.

Additionally, individual patient characteristics could modulate exercise response. Previous research highlighted the baseline differences in fiber type composition between male and female subjects without CHF, whereby males reportedly had a higher proportion of type II fibers than

women (Landen et al., 2023). Similar observations were true for patients with CHF (Duscha et al., 2001; Keteyian et al., 2003). Keteyian et al. (2003) reported a higher baseline percentage of type I fibers in female patients with no further increases following a 14- to 24-week MIE intervention. Statistical significant changes following intervention were only observed in males, with an increase in the proportion of type I fibers. Duscha et al. (2001) also documented a higher capillary density in female patients. The increased capillary density, coupled with a greater proportion of oxidative MyHC isoforms in female patients at baseline, suggests that female skeletal muscle may adapt differently to the pathology of CHF itself, further amplifying sex-specific exercise response.

Disease severity is associated with further reductions in exercise capacity (Del Buono et al., 2019), suggesting progressive deterioration of muscle function. If confirmed, these findings would imply that exercise stimuli should be adjusted to accommodate the specific needs and limitations of patients at different stages of CHF progression. Along the same lines, two studies where no significant changes in CS activity were observed (Groennebaek et al., 2019; Pu et al., 2001) also had patients with a mean LVEF higher than the average reported for all the included studies (35 ± 6% and 36.3 ± 8.1% for patients from Groennebaek et al. (2019) and Pu et al. (2001) studies, respectively, versus 28.8 ± 4% across all 21 studies). Based on these observations, more potent exercise stimuli could be required to enhance CS activity in patients with less impaired left ventricular function. Additionally, the lack of exercise-induced elevations in CS activity in these studies could potentially be attributed to vascular restriction in the study of Groennebaek et al. (2019) and the inclusion of a female-only sample in Pu et al. (2001), but the validity of these assumptions should be explored further.

The present review did not include a meta-analysis that could have provided a comprehensive understanding of how protocol-specific variables and individual patient characteristics influenced skeletal muscle fiber composition and enzymatic activity in CHF. Further research with robust statistical analyses is thus required to assess the impact of potential moderating variables quantitatively.

CONCLUSIONS

The increased relative proportion of fast-twitch glycolytic fibers and diminished enzymatic activity were previously cited as contributing factors to profound exercise intolerance in patients with CHF. In healthy populations, the potential of exercise to restore fiber type composition by upregulating the expression of metabolically efficient oxidative fiber types, and increase the activity of oxidative enzymes, has been widely recognized. Therefore, the primary purpose of this review was to confirm whether these findings could be extended to patients with CHF. Results from the publications included in this review could not support the benefits of exercise on fiber type composition in patients diagnosed with CHF. However, enzymatic activity responded well to a wide range of exercise protocols. Importantly, the increases in CS activity as a reflection of improved mitochondrial function highlight the need to consider exercise as an integral part of CHF treatment strategies to address the underlying muscle pathology.

The lack of a robust meta-analytic procedure in the present review precluded the identification of parameters specific to exercise prescription that could enhance the physiological effects of exercise. This limitation should be addressed in future studies. On the other hand, the role of individual patient characteristics as the source of potential heterogeneity in the exercise response should be further explored. Examining all the possible variables that could modify exercise-induced adaptations would facilitate the optimization of exercise protocols targeting muscle dysfunction in CHF and inform treatment strategies.

REFERENCES

Adamopoulos, S., Coats, A. J. S., Brunotte, F., Arnolda, L., Meyer, T., Thompson, C. H., . . . Rajagopalan, B. (1993). Physical training improves skeletal muscle metabolism in patients with chronic heart failure [Article]. *J Am Coll Cardiol*, *21*(5), 1101-1106.

Adams, V., Linke, A., & Winzer, E. (2017). Skeletal muscle alterations in HFrEF vs. HFpEF. *Curr Heart Fail Rep*, *14*(6), 489-497. https://doi.org/10.1007/s11897-017-0361-9

Ades, P. A., Waldmann, M. L., Meyer, W. L., Brown, K. A., Poehlman, E. T., Pendlebury, W. W., . . . LeWinter, M. M. (1996). Skeletal muscle and cardiovascular adaptations to exercise conditioning in older coronary patients [Article]. *Circulation*, *94*(3), 323-330. https://doi.org/10.1161/01.CIR.94.3.323

Antunes-Correa, L. M., Trevizan, P. F., Bacurau, A. V. N., Ferreira-Santos, L., Gomes, J. L. P., Urias, U., . . . Negrão, C. E. (2020). Effects of aerobic and inspiratory training on skeletal muscle microRNA-1 and downstream-associated pathways in patients with heart failure [Article]. *Journal of Cachexia, Sarcopenia and Muscle*, *11*(1), 89-102. https://doi.org/10.1002/jcsm.12495

Bekfani, T., Bekhite Elsaied, M., Derlien, S., Nisser, J., Westermann, M., Nietzsche, S., . . . Schulze, P. C. (2020). Skeletal Muscle Function, Structure, and Metabolism in Patients With Heart Failure With Reduced Ejection Fraction and Heart Failure With Preserved Ejection Fraction. *Circ Heart Fail*, *13*(12), e007198. https://doi.org/10.1161/circheartfailure.120.007198

Belardinelli, R., Georgiou, D., Scocco, V., Barstow, T. J., & Purcaro, A. (1995). Low-intensity exercise training in patients with chronic heart-failure. *J Am Coll Cardiol*, *26*(4), 975-982. https://doi.org/10.1016/0735-1097(95)00267-1

Belardinelli, R., Scocco, V., & Georgiou, D. (1996). Value of low-intensity exercise training in chronic heart failure. *Cardiology Review*, *13*(6), 27-33.

Belardinelli, R., Scocco, V., Gili, A., & Purcaro, A. (1993). Low-intensity exercise training and changes in volume density of mitochondria of vastus lateralis muscle in patients with chronic heart-failure. *Circulation*, *88*(4), 591-591.

Bishop, D. J., Botella, J., Genders, A. J., Lee, M. J., Saner, N. J., Kuang, J., . . . Granata, C. (2019). High-Intensity Exercise and Mitochondrial Biogenesis: Current Controversies and Future Research Directions. *Physiology (Bethesda)*, *34*(1), 56-70. https://doi.org/10.1152/physiol.00038.2018

Bosch, L., Assmann, P., de Grauw, W. J. C., Schalk, B. W. M., & Biermans, M. C. J. (2019). Heart failure in primary care: prevalence related to age and comorbidity. *Primary Health Care Research & Development*, *20*, e79, Article e79. https://doi.org/10.1017/S1463423618000889

Bottinelli, R., & Reggiani, C. (2000). Human skeletal muscle fibres: molecular and functional diversity. *Prog Biophys Mol Biol*, *73*(2-4), 195-262. https://doi.org/10.1016/s0079-6107(00)00006-7

Braith, R. W., Magyari, P. M., Pierce, G. L., Edwards, D. G., Hill, J. A., White, L. J., & Aranda, J. M., Jr. (2005). Effect of resistance exercise on skeletal muscle myopathy in heart transplant recipients. *Am J Cardiol*, *95*(10), 1192-1198. https://doi.org/10.1016/j.amjcard.2005.01.048

Brassard, P., Maltais, F., Noel, M., Doyon, J. F., LeBlanc, P., Allaire, J., . . . Jobin, J. (2006). Skeletal muscle endurance and muscle metabolism in patients with chronic heart failure. *Can J Cardiol*, *22*(5), 387-392. https://doi.org/10.1016/s0828-282x(06)70923-0

Clark, A. L., Poole-Wilson, P. A., & Coats, A. J. S. (1996). Exercise limitation in chronic heart failure: Central role of the periphery. *J Am Coll Cardiol*, *28*(5), 1092-1102. https://doi.org/https://doi.org/10.1016/S0735-1097(96)00323-3

Coats, A. J., Clark, A. L., Piepoli, M., Volterrani, M., & Poole-Wilson, P. A. (1994). Symptoms and quality of life in heart failure: the muscle hypothesis. *Br Heart J*, *72*(2 Suppl), S36-39. https://doi.org/10.1136/hrt.72.2_suppl.s36

Del Buono, M. G., Arena, R., Borlaug, B. A., Carbone, S., Canada, J. M., Kirkman, D. L., . . . Abbate, A. (2019). Exercise Intolerance in Patients With Heart Failure: JACC State-of-the-Art Review. *J Am Coll Cardiol*, *73*(17), 2209-2225. https://doi.org/10.1016/j.jacc.2019.01.072

Drexler, H., Riede, U., Münzel, T., König, H., Funke, E., & Just, H. (1992). Alterations of skeletal muscle in chronic heart failure. *Circulation*, *85*(5), 1751-1759. https://doi.org/10.1161/01.cir.85.5.1751

Duscha, B. D., Annex, B. H., Keteyian, S. J., Green, H. J., Sullivan, M. J., Samsa, G. P., . . . Kraus, W. E. (2001). Differences in skeletal muscle between men and women with chronic heart failure. *90*(1), 280-286. https://doi.org/10.1152/jappl.2001.90.1.280

Duscha, B. D., Schulze, P. C., Robbins, J. L., & Forman, D. E. (2008). Implications of chronic heart failure on peripheral vasculature and skeletal muscle before and after exercise training. *Heart Fail Rev*, *13*(1), 21-37. https://doi.org/10.1007/s10741-007-9056-8

Erbs, S., Hoellriegel, R., Linke, A., Adams, V., Beck, E., Kraenkel, N., . . . Hambrecht, R. (2005). Anabolic properties of physical exercise training in patients with end-stage heart failure: Association between ubiquitin-protein ligase MURF-1 expression and skeletal muscle size. *Circulation*, *112*(17), U734-U735.

Erbs, S., Hoellriegel, R., Linke, A., Adams, V., Beck, E. B., Gielen, S., . . . Schuler, G. (2007). Impact of a 3 months exercise training program on the regulation of the catabolic ubiquitin-proteasome system in patients with end-stage chronic heart failure. *Eur Heart J*, *28*, 142-143.

Erbs, S., Hollriegel, R., Linke, A., Mobius-Winkler, S., Gielen, S., Adams, V., . . . Schuler, G. (2007). Regulation of the catabolic ubiquitin-proteasome system in end-stage chronic heart failure: Impact of physical exercise training and association to skeletal muscle mass. *Circulation*, *116*(16), 648-648.

Esbjörnsson, M., Hellsten-Westing, Y., Balsom, P. D., Sjödin, B., & Jansson, E. (1993). Muscle fibre type changes with sprint training: effect of training pattern. *Acta Physiol Scand*, *149*(2), 245-246. https://doi.org/10.1111/j.1748-1716.1993.tb09618.x

Forman, D. E., Hunt, B., Santoro, C. J., Bairos, L., Levesque, S., Roubenoff, R., . . . Manfredi, T. G. (2000). Progressive resistance training safely improves aerobic metabolism, clinical function, and underlying mitochondrial morphometry in elderly heart failure patients. *Circulation*, *102*(18), 678-678.

Franciosa, J. A., Park, M., & Levine, T. B. (1981). Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. *Am J Cardiol*, *47*(1), 33-39. https://doi.org/10.1016/0002-9149(81)90286-1

Georgiadou, P., & Adamopoulos, S. (2012). Skeletal Muscle Abnormalities in Chronic Heart Failure. *Curr Heart Fail Rep*, *9*(2), 128-132. https://doi.org/10.1007/s11897-012-0090-z

Gibala, M. J., McGee, S. L., Garnham, A. P., Howlett, K. F., Snow, R. J., & Hargreaves, M. (2009). Brief intense interval exercise activates AMPK and p38 MAPK signaling and increases the expression of PGC-1alpha in human skeletal muscle. *J Appl Physiol (1985)*, *106*(3), 929-934. https://doi.org/10.1152/japplphysiol.90880.2008

Gielen, S., Adams, V., Linke, A., Erbs, S., Möbius-Winkler, S., Schubert, A., . . . Hambrecht, R. (2005). Exercise training in chronic heart failure: Correlation between reduced local inflammation and improved oxidative capacity in the skeletal muscle [Article]. *European Journal of Cardiovascular Prevention and Rehabilitation*, *12*(4), 393-400. https://doi.org/10.1097/01.hjr.0000174824.94892.43

Gielen, S., Sandri, M., Adams, V., Kozarez, I., Hoellriegel, R., Mangner, N., . . . Schuler, G. (2010). Differential Response of Murf-1 and Mafbx Expression in the Skeletal Muscle to Training Interventions in Heart Failure Patients. *Circulation*, *122*(21).

Gielen, S., Sandri, M., Kozarez, I., Kratzsch, J., Teupser, D., Thiery, J., . . . Adams, V. (2012). Exercise Training Attenuates MuRF-1 Expression in the Skeletal Muscle of Patients With Chronic Heart Failure Independent of Age The Randomized Leipzig Exercise Intervention in Chronic Heart Failure and Aging Catabolism Study. *Circulation*, *125*(22), 2716-2727. https://doi.org/10.1161/circulationaha.111.047381

Gollnick, P. D., Armstrong, R. B., Saubert, C. W. t., Piehl, K., & Saltin, B. (1972). Enzyme activity and fiber composition in skeletal muscle of untrained and trained men. *J Appl Physiol*, *33*(3), 312-319. https://doi.org/10.1152/jappl.1972.33.3.312

Gordon, A., Gustafsson, T., Tyni-Lenne, R., Sylven, C., & Jansson, E. (2000). Increased expression of VEGF mRNA and protein in skeletal muscle following exercise training in patients with chronic heart failure. *Circulation*, *102*(18), 759-759.

Gordon, A., Tyni-Lenné, R., Jansson, E., Jensen-Urstad, M., & Kaijser, L. (1999). Beneficial effects of exercise training in heart failure patients with low cardiac output response to exercise - a comparison of two training models. *J Intern Med*, *246*(2), 175-182. https://doi.org/10.1046/j.1365-2796.1999.00555.x

Gordon, A., Tyni-Lenné, R., Jansson, E., Kaijser, L., Theodorsson-Norheim, E., & Sylvén, C. (1997). Improved ventilation and decreased sympathetic stress in chronic heart failure patients following local endurance training with leg muscles. *J Card Fail*, *3*(1), 3-12. https://doi.org/10.1016/s1071-9164(97)90002-6

Gordon, A., TyniLenne, R., Persson, H., Kauser, L., Hultman, E., & Sylven, C. (1996). Markedly improved skeletal muscle function with local muscle training in patients with chronic heart failure. *Clinical Cardiology*, *19*(7), 568-574. https://doi.org/10.1002/clc.4960190709

Green, H., Goreham, C., Ouyang, J., Ball-Burnett, M., & Ranney, D. (1999). Regulation of fiber size, oxidative potential, and capillarization in human muscle by resistance exercise. *276*(2), R591-R596. https://doi.org/10.1152/ajpregu.1999.276.2.R591

Groennebaek, T., Sieljacks, P., Nielsen, R., Pryds, K., Jespersen, N. R., Wang, J., . . . Botker, H. E. (2019). Effect of Blood Flow Restricted Resistance Exercise and Remote Ischemic Conditioning on Functional Capacity and Myocellular Adaptations in Patients With Heart Failure. *Circulation-Heart Failure*, *12*(12), Article e006427. https://doi.org/10.1161/circheartfailure.119.006427

Groennebaek, T., & Vissing, K. (2017). Impact of Resistance Training on Skeletal Muscle Mitochondrial Biogenesis, Content, and Function. *8*. https://doi.org/10.3389/fphys.2017.00713

Häggmark, T., Eriksson, E., & Jansson, E. (1986). Muscle fiber type changes in human skeletal muscle after injuries and immobilization. *Orthopedics*, *9*(2), 181-185. https://doi.org/10.3928/0147-7447-19860201-08

Hambrecht, R., Fiehn, E., Niebauer, J., Dieterle, T., Offner, B., Riede, U., & Schuler, G. (1995). Effects of physical exercise on oxidative enzyme-activity and fiber-type distribution in skeletal-muscle of patients with chronic heart-failure. *Circulation*, *92*(8), 1578-1578.

Hambrecht, R., Fiehn, E., Yu, J. T., Niebauer, J., Weigl, C., Hilbrich, L., . . . Schuler, G. (1997). Effects of endurance training on mitochondrial ultrastructure and fiber type distribution in skeletal muscle of patients with stable chronic heart failure. *J Am Coll Cardiol*, *29*(5), 1067-1073. https://doi.org/10.1016/s0735-1097(97)00015-6

Hambrecht, R., Niebauer, J., Fiehn, E., Kalberer, B., Offner, B., Hauer, K., . . . Schuler, G. (1995). Physical-training in patients with stable chronic heart-failure - effects on cardiorespiratory fitness and ultrastructural abnormalities of leg muscles. *J Am Coll Cardiol*, *25*(6), 1239-1249. https://doi.org/10.1016/0735-1097(94)00568-b

Harber, M. P., Konopka, A. R., Undem, M. K., Hinkley, J. M., Minchev, K., Kaminsky, L. A., . . . Trappe, S. (2012). Aerobic exercise training induces skeletal muscle hypertrophy and age-dependent adaptations in myofiber function in young and older men. *113*(9), 1495-1504. https://doi.org/10.1152/japplphysiol.00786.2012

Harjola, V. P., Kiilavuori, K., & Virkamaki, A. (2006). The effect of moderate exercise training on skeletal muscle myosin heavy chain distribution in chronic heart failure. *Int J Cardiol*, *109*(3), 335-338. https://doi.org/10.1016/j.ijcard.2005.06.025

Henriksson, J., & Reitman, J. S. (1976). Quantitative Measures of Enzyme Activities in Type I and Type II Muscle Fibres of Man after Training. *97*(3), 392-397. https://doi.org/https://doi.org/10.1111/j.1748-1716.1976.tb10279.x

Hikida, R. S., Staron, R. S., Hagerman, F. C., Walsh, S., Kaiser, E., Shell, S., & Hervey, S. (2000). Effects of High-Intensity Resistance Training on Untrained Older Men. II. Muscle Fiber Characteristics and Nucleo-Cytoplasmic Relationships. *The Journals of Gerontology: Series A*, *55*(7), B347-B354. https://doi.org/10.1093/gerona/55.7.B347

Hoellriegel, R., Erbs, S., Adams, V., Linke, A., Beck, E., Gielen, S., . . . Hambrecht, R. (2005). Anabolic effects of exercise training in patients with advanced heart failure: relationship between ubiquitin-protein ligase MURF-1 expression and skeletal muscle. *Eur Heart J*, *26*, 125-125.

Hoellriegel, R., Erbs, S., Adams, V., Linke, A., Beck, E. B., Gielen, S., . . . Hambrecht, R. (2006). Anabolic effects of regular exercise training: Correlation between ubiquitin-protein ligase MURF-1 expression and skeletal muscle size in patients with severe chronic heart failure. *Circulation*, *114*(18), 852-852.

Holloszy, J. O., & Coyle, E. F. (1984). Adaptations of skeletal muscle to endurance exercise and their metabolic consequences. *J Appl Physiol Respir Environ Exerc Physiol*, *56*(4), 831-838. https://doi.org/10.1152/jappl.1984.56.4.831

Hollriegel, R., Beck, E. B., Linke, A., Adams, V., Mobius-Winkler, S., Mangner, N., . . . Erbs, S. (2013). Anabolic effects of exercise training in patients with advanced chronic heart failure (NYHA IIIb): Impact on ubiquitin-protein ligases expression and skeletal muscle size. *Int J Cardiol*, *167*(3), 975-980. https://doi.org/10.1016/j.ijcard.2012.03.083

Hoppeler, H., Lüthi, P., Claassen, H., Weibel, E. R., & Howald, H. (1973). The ultrastructure of the normal human skeletal muscle. *Pflügers Archiv*, *344*(3), 217-232. https://doi.org/10.1007/BF00588462

Hortobágyi, T., Dempsey, L., Fraser, D., Zheng, D., Hamilton, G., Lambert, J., & Dohm, L. (2000). Changes in muscle strength, muscle fibre size and myofibrillar gene expression after immobilization and retraining in humans. *J Physiol*, *524 Pt 1*(Pt 1), 293-304. https://doi.org/10.1111/j.1469-7793.2000.00293.x

Howald, H., Hoppeler, H., Claassen, H., Mathieu, O., & Straub, R. (1985). Influences of endurance training on the ultrastructural composition of the different muscle fiber types in humans. *Pflugers Arch*, *403*(4), 369-376. https://doi.org/10.1007/bf00589248

Ingjer, F. (1978). Maximal aerobic power related to the capillary supply of the quadriceps femoris muscle in man. *Acta Physiol Scand*, *104*(2), 238-240. https://doi.org/10.1111/j.1748-1716.1978.tb06273.x

Jacobs, R. A., Flück, D., Bonne, T. C., Bürgi, S., Christensen, P. M., Toigo, M., & Lundby, C. (2013). Improvements in exercise performance with high-intensity interval training coincide with an increase in skeletal muscle mitochondrial content and function. *J Appl Physiol (1985)*, *115*(6), 785-793. https://doi.org/10.1152/japplphysiol.00445.2013

James, S. L., Abate, D., & Abate, K. H. (2018). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*, *392*(10159), 1789-1858. https://doi.org/10.1016/s0140-6736(18)32279-7

Jansson, E., Esbjörnsson, M., Holm, I., & Jacobs, I. (1990). Increase in the proportion of fast-twitch muscle fibres by sprint training in males. *Acta Physiol Scand*, *140*(3), 359-363. https://doi.org/10.1111/j.1748-1716.1990.tb09010.x

Keteyian, S. J., Duscha, B. D., Brawner, C. A., Green, H. J., Marks, C. R., Schachat, F. H., . . . Kraus, W. E. (2003). Differential effects of exercise training in men and women with chronic heart failure. *Am Heart J*, *145*(5), 912-918. https://doi.org/10.1016/s0002-8703(03)00075-9

Kiilavuori, K., Naveri, H., Salmi, T., & Harkonen, M. (2000). The effect of physical training on skeletal muscle in patients with chronic heart failure. *Eur J Heart Fail*, *2*(1), 53-63. https://doi.org/10.1016/s1388-9842(00)00058-1

Landen, S., Hiam, D., Voisin, S., Jacques, M., Lamon, S., & Eynon, N. (2023). Physiological and molecular sex differences in human skeletal muscle in response to exercise training. *601*(3), 419-434. https://doi.org/https://doi.org/10.1113/JP279499

Larsen, A. I., Lindal, S., Aukrust, P., Toft, I., Aarsland, T., & Dickstein, K. (2002). Effect of exercise training on skeletal muscle fibre characteristics in men with chronic heart failure. Correlation between skeletal muscle alterations, cytokines and exercise capacity. *Int J Cardiol*, *83*(1), 25-32. https://doi.org/10.1016/s0167-5273(02)00014-1

Lee, C. T., Chen, L. W., & Chien, M. Y. (2017). Effects of exercise training on anabolic and catabolic markers in patients with chronic heart failure: a systematic review. *Heart Fail Rev*, *22*(6), 723-730. https://doi.org/10.1007/s10741-017-9639-y

Lenk, K., Erbs, S., Hollriegel, R., Beck, E., Linke, A., Gielen, S., . . . Adams, V. (2012). Exercise training leads to a reduction of elevated myostatin levels in patients with chronic heart failure. *European Journal of Preventive Cardiology*, *19*(3), 404-411. https://doi.org/10.1177/1741826711402735

Linke, A., Adams, V., Schulze, P. C., Erbs, S., Gielen, S., Fiehn, E., . . . Hambrecht, R. (2005). Antioxidative effects of exercise training in patients with chronic heart failure: Increase in radical scavenger enzyme activity in skeletal muscle [Article]. *Circulation*, *111*(14), 1763-1770. https://doi.org/10.1161/01.CIR.0000165503.08661.E5

Little, J. P., Safdar, A., Wilkin, G. P., Tarnopolsky, M. A., & Gibala, M. J. (2010). A practical model of low-volume high-intensity interval training induces mitochondrial biogenesis in human skeletal muscle: potential mechanisms. *J Physiol*, *588*(Pt 6), 1011-1022. https://doi.org/10.1113/jphysiol.2009.181743

Magnusson, G., Gordon, A., Kaijser, L., Sylvén, C., Isberg, B., Karpakka, J., & Saltin, B. (1996). High intensity knee extensor training, in patients with chronic heart failure. Major skeletal muscle improvement. *Eur Heart J*, *17*(7), 1048-1055. https://doi.org/10.1093/oxfordjournals.eurheartj.a015001

Malakar, A. K., Choudhury, D., Halder, B., Paul, P., Uddin, A., & Chakraborty, S. (2019). A review on coronary artery disease, its risk factors, and therapeutics. *234*(10), 16812-16823. https://doi.org/https://doi.org/10.1002/jcp.28350

Mancini, D. M., Coyle, E., Coggan, A., Beltz, J., Ferraro, N., Montain, S., & Wilson, J. R. (1989). Contribution of intrinsic skeletal muscle changes to 31P NMR skeletal muscle metabolic abnormalities in patients with chronic heart failure. *Circulation*, *80*(5), 1338-1346. https://doi.org/10.1161/01.cir.80.5.1338

Mancini, D. M., Eisen, H., Kussmaul, W., Mull, R., Edmunds, L. H., Jr., & Wilson, J. R. (1991). Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation*, *83*(3), 778-786. https://doi.org/10.1161/01.cir.83.3.778

McDonagh, T. A., Metra, M., Adamo, M., Gardner, R. S., Baumbach, A., Böhm, M., . . . Group, E. S. D. (2021). 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J*, *42*(36), 3599-3726. https://doi.org/10.1093/eurheartj/ehab368

Mettauer, B., Zoll, J., Sanchez, H., Lampert, E., Ribera, F., Veksler, V., . . . Ventura-Clapier, R. (2001). Oxidative capacity of skeletal muscle in heart failure patients versus sedentary or active control subjects. *J Am Coll Cardiol*, *38*(4), 947-954. https://doi.org/10.1016/s0735-1097(01)01460-7

Middlekauff, H. R. (2010). Making the case for skeletal myopathy as the major limitation of exercise capacity in heart failure. *Circ Heart Fail*, *3*(4), 537-546. https://doi.org/10.1161/circheartfailure.109.903773

Mosterd, A., & Hoes, A. W. (2007). Clinical epidemiology of heart failure. *Heart*, *93*(9), 1137-1146. https://doi.org/10.1136/hrt.2003.025270

Munkvik, M., Rehn, T. A., SlettalØkken, G., Hasic, A., Hallén, J., Sjaastad, I., . . . Lunde, P. K. (2010). Training effects on skeletal muscle calcium handling in human chronic heart failure [Article].

Medicine and Science in Sports and Exercise, *42*(5), 847-855. https://doi.org/10.1249/MSS.0b013e3181c29ec1

Murach, K. A., Dungan, C. M., Kosmac, K., Voigt, T. B., Tourville, T. W., Miller, M. S., . . . Toth, M. J. (2019). Fiber typing human skeletal muscle with fluorescent immunohistochemistry. *J Appl Physiol (1985)*, *127*(6), 1632-1639. https://doi.org/10.1152/japplphysiol.00624.2019

Myers, J., Prakash, M., Froelicher, V., Do, D., Partington, S., & Atwood, J. E. (2002). Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med*, *346*(11), 793-801. https://doi.org/10.1056/NEJMoa011858

Nader, G. A., & Esser, K. A. (2001). Intracellular signaling specificity in skeletal muscle in response to different modes of exercise. *J Appl Physiol (1985)*, *90*(5), 1936-1942. https://doi.org/10.1152/jappl.2001.90.5.1936

Nicoletti, I., Cicoira, M., Zanolla, L., Franceschini, L., Brighetti, G., Pilati, M., & Zardini, P. (2003). Skeletal muscle abnormalities in chronic heart failure patients: relation to exercise capacity and therapeutic implications. *Congest Heart Fail*, *9*(3), 148-154. https://doi.org/10.1111/j.1527-5299.2002.01219.x

Notarius, C. F., Levy, R. D., Tully, A., Fitchett, D., & Magder, S. (1998). Cardiac versus noncardiac limits to exercise after heart transplantation. *Am Heart J*, *135*(2 Pt 1), 339-348. https://doi.org/10.1016/s0002-8703(98)70103-6

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., . . . Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Bmj*, *372*, n71. https://doi.org/10.1136/bmj.n71

Pette, D., & Staron, R. S. (2000). Myosin isoforms, muscle fiber types, and transitions. *Microsc Res Tech*, *50*(6), 500-509. https://doi.org/10.1002/1097-0029

Piepoli, M. F., & Coats, A. J. S. (2013). The 'skeletal muscle hypothesis in heart failure' revised. *Eur Heart J*, *34*(7), 486-488. https://doi.org/10.1093/eurheartj/ehs463

Pu, C. T., Johnson, M. T., Forman, D. E., Hausdorff, J. M., Roubenoff, R., Foldvari, M., . . . Singh, M. A. (2001). Randomized trial of progressive resistance training to counteract the myopathy of chronic heart failure. *J Appl Physiol (1985)*, *90*(6), 2341-2350. https://doi.org/10.1152/jappl.2001.90.6.2341

Robinson, M. M., Dasari, S., Konopka, A. R., Johnson, M. L., Manjunatha, S., Esponda, R. R., . . . Nair, K. S. (2017). Enhanced Protein Translation Underlies Improved Metabolic and Physical Adaptations to Different Exercise Training Modes in Young and Old Humans. *Cell Metab*, *25*(3), 581-592. https://doi.org/10.1016/j.cmet.2017.02.009

Roth, G. A., Mensah, G. A., Johnson, C. O., Addolorato, G., Ammirati, E., Baddour, L. M., . . . Fuster, V. (2020). Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. *J Am Coll Cardiol*, *76*(25), 2982-3021. https://doi.org/10.1016/j.jacc.2020.11.010

Roy, R. R., Baldwin, K. M., & Edgerton, R. V. (1991). The Plasticity of Skeletal Muscle: Effects of Neuromuscular Activity. *19*(1), 269-312.

Russell, A. P., Feilchenfeldt, J., Schreiber, S., Praz, M., Crettenand, A., Gobelet, C., . . . Dériaz, O. (2003). Endurance training in humans leads to fiber type-specific increases in levels of peroxisome proliferator-activated receptor-gamma coactivator-1 and peroxisome proliferator-activated receptor-alpha in skeletal muscle. *Diabetes*, *52*(12), 2874-2881. https://doi.org/10.2337/diabetes.52.12.2874

Sakamoto, K., & Goodyear, L. J. (2002). Invited review: intracellular signaling in contracting skeletal muscle. *J Appl Physiol (1985)*, *93*(1), 369-383. https://doi.org/10.1152/japplphysiol.00167.2002

Saltin, B., Henriksson, J., Nygaard, E., Andersen, P., & Jansson, E. (1977). Fiber types and metabolic potentials of skeletal muscles in sedentary man and endurance runners. *Ann N Y Acad Sci*, *301*, 3-29. https://doi.org/10.1111/j.1749-6632.1977.tb38182.x

Schiaffino, S. (2010). Fibre types in skeletal muscle: a personal account. *Acta Physiol (Oxf)*, *199*(4), 451-463. https://doi.org/10.1111/j.1748-1716.2010.02130.x

Smart, N. A., Waldron, M., Ismail, H., Giallauria, F., Vigorito, C., Cornelissen, V., & Dieberg, G. (2015). Validation of a new tool for the assessment of study quality and reporting in exercise training studies: TESTEX. *Int J Evid Based Healthc*, *13*(1), 9-18. https://doi.org/10.1097/xeb.0000000000000020

Staron, R. S., Malicky, E. S., Leonardi, M. J., Falkel, J. E., Hagerman, F. C., & Dudley, G. A. (1990). Muscle hypertrophy and fast fiber type conversions in heavy resistance-trained women. *European Journal of Applied Physiology and Occupational Physiology*, *60*(1), 71-79. https://doi.org/10.1007/BF00572189

Sullivan, M. J., Green, H. J., & Cobb, F. R. (1990). Skeletal muscle biochemistry and histology in ambulatory patients with long-term heart failure. *Circulation*, *81*(2), 518-527. https://doi.org/10.1161/01.cir.81.2.518

Sullivan, M. J., Green, H. J., & Cobb, F. R. (1991). Altered skeletal muscle metabolic response to exercise in chronic heart failure. Relation to skeletal muscle aerobic enzyme activity. *Circulation*, *84*(4), 1597-1607. https://doi.org/10.1161/01.cir.84.4.1597

Sullivan, M. J., & Hawthorne, M. H. (1995). Exercise intolerance in patients with chronic heart failure. *Prog Cardiovasc Dis*, *38*(1), 1-22. https://doi.org/10.1016/s0033-0620(05)80011-8

Tryfonos, A., Tzanis, G., Pitsolis, T., Karatzanos, E., Koutsilieris, M., Nanas, S., & Philippou, A. (2021). Exercise Training Enhances Angiogenesis-Related Gene Responses in Skeletal Muscle of Patients with Chronic Heart Failure. *Cells*, *10*(8). https://doi.org/10.3390/cells10081915

Tyni-Lenné, R., Gordon, A., Europe, E., Jansson, E., & Sylvén, C. (1998). Exercise-based rehabilitation improves skeletal muscle capacity, exercise tolerance, and quality of life in both women and men with chronic heart failure [Article]. *Journal of Cardiac Failure*, *4*(1), 9-17. https://doi.org/10.1016/S1071-9164(98)90503-6

Tyni-Lenné, R., Gordon, A., Jansson, E., Bermann, G., & Sylven, C. (1997). Skeletal muscle endurance training improves peripheral oxidative capacity, exercise tolerance, and health-related quality of life in women with chronic congestive heart failure secondary to either ischemic cardiomyopathy or idiopathic dilated cardiomyopathy. *American Journal of Cardiology*, *80*(8), 1025-1029. https://doi.org/10.1016/s0002-9149(97)00597-3

Tyni-Lenné, R., Gordon, A., Jensen-Urstad, M., Dencker, K., Jansson, E., & Sylven, C. (1999). Aerobic training involving a minor muscle mass shows greater efficiency than training involving a major muscle mass in chronic heart failure patients. *Journal of Cardiac Failure*, *5*(4), 300-307. https://doi.org/10.1016/s1071-9164(99)91334-9

Tyni-Lenné, R., Jansson, E., & Sylven, C. (1999). Female-related skeletal muscle phenotype in patients with moderate chronic heart failure before and after dynamic exercise training. *Cardiovasc Res*, *42*(1), 99-103. https://doi.org/10.1016/s0008-6363(98)00313-7

Udelson, J. E., & Stevenson, L. W. (2016). The Future of Heart Failure Diagnosis, Therapy, and Management. *Circulation*, *133*(25), 2671-2686. https://doi.org/10.1161/circulationaha.116.023518

Vanderent, M., Jeneson, J. A., Remme, W. J., Bartels, G. L., & Berger, R. (1994). Early impairment of type-I fiber mitochondrial-function at low exercise levels in mild-to-moderate heart-failure - a spectroscopy study. *Circulation*, *90*(4), 469-469.

von Haehling, S., Arzt, M., Doehner, W., Edelmann, F., Evertz, R., Ebner, N., . . . Laufs, U. (2021). Improving exercise capacity and quality of life using non-invasive heart failure treatments: evidence from clinical trials. *Eur J Heart Fail*, *23*(1), 92-113. https://doi.org/10.1002/ejhf.1838

Wahl, P., Bloch, W., & Proschinger, S. (2022). The Molecular Signature of High-intensity Training in the Human Body. *Int J Sports Med*, *43*(3), 195-205. https://doi.org/10.1055/a-1551-9294

Wang, X. W., Yan, K. Y., Wen, C. F., & Wang, J. Q. (2022). Simvastatin Combined with Resistance Training Improves Outcomes in Patients with Chronic Heart Failure by Modulating

Mitochondrial Membrane Potential and the Janus Kinase/Signal Transducer and Activator of Transcription 3 Signaling Pathways. *Cardiovascular Therapeutics*, *2022*, Article 8430733. https://doi.org/10.1155/2022/8430733

Wang, Y., & Pessin, J. E. (2013). Mechanisms for fiber-type specificity of skeletal muscle atrophy. *Curr Opin Clin Nutr Metab Care*, *16*(3), 243-250. https://doi.org/10.1097/MCO.0b013e328360272d

Williams, A. D., Carey, M. F., Selig, S., Hayes, A., Krum, H., Patterson, J., . . . Hare, D. L. (2007). Circuit Resistance Training in Chronic Heart Failure Improves Skeletal Muscle Mitochondrial ATP Production Rate-A Randomized Controlled Trial [Article]. *Journal of Cardiac Failure*, *13*(2), 79-85. https://doi.org/10.1016/j.cardfail.2006.10.017

Wilson, D. F. (1995). Energy metabolism in muscle approaching maximal rates of oxygen utilization. *Med Sci Sports Exerc*, *27*(1), 54-59.

Winzer, E. B., Augstein, A., Schauer, A., Mueller, S., Fischer-Schaepmann, T., Goto, K., . . . Adams, V. (2022). Impact of Different Training Modalities on Molecular Alterations in Skeletal Muscle of Patients With Heart Failure With Preserved Ejection Fraction: A Substudy of the OptimEx Trial. *Circulation-Heart Failure*, *15*(10), Article e009124. https://doi.org/10.1161/circheartfailure.121.009124

Zizola, C., & Schulze, P. C. (2013). Metabolic and structural impairment of skeletal muscle in heart failure. *Heart Fail Rev*, *18*(5), 623-630. https://doi.org/10.1007/s10741-012-9353-8

Zwaard, S. v. d., Ruiter, C. J. d., Noordhof, D. A., Sterrenburg, R., Bloemers, F. W., Koning, J. J. d., . . . Laarse, W. J. v. d. (2016). Maximal oxygen uptake is proportional to muscle fiber oxidative capacity, from chronic heart failure patients to professional cyclists. *121*(3), 636-645. https://doi.org/10.1152/japplphysiol.00355.2016

SUPPLEMENTARY MATERIAL

Table S1. Methodological quality assessment of included studies judged using TESTEX scale.

	Study quality						Study reporting							
Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Overall	Judgement
Belardinelli et al. (1995)	1	0	0	1	0	1	0	1	0	1	1	0	6	Fair
Gielen et al. (2005)	1	0	0	1	0	1	0	1	1	0	0	0	5	Poor
Gordon et al. (1996)	1	0	0	1	0	2	0	1	1	1	0	1	8	Fair
Gordon et al. (1997)	1	0	0	1	0	1	0	0	1	0	0	1	5	Poor
Gordon et al. (2000)	1	0	0	0	0	1	0	0	1	0	1	0	4	Poor
Groennebaek et al. (2019)	1	1	1	1	1	3	0	1	1	0	0	1	11	Good
Hambrecht, Niebauer, et al. (1995)	1	0	0	1	0	2	0	1	1	1	0	1	8	Fair
Hambrecht et al. (1997)	1	0	0	1	0	1	0	1	1	0	0	0	5	Poor
Harjola et al. (2006)	1	0	0	1	0	1	0	1	1	0	1	1	7	Fair
Keteyian et al. (2003)	1	0	0	0	0	2	0	0	1	0	0	0	4	Poor
Kiilavuori et al. (2000)	1	0	0	1	0	2	0	1	1	0	1	1	8	Fair
Larsen et al. (2002)	1	0	0	0	0	0	0	1	1	0	0	1	4	Poor
Magnusson et al. (1996)	1	0	0	1	0	1	0	1	0	1	0	1	6	Fair
Munkvik et al. (2010)	1	0	0	1	0	0	0	1	0	0	0	0	3	Poor
Pu et al. (2001)	1	0	0	1	1	3	0	1	1	1	1	1	11	Good
Tyni-Lenné et al. (1997)	1	0	0	1	0	3	0	1	1	0	0	1	8	Fair
Tyni-Lenné et al. (1998)	1	0	0	1	0	3	0	0	1	0	0	1	7	Fair
Tyni-Lenné, Gordon, et al. (1999)	1	1	0	1	0	3	0	0	1	0	1	1	9	Good

Table S1. Continued.

	Study quality						Study reporting							
Study	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Overall	Judgement
Tyni-Lenné, Jansson, et al. (1999)	1	0	0	0	0	2	0	0	1	0	0	0	4	Poor
Williams et al. (2007)	1	1	0	1	0	3	0	1	1	0	1	0	9	Good
Winzer et al. (2022)	1	1	0	1	1	1	0	1	1	0	1	1	9	Good

Item 1 = Eligibility criteria specified; Item 2 = Randomization specified; Item 3 = Allocation concealment; Item 4 = Groups similar at baseline; Item 5 = Assessor blinding; Item 6 = Outcome measures assessed in 85% of patients; Item 7 = Intention-to-treat analysis; Item 8 = Between-group statistical comparisons reported; Item 9 = Point measures and measures of variability for all reported outcome measures; Item 10 = Activity monitoring in control groups; Item 11 = Relative exercise intensity remained constant; Item 12 = Exercise volume and energy expenditure.