Systematic Review

Exercise Training-Induced Extracellular Matrix Protein Adaptation in Locomotor Muscles: A Systematic Review

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Abstract: Exercise training promotes muscle adaptation and remodelling by balancing the processes of anabolism and catabolism; however, the mechanisms by which exercise delays accelerated muscle wasting are not fully understood. Intramuscular extracellular matrix (ECM) proteins are essential to tissue structure and function, as they create a responsive environment for the survival and repair of the muscle fibres. However, their role in muscle adaptation is underappreciated and underinvestigated. The PubMed, COCHRANE, Scopus and CIHNAL databases were systematically searched from inception until February 2021. The inclusion criteria were on ECM adaptation after exercise training in healthy adult population. Evidence from 21 studies on 402 participants demonstrates that exercise training induces muscle remodelling, and this is accompanied by ECM adaptation. All types of exercise interventions promoted a widespread increase in collagens, glycoproteins and proteoglycans ECM transcriptomes in younger and older participants. The ECM controlling mechanisms highlighted here were concerned with myogenic and angiogenic processes during muscle adaptation and remodelling. Further research identifying the mechanisms underlying the link between ECMs and muscle adaptation will support the discovery of novel therapeutic targets and the development of personalised exercise training medicine.

Keywords: extracellular matrix; skeletal muscle; glycoproteins; proteoglycans; collagens; exercise training; ageing; remodelling; adaptation; myogenesis

1. Introduction

Skeletal muscle mass accounts for 40% of total body mass. Muscle is a highly plastic tissue, and adaptation is seen after increased locomotory and metabolic demands of exercise training. Adaptation in terms of altered muscle physiology and improved performance varies greatly according to the activities imposed, such as force, duration, as well as individual’s capacity to respond, which is controlled by their genetic makeup [1].

Ageing is associated with progressive decline in skeletal muscle mass, muscle strength and regenerative capacity [2]. Weakened muscles increase the likelihood of injury and ineffective repair processes, negatively affecting quality of life. Exercise training is applied as a therapeutic intervention capable of improving aged muscle regeneration, muscle strength and muscle mass [3–5]. Most of the investigations have traditionally focused on elucidating the phenotypic changes on muscle strength, size and fibre type distribution. At the cellular and molecular level, several markers of cellular anabolism and catabolism have been investigated [2,3,6]. However, studies on the effect of exercise...
training promoting muscle extracellular matrix (ECM) adaptation are limited and have been frequently overlooked.

The intramuscular ECM is widely distributed throughout muscle tissue, maintaining its structure. The ECM endomysium embeds the individual muscle fibres and the neighbouring myofibers are organized into fascicles encased by the perimysium. The whole muscle is enshathed by another layer of ECM connective tissue named the epimysium [7]. Intramuscular ECMs provide mechanical support to muscle tissue, nerves and blood vessels. Recent research has demonstrated that the ECM plays an important role in muscle growth [8] and repair processes [9], as well as the transmission of contractile force [10]. Nevertheless, the role of ECM adaptation on muscle regeneration and remodelling after exercise training stimulus is still unclear. The intramuscular ECM adaptation seen during ageing has been reviewed elsewhere [11].

As a post-mitotic tissue, the homeostasis of the skeletal muscles depends on the capacity of the satellite cells to adapt and regenerate. Under normal conditions, adult muscle turnover as result of daily life activities relies on sporadic proliferation and fusion of satellite cells to muscle fibres. Satellite cells are found in a cell niche, which consists of a mesh of components containing a mixture of glycoproteins and proteoglycans and growth factors. The ECMs in the niche provide a dynamic environment, transmitting mechanical and biochemical signals. The function of these ECM molecules is to maintain satellite cell quiescence, activation, proliferation and differentiation [9,11,12].

Exercise training is the most potent strategy to improve muscle fibre cross-sectional area. This intervention remodels peripheral skeletal muscle architecture and alters the ECM expression involved in this process [13–15]. However, the extent to which ECMs contribute to the regeneration and remodelling of the skeletal muscle upon exercise training is still unclear. The aim of this systematic review is to provide up-to-date information on the effect of exercise training inducing ECM adaptation and the involvement of ECMs on skeletal muscle remodelling.

2. Materials and Methods

This systematic review was compiled using guidelines described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [16]. The review protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO ID: CRD42021206259).

2.1. Search Strategy

A literature search of online databases, PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and CINAHL was conducted from their inception to March 2021. These databases were chosen due to their relevance in the field, use in other systematic reviews [17–19] and in consultation with a university librarian. All databases were accessed via the Northumbria University library platform. A search on PEDro database did not retrieve study results framework. In addition to the database search, citations from studies in the field were screened for the criteria and inserted as other sources.

To develop the search strategy, relevant terminology was determined from published reviews associated with ECM in skeletal muscle and with exercise training [11,20]. Following this, search strings based on a combination of a mix of Medical Subject Headings (MeSH) or free text words related to “extracellular matrix proteins”, “exercise”, “activity”, “skeletal muscle remodelling”, “ cachexia” and “skeletal muscle wasting” were used to form the PICO (population, intervention, comparators, outcome) framework (Supplementary Table S1).

2.2. Study Selection and Data Extraction

Peer reviewed studies published in the English language and involving healthy human participants were eligible to be included in this systematic review. Studies evaluating
the effect of exercise training intervention on primary or secondary outcome demonstrating ECM expression at mRNA and protein level were included. ECM-related molecules were not part of the outcome search. No chronological and study design limitations were determined.

Studies exclusively testing animal or in vitro models were excluded from this systematic review. Studies describing immobilization and/or disuse interventions, as well as studies testing the effect of a single bout of exercise were excluded. Other studies excluded were those that analysed non-peripheral skeletal muscle, pharmacological interventions, and those on neuromuscular pathologies. Studies that did not contain any ECM marker in their outcomes were also excluded from the current review.

Selected outcomes were exported to EndNote software (Thomson Reuters, New York, NY, USA). Duplicates were removed using the systematic review management software program Rayyan (Qatar Computing Research Institute, Doha, Qatar). Titles and abstracts were screened by two reviewers (E.K. and R.A.), articles were fully text read and assessed for inclusion eligibility. Any disputes were resolved by a third reviewer (D.C.M.S.). Data were extracted individually by two reviewers (E.K. and R.A.).

2.3. Quality Assessment

The outcomes were assessed for risk of bias (E.K., R.A.), and discrepancies resolved (E.K.). As the studies included randomized controlled trials (RCTs) or non-RCTs, the revised versions of Cochrane Collaboration’s tool (RoB2) and ROBINS-I were used to assess the risk of bias, respectively [21–23]. ROBINS-I is the preferentially recommended tool to evaluate the risk of bias of non-RCTs [23]. This tool was specifically developed to evaluate the risk of bias estimating the comparative effectiveness of interventions in studies not adopting randomisation in allocating units (individual or cluster of individuals) into comparison groups [21]. Additionally, bias domains that are included in ROBINS-I considered the pre-intervention, at-intervention and post-intervention periods. Whereas RoB2 is a suitable tool for assessing the risk of bias for RCTs [23]. RoB2 domains of assessing bias included signalling questions that were based on the randomisation process, deviations from the intended interventions, missing outcome data, missing reported results, selections of the reported results and an overall bias [22]. The interpretation of the domain-level and overall risk of bias judgements in both assessment tools are “Low risk”, “Moderate risk”, “Serious risk” and “Critical risk” of bias, which were calculated from the checklist scores according to ROBINS-I and RoB2 guidance [21,22].

3. Results

The systematic search of the online database identified 2236 articles. Twelve articles were added from other sources. All articles were screened using the eligibility and exclusion criteria. The PRISMA flow diagram (Figure 1) summarizes the search strategy and the study selection process.

3.1. Analysis of Risk of Bias

Of the 21 studies included, the overall bias of 13 studies was moderate, in 7 of them it was low and 1 of them it was high. The bias sections where the outcome was not clearly stated, they were marked as “unclear”. The risk of bias classification for each article using the ROBINS-I and ROB2 tools are displayed in Tables 1 and 2, respectively.
Figure 1. PRISMA flow diagram of the identification and selection process.

Table 1. ROBINS-I quality assessment scores for the non-RCTs included studies.

| Author                | Bias Due to Confounding | Bias in Selection of Participants into the Study | Bias in Classification of Interventions | Bias Due to Deviations from Intended Interventions | Bias Due to Missing Data | Bias in Measurement of Outcomes | Bias in Selection of the Reported Result | Overall Bias |
|-----------------------|-------------------------|-----------------------------------------------|----------------------------------------|-----------------------------------------------|------------------------|----------------------------------|---------------------------------------------|--------------|
| Damas et al., 2018    | Low                     | Low                                           | Low                                    | Low                                           | Low                    | Low                              | Low                                         | Low          |
| Deshmukh et al., 2021 | Low                     | Low                                           | Low                                    | Low                                           | Low                    | Moderate                         | Low                                         | Low          |
| Hjorth et al., 2015   | Low                     | Low                                           | Low                                    | Low                                           | Low                    | Unclear                         | Low                                         | Low          |
| Kanzleiter et al., 2014 | Low                   | Moderate                                      | Low                                    | Low                                           | Low                    | Unclear                         | Low                                         | Low          |
| Karlsen et al., 2020  | Low                     | Low                                           | Low                                    | Low                                           | Low                    | Unclear                         | Low                                         | Low          |
| Kern et al., 2014     | Low                     | Low                                           | Low                                    | Low                                           | Low                    | Moderate                         | Low                                         | Low          |
| Makhnovskii et al., 2020 | Low                   | Moderate                                      | Unclear                                | Low                                           | Low                    | Low                              | Moderate                                     | Low          |
| Nishida et al., 2010  | Low                     | Low                                           | Low                                    | Low                                           | Low                    | Low                              | Low                                         | Low          |
| Norheim et al., 2011  | Low                     | Unclear                                       | Low                                    | Low                                           | Low                    | Low                              | Low                                         | Low          |
| Norheim et al., 2014  | Low                     | Low                                           | Low                                    | Low                                           | Low                    | Unclear                         | Low                                         | Moderate     |
Table 2. RoB 2 quality assessment scores for RCTs included studies.

| Author                      | Randomization Process Bias | Deviation from the Intended Intervention Bias | Missing Outcome Bias | Measurement of the Outcome Bias | Selection of Reported Results Bias | Overall Risk of Bias |
|-----------------------------|-----------------------------|-----------------------------------------------|----------------------|---------------------------------|-----------------------------------|---------------------|
| Alghadir et al., 2016       | High                        | Low                                           | Low                  | High                            | Moderate                          | High                |
| Fragala et al., 2014        | Low                         | Low                                           | Low                  | Unclear                         | Low                               | Moderate            |
| Kim et al., 2015            | Low                         | Low                                           | Low                  | Unclear                         | Low                               | Moderate            |

3.2. Study and Subject Characteristics

Of the 21 studies included in the systematic review, 18 were non-RCT of pre–post study design [24–41] and 3 RCTs [42–44]. Even though our systematic review focuses on healthy subjects, two studies were on clinical populations [34,44]. However, no fibrosis or other neuromuscular pathologies were observed in these studies. The exercise training interventions prescribed were aerobic exercise training (AET) [30,31,35,37,39–41,44], resistance training (RET) [24,25,28,33,34,36,42,43], combined aerobic and resistance training (CT) [26,27,32], electrical stimulation (ES) [29] and one comparing resistance training, high-intensity interval training (HIIT) and combined training after a sedentary period [38]. The duration of the exercise interventions ranged from 5 to 13 weeks, the frequency was 2 to 9 sessions per week, and the mean calculated (duration x number of sessions) dosage was 35.3 hrs. We were able to accurately estimate dosage in 18 out of the 21 studies included. Notably, the training duration was different among age groups. In older age populations, longer training intervention for more than 9 weeks was preferably prescribed, whereas in the younger age groups, the training tended to be shorter than 9 weeks. The characteristics of the studies’ interventions are presented in Table 3, with the clinical studies placed at bottom of the Tables. No adverse events were mentioned throughout the duration of these studies.

A total of 402 healthy individuals, with an average age of 46.8 years old (19–77.4 years old) and 85 individuals from a clinical population with an average age 57.9 years participated across the studies. The majority of studies included only male participants representing 69% of the total population, four studies included males and females [29,36,38,41], and two studies exclusively females [34,43]. Among the healthy individuals, 69% were male and 31% female. The majority of the studies involved either a young group (<38 years old) with an average age 25.1 ± 1.8 years old or an old group with an average age 65.7 ± 9.9 years old. Direct comparison of the effect of exercise on ECMS in young and old populations was limited to data from only two studies [36,38]. A summary of participants’ characteristics and physiological changes as result of exercise intervention is shown in Table 3.
3.3. Exercise Training Increases the Expression of ECMs Associated with Skeletal Muscle Remodelling

Muscle adaptations were quantified in several studies and are presented in Table 3 as muscle strength, body composition and muscle architecture. The changes in muscle strength and capacity were demonstrated as significant increase in leg and knee extension strength, peak torque and grip strength [26,28,29,34,36,38,42,43]. Body composition with increased body fat free mass (FFM), lean body mass (LBM), and decreased percentage of fat was also observed in participants after various exercise training interventions [26,28,31,37,38,42,43]. Muscle architecture also changed significantly with exercise intervention increasing muscle cross-sectional area, fibre size, capillary-to-fibre ratio [26,28,36,40,42]. The studies analysing muscle remodelling and adaptation demonstrated that the exercise training interventions were adequate and sufficient to promote peripheral skeletal muscle changes in both age groups (Table 3). The phenotypical changes in the muscle were accompanied by widespread increase in the expression of ECMs at mRNA and protein level, as listed in Table 4. Among the 54 ECMs reported at the mRNA level, only glypican 4, chondroadherin and LAMβ3 were recoded to be downregulated in older participants. In addition, decorin was downregulated only in young participants when training duration was 12 weeks, otherwise upregulated in all the other conditions tested. At the protein level, 21 ECMs were significantly upregulated in total muscle tissue after exercise training [25,30,40]; however, dermatopontin, irisin, laminin subunit alpha 4 were significantly reduced. Seven studies provide data on direct association of ECM expression and muscle remodelling, which is represented in Table 4. Our findings demonstrate that exercise training induces muscle remodelling as well as ECM changes at transcription and translation levels.

The duration of exercise training was different among age groups. The exercise duration prescribed to younger participants tended to be less than 9 weeks, whereas for older participants training lasted more than 9 weeks. Figure 2 illustrates the overlap in ECMs transcriptomes categorised as collagens, glycoproteins and proteoglycans upregulated in young and old populations, when duration of intervention was less and more than 9 weeks. Similar transcriptomes per ECM category were reported in both age groups independent of training duration. The upregulation of collagens, glycoproteins and proteoglycans ECMs were observed across all types of exercise training interventions. Despite the tendency of prescribing AET and HIIT to young participants, and CT to older age groups, similar ECM transcriptomes were reported in both age groups. When comparing the effect of exercise training modalities, Robinson et al. [38] demonstrated that all types of training including CT, RET and HIIT induced similarly ECM transcriptomes in both age groups. However, COL14a1, lumican and elastin were the exceptions. The HIIT training upregulated these transcriptomes only in the older participants.

ECM-related molecules were also reported in some of the studies. As they were not part of the outcome search, they were not analysed in this systematic review, but a list is provided in Supplementary Table S2.
| First Author, Year of Publication | Country | Participant Group (n); Sex (n, %) | Age ± SD or ± SEM(*) | Study Design | Experimental Group Intervention Duration and Frequency, Dosage (h) | Attrition (Reasons) | Outcome Measures | Δ Muscle Remodelling Post-Training (within Group) | Δ Muscle Remodelling Post-Training (between Groups) |
|----------------------------------|---------|----------------------------------|----------------------|-------------|---------------------------------------------------------------|-------------------|----------------|-----------------------------------------------|-----------------------------------------------|
| Damas et al., 2018 [24]          | Brazil  | Exercise (9); Male (9, 100%)     | 26 ± 2               | Pre–post study | RET: it involved two exercises for lower body. 10 weeks (2x/week) Dosage = N/A | 1 participant (male) removed | N/A            | N/A                                                          | N/A                                                          |
| Deshmukh et al., 2021 [25]       | Denmark | Exercise (5); Male (5, 100%)     | 24 ± 1 *             | Sub-cohort of pre–post study | AET: participants performed indoor cycling exercise (intensity ranged from 75%–90% of maximal heart rate); 3 out of 4 sessions performed at home, 1 out of 4 at the laboratory. 12 weeks (4x/weeks) Dosage = 48 | None            | NA             | NA                                                         | NA                                                          |
| Fraçala et al., 2014 [43]        | USA     | Exercise (12); Male (7, 58.3%), Female (5, 41.7%) | 70.5 ± 6.9          | Pilot RCT | Supervised RET: 60–90 min (=70–85% of RM). 6 weeks (2x/week) Dosage = 12–18 | None            | Muscle strength/capacity | Exercise: ↑ 29.0% (p < 0.001) | Control: NS  |
|                                  |         | Control (11); Male (6, 54.5%), Female (5, 45.5%) | 69.6 ± 5.5          |             | Maintenance of normal physical activities. |                      | Leg extension strength (kg) | Exercise: ↓ 28.0% (p < 0.001) | Control: NS |
|                                  |         |                                   |                      |             |                                                   | Muscle quality (relative strength) | Body composition |                              |                                |
| Study                                      | Location         | Exercise Details                                                                 | LBM (kg) | Muscle architecture | Muscle cross-sectional area (CSA) (cm²) | Body composition | Muscle strength/capacity | VO₂,max (mL/kg*min) |
|--------------------------------------------|------------------|----------------------------------------------------------------------------------|----------|---------------------|----------------------------------------|------------------|--------------------------|---------------------|
| Hjorth et al., 2015 [26]                  | Norway           | Supervised CT: 2 intervals bicycle sessions and 2 whole body strength-training sessions per week. Each session lasted 1 h. 12 weeks (4x/week) Dosage = 48 | None     | Exercise: ↑ 0.2% (NS) Control: NS | Muscle architecture: Exercise: ↑ 8.3% (NS) Control: NS | Body composition: Fat mass (L) ↓ 8.2% (p < 0.001) | Muscle architecture: Thigh muscle area (cm²) ↑ 7.5% (p < 0.001) | Ventilatory changes: VO₂,max (mL/kg*min) ↑ 11.2% (p < 0.001) |
| Kanzleiter et al., 2014 [27]              | Norway/Germany   | Supervised CT: 2 intervals bicycle sessions and 2 whole body strength-training sessions per week. Each session lasted 1 h. 12 weeks (4x/week) Dosage = 48 | None     | N/A                 | N/A                                    | N/A              | N/A                      | N/A                 |
| Karlsen et al., 2020 [28]                 | Denmark          | Supervised heavy-load 13 weeks (3x/week) ² Five old and two young | N/A      | N/A                 | N/A                                    | N/A              | N/A                      | N/A                 |
RET: sessions involved 3 exercises for lower body and 2 optional for upper body.

Dosage = N/A

Participants did not complete the intervention.

Isometric knee extensor peak torque (Nm)

Young: ↑ 14.4 %
  \((p < 0.01)\)

Older: ↑ 14.3 %
  \((p < 0.001)\)

Isokinetic knee extensor peak torque (Nm)

Young: ↑ 11.9 %
  \((p < 0.05)\)

Older: ↑ 9 %
  \((p < 0.05)\)

Body composition

Thin lean mass (kg)

Young: ↑ 6.7 %
  \((p < 0.001)\)

Older: ↑ 6 %
  \((p < 0.001)\)

Muscle architecture

CSA VL (μm²)

Young: ↑ 11.9 %
  \((p < 0.001)\)

Older: ↑ 14.5 %
  \((p < 0.001)\)

CSA QF (μm²)

Young: ↑ 8.9 %
  \((p < 0.01)\)

Older: ↑ 10.8 %
  \((p < 0.001)\)

Young: ↓ 0.2 %

CSA type I fibres (μm²)

Young: ↑ 5.7 %
  \((NS)\)

Older: ↑ 5.7 %
  \((NS)\)
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| Study (ref) | Country | Exercise | Age Distribution | Muscles | Pre-post Study | RET | Muscle Strength/Capacity | Notes |
|-------------|---------|----------|------------------|---------|----------------|-----|--------------------------|-------|
| Kern et al., 2014 [29] | Italy/Austria | Exercise (16); Male (8, 50%), Female (8, 50%) | 73.1 ± 6.9 | Pre-post study | ES training at home: performed with a two-channel custom-built battery-powered stimulator; 3 × 10 min each session. | 9 weeks (2x/week for the first 3 weeks and 3x/week for the following 6 weeks) | Dosage = 12 | Type I fibres size (μm) | | Type I fibres percentage (%) | | Type I fibres size (μm) | | Type I fibres percentage (%) | | |
| Kim et al., 2015 [44] | Korea | Exercise (22); Female (22, 100%) | 74.5 ± 0.6 * | RCT | RET: it involved 2 supervised and 3 home-based sessions. Progressive intensity of the intervention. | 12 weeks (5x/week) Dosage = 60 | | Grip strength (kg) | | | Exercise: ↑ 27.0% (p < 0.001) | | | | | |

**Muscle Strength/Capacity**

- **CSA type II fibres (μm²)**
  - Young: ↑ 10.2% (NS)
  - Older: ↑ 25.8% (p < 0.001)
- **Type I fibres (%)**
  - Young: ↓ 2.3% (NS)
  - Older: ↑ 1.9% (NS)
- **All fibres size (μm)**
  - NS
- **Type I fibres size (μm)**
  - ↓ 3.6% (p < 0.001)
- **Type I fibres percentage (%)**
  - ↓ 7.2% (N.S)
- **Type IIa fibres size (μm)**
  - ↑ 2.2% (p < 0.001)
- **Type IIa fibres percentage (%)**
  - ↑ 8.9% (N.S)
- **Torque (Nm/kg)**
  - ↑ 6.0 ± 4.9 (p < 0.05)
- **Muscle architecture**
  - | None |
  - | N/A |

**Muscle strength/capacity**

- **Grip strength (kg)**
  - Exercise: ↑ 27.0% (p < 0.001)
- **Knee extensor strength 60°/s (N)**
  - Exercise: ↑ 42.1% (p < 0.001)

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1. Young: ↑ 10.2% (NS)
2. Older: ↑ 25.8% (p < 0.001)
3. Type I fibres: ↓ 2.3% (NS)
4. Type I fibres percentage: ↑ 1.9% (NS)
5. All fibres size (μm): NS
6. Type I fibres size (μm): ↓ 3.6% (p < 0.001)
7. Type I fibres percentage: ↓ 7.2% (N.S)
8. Type IIa fibres size (μm): ↑ 2.2% (p < 0.001)
9. Type IIa fibres percentage: ↑ 8.9% (N.S)
10. Torque (Nm/kg): ↑ 6.0 ± 4.9 (p < 0.05)

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**Notes**

- Ten participants did not complete the intervention.
| Study | Country | Exercise Duration | Gender | Sample Size | Intervention Details | Pre-post Study Duration | Dosage | Body Composition Changes |
|-------|---------|-------------------|--------|-------------|----------------------|------------------------|--------|-------------------------|
| Makhnovskii et al., 2020 [30] | Russia | Exercise (7); Male (7, 100%) | 22.5 ± 1.5 * | Pre-post study | AET: participants alternated continuous (intensity at 70% LT) and intermittent exercise ((3 min, 50% LT) + 2 min, 85% LT) x12) on different days. | 5 weeks (7x/week) Dosage = 35 | None | N/A |
| Nishida et al., 2010 [31] | Japan | Exercise (6); Male (6, 100%) | 19–32 | Pre-post study | Supervised AET: participants performed the session for 60 min using an upright cycle ergometer. | 12 weeks (5x/week) Dosage = 60 | None | Body composition (Fat percentage (%)) ↓ 2.2% (NS) |

| Exercise | Maintenance of normal physical activities and performance of one hour stretching once a week | Knee flexor strength (N) Exercise: ↓ 1.5% (NS) | Knee extensor strength 180°/s (N) Exercise: ↑ 33.7% (NS) | Knee flexor strength (N) Exercise: ↓ 19.4% (p < 0.001) |
|----------|--------------------------------------|----------------------------------------|----------------------------------------|----------------------------------------|
| Waist-hip ratio (WHR) | Exercise: ↓ 1.2% (NS) | Arm circumference (cm) Exercise: ↓ 5.1% (NS) | Thigh circumference (cm) Exercise: ↓ 1.3% (NS) | |
| Body composition | |

NS: Not significant.
| Study                                | Country | Design Details                                                                 | VO2max at LT (%) | Training intensity at the LT level                                                                 | Ventilatory changes |
|--------------------------------------|---------|---------------------------------------------------------------------------------|------------------|---------------------------------------------------------------------------------------------------|---------------------|
| Norheim et al., 2011 [32]            | Norway  | Exercise (13); Male (13, 100%); Sub-cohort of pre-post study                   | 48.9% (p < 0.05) | RET: it involved 1–3 sets of leg press, leg extension, leg curl, seated chest press, seated rowing, latissimus dorsi pull-down, biceps curl, and shoulder press. |                     |
|                                      |         | 26.8 (19–35)                                                                   |                  | 11 weeks (3x/week) Dosage = N/A                                                                   |                     |
|                                      |         |                                                                                  |                  | None                                                                                              |                     |
|                                      |         |                                                                                  |                  | N/A                                                                                               |                     |
|                                      |         |                                                                                  |                  | N/A                                                                                               |                     |
|                                      |         |                                                                                  |                  | N/A                                                                                               |                     |
| Norheim et al., 2014 [33]            | Norway  | Exercise (26); Male (26, 100%), Normal glucose group (13), Pre-diabetes group (13) |                  | Supervised CT: it involved 2 interval bicycle sessions and 2 whole body strength-training sessions per week. Each session lasted 1 h. |                     |
|                                      |         | 51.2 ± 6.6                                                                      |                  | 12 weeks (4x/week) Dosage = 48                                                                   |                     |
|                                      |         |                                                                                  |                  | None                                                                                              |                     |
|                                      |         |                                                                                  |                  | N/A                                                                                               |                     |
|                                      |         |                                                                                  |                  | N/A                                                                                               |                     |
|                                      |         |                                                                                  |                  | N/A                                                                                               |                     |
| Radom-Aizak et al., 2005 [35]        | Israel  | Exercise (6); Male (6, 100%); Pre–post study                                   |                  | AET: participants performed 45 min sessions (from the 3rd–12th week) on a cycle ergometer at 80% of the predetermined HRmax. |                     |
|                                      |         | 68.0 ± 2.7 *                                                                    |                  | 12 weeks (3x/week) Dosage = 27                                                                    |                     |
|                                      |         |                                                                                  |                  | None                                                                                              |                     |
|                                      |         |                                                                                  |                  | Anaerobic threshold (%) Up 21% (p = 0.008)                                                        | N/A                 |
|                                      |         |                                                                                  |                  | VO2max (L/min) Up 17.8% (p = 0.009)                                                               |                     |
| Study                          | Country | Exercise Type | Participants | Study Design | Intervention Details | Muscle Strength/Capacity | Body Composition | Body Composition | Ventilatory Changes | Ventilatory Changes | Absolute VO<sub>2max</sub> (mL/min) in Young | Absolute VO<sub>2max</sub> (mL/min) in Older |
|-------------------------------|---------|---------------|--------------|--------------|----------------------|-------------------------|---------------------|---------------------|---------------------|---------------------|---------------------------------------------|---------------------------------------------|
| Raue et al., 2012 [36]        | USA     | Pre–post study | Young (16); Male (8, 50%), Female (8, 50%); Older (12); Male (6, 50%), Female (6, 50%) | 24 ± 4 | RET: it involved 3 sets of 10 bilateral knee extensions (70–75% of 1 RM). 12 weeks (3x/week) Dosage = N/A | None | Leg extension strength (kg)↑ 5.7–41.3 kg | N/A | Thigh muscle CSA (cm<sup>2</sup>)↓ 1.2–10.4 cm<sup>2</sup> |
| Riedl et al., 2010 [37]       | Japan   | Pre–post study | Exercise (7); Male (7, 100%) | 64 ± 3 | Supervised AET: participants performed sessions of 60 min on a cycle ergometer. Training intensity at the LT level 6 weeks (5x/week) Dosage = 30 | None | Fat percentage (%)↓ 9.9% (p < 0.05) | N/A | VO<sub>2</sub> at LT (%)↑ 8.3% (p < 0.05) |
| Robinson et al., 2017 [38]    | USA     | Pre–post study | Young HIIT exercise (10); Male, Female | 25.4 ± 4.3 | HIIT: participants performed 3 sessions per week of cycling (4 × 4 min at >90% of VO<sub>2max</sub>) separated by 3 min of pedalling at no load) and 2 sessions per week of treadmill 4 weeks (5x/week) Dosage = 34.8 | None | VO<sub>2max</sub> (mL/kg BW/min)↑ (p < 0.001) | ↓ (p < 0.05) | FFM (kg)↑ (NS) | Absolute VO<sub>2max</sub> (mL/min) in young: ↑ following HIIT (p < 0.0001) > ↑ following RET (p < 0.048) and CT (p = 0.0001) |
|                              |         |               | Older HIIT exercise (8); Male, Female | 70.7 ± 4.6 | Body composition | Young HIIT Ventilatory changes | Ventilatory changes | Ventilatory Changes | Ventilatory Changes | Ventilatory Changes | Absolute VO<sub>2max</sub> (mL/min) in Older | Absolute VO<sub>2max</sub> (mL/min) in Older |
|                              |         |               |                      | 23.7 ± 3.5 | 4 Five young and three older participants did not complete the intervention. There was no information on number of males and females completing the study | None | VO<sub>2max</sub> (mL/kg BW/min) | ↓ (p < 0.05) | FFM (kg)↑ (NS) | Absolute VO<sub>2max</sub> (mL/min) in Older | Absolute VO<sub>2max</sub> (mL/min) in Older |

Note: HIIT = High-Intensity Interval Training; VO<sub>2max</sub> = Maximum Oxygen Uptake; CT = Continuous Training; FFM = Fat-Free Mass; RM = Repetition Maximum; LT = Lactic Threshold; CSA = Cross-Sectional Area.
Young RET (10); Male, Female

walking (45 min at 70% of VO_{2max}).

RET: participants performed 2 sessions of lower and upper body exercises (4 sets of 8–12 repetitions), 2 days each per week.

Older RET (8); Female

70.3 ± 3.9

RET: 12 weeks (5x/week)
Dosage = N/A

Young Combined exercise (8); Male, Female

26.3 ± 2.7

CT after a 3 months SED: Following SED, participants underwent metabolic studies and performed CT of 5 days per week cycling (30 min at 70% VO_{2max}) and 4 days per week weightlifting with fewer repetitions than RET.

Older Combined exercise (7); Male, Female

68.6 ± 3.4

Combined: 12 weeks (9x/week) Dosage > 30

Maximal leg strength (1 RM) leg press (AU/kg Leg FFM)

older: ↑ following HIIT (p < 0.0091) and CT (p = 0.0096) > ↑ following RET (ns)

Older HIIT Ventilatory changes

VO_{2max} (mL/kg BW/min) ↑ (p < 0.01)

~28% following HIIT (p < 0.0001) > ↑

Body composition FFM (kg) ↑ (p < 0.05)

~17% following CT (p < 0.0001) > RET (ns)

Muscle strength/capacity

Maximal leg strength (1 RM) leg press (AU/kg Leg FFM)

Relative VO_{2max} (mL/min) in older: ↑ ~21% following CT (p < 0.0001) > ↑ ~17% following HIIT (p < 0.0001) > RET (ns)

Young RET Ventilatory changes

VO_{2max} (mL/kg BW/min) ↑ (NS)

Body composition


FFM (kg) $\uparrow$ 4% ($p < 0.0001$)  
Leg strength: $\uparrow$ 
Following RET and CT > HIIT (NS)

Muscle strength/Maximal leg strength 
(1 RM) leg press 
(AU/kg Leg FFM) $\uparrow$ ($p < 0.05$) $\uparrow$

Older RET 
Ventilatory changes 
$\uparrow$ (NS) $\uparrow$

Body composition 
FFM (kg) $\uparrow$ ($p < 0.01$) $\uparrow$

Muscle strength/capacity 
Maximal leg strength (1 RM) leg press (AU/kg Leg FFM) $\uparrow$ ($p < 0.05$) $\uparrow$

Young CT 
Ventilatory changes 
$\uparrow$ ($p < 0.001$) $\uparrow$

Body composition 
FFM (kg) $\uparrow$ ($p < 0.05$) $\uparrow$

Muscle strength/capacity $\uparrow$ ($p < 0.05$) $\uparrow$
| Study                        | Country          | Sample Size | Mean Age (±SD) | Study Type | Intervention | Duration | Other Details |
|------------------------------|------------------|-------------|----------------|------------|--------------|----------|---------------|
| Timmons et al., 2010 [39]    | Denmark, UK, USA | Exercise (24); Male (24, 100%) | 23 | Pre-post study | Supervised AET: participants performed 45 min cycling sessions. Training intensity customized to 70% of the pretraining VO2max. | 6 weeks (4x/week) | Dosage = 18 | None | VO2 max (L/min) ↑ 14% (N/A) | Ventilatory changes |
| Valdivierzo et al., 2017 [40]| Switzerland      | Exercise (61); Male (61, 100%), A/A alleles (12), A/T alleles (38), T/T alleles (11) | 29.5 ± 9.3 | Pre-post study | AET: participants performed 30 min sessions on a cycle ergometer at a heart rate | 6 weeks (5x/week) | Dosage = 15 | None | Muscle fibre area (μm²) ↑ 8.3% (NS) | Muscle architecture |
|                              |                  |             |                |            |              |          |               |                | Biopsy myofi-brils (%) ↓ 4.0% (p < 0.05) |                  |
corresponding to 65% of \( P_{\text{max}} \). Training intensity maintained at \( \approx 90\% \) of maximal heart rate

| A/A genotype | Capillary-to-fibre ratio (ALL) | \( \uparrow \) 12.1\% (\( p < 0.05 \)) |
| A/T genotype | \( \uparrow \) 25.0\% (NS) A/A vs. T/T (\( p < 0.05 \)) |
| T/T genotype | \( \downarrow \) 5.5\% (\( p < 0.05 \)) |

**Capillary density (mm\(^{-2}\))**

- A/A genotype: \( \uparrow \) 25.0\% (NS) A/A vs. T/T (\( p < 0.05 \))
- A/T genotype: \( \uparrow \) 12.6\% (\( p < 0.05 \)) A allele carriers vs. T/T (\( p < 0.05 \))
- T/T genotype: \( \downarrow \) 12.5\% (NS)

**Ventilatory changes**

- VO\(_{2}\max\) (mL/kg * min): \( \uparrow \) 8.5\% (\( p < 0.05 \))
- P\(_{\text{max}}\) (ergospirometry) (W): \( \uparrow \) 12.7\% (\( p < 0.05 \))

**Walton et al., 2019 [41]**

| USA | Exercise (20); Male (4, 25\%), Female (16, 75\%) | 49.8 \pm 2.3 \* | Pre–post study | 12 weeks (3x/week) | Dosage = 27 | None | N/A | N/A | N/A |
| Study (year)          | Country     | Design | Intervention                                                                 | Duration        | Dropout Reason(s) | Analysis Reason(s) | Other Notes |
|----------------------|-------------|--------|-------------------------------------------------------------------------------|-----------------|-------------------|---------------------|-------------|
| Alghadir et al., 2016 [42] | Saudi Arabia | RCT | Supervised exercise training (AET): 50 min in intensity defined by heart rate (THR max; 60–70%) | 12 weeks (3x/week) Dosage = 30 | None | N/A | N/A | N/A |
| Olstad et al., 2020 [34] | Norway | Pre-post study | Supervised heavy-load resistance exercise training (RET): it involved all major muscle groups. Gradual progression on the training loads was applied. Each session lasted ≈60 min. | 13 weeks (3x/week) Dosage = 39 | 5 One participant did not complete the study | | Muscle strength/ capacity: Healthy: ↑ 32 ± 16% | N/A |

The last two entries are from clinical populations. Data are presented as mean ± SD or ± SEM (*); number (n); hours (h); randomised controlled trial (RCT); resistance exercise training (RET); combined training (CT); aerobic exercise training (AET); high intensity interval training (HIIT); sedentary period (SED); electrical stimulation (ES); decrease (↓); not significant (NS); not available (N/A); repetition maximum (RM); lean body mass (LBM); cross sectional area (CSA); increase (↑); maximum training heart rate (max THR); maximal aerobic capacity (VO2max); maximal accumulated oxygen deficit (MAOD); voluntary repetition maximum (VRM); submaximal exercise respiratory exchange ratio (Submax RER); lactate threshold (LT); lactate threshold at 4 mmol/l (LT4); body weight (BW); fat free mass (FFM); absolute units (AU); intravenous failure (IV failure); Type 2 Diabetes (T2D); vastus lateralis (VL); quadriceps femoris (QF). Attrition: 1 A male participant was removed from analysis because of poor sample quality. 2 Three subjects were removed from the analysis due to technical issues. 3 Ten subjects (4 in the exercise group, 6 in the control group) could not complete the study. Reasons: difficulties of time commitment and loss of motivation. 4 Five young adults dropped out from the study. Reasons: (a) time constraints (n = 2), (b) medical unrelated to the study (n = 2), (c) and IV failure (n = 1). Three older adults dropped out. Reasons: (a) medical unrelated to the study (n = 1), (b) did not want to perform follow up testing (n = 1), and (c) completed sedentary-only portion (n = 1). 5 A compression fracture in the spine was attained during an accident in the squat exercise. Recovery of the patients was succeeded after 3 months of reduced loading.
| First Author, Year of Publication | Outcome Measure         | Δ ECM Outcome Post Training within Group | Association between ECM and Muscle Remodelling Outcome within the Study |
|----------------------------------|-------------------------|----------------------------------------|---------------------------------------------------------------------|
| **mRNA expression**              |                         |                                        |                                                                     |
| Collagens                        |                         |                                        |                                                                     |
| COL3A1                           | ↑ 146% (p < 0.05)       |                                        |                                                                     |
| COL4A1                           | ↑ 112% (p < 0.05)       |                                        |                                                                     |
| COL5A2                           | ↑ 95% (p < 0.05)        |                                        |                                                                     |
| **Glycoproteins**                |                         |                                        |                                                                     |
| CTHRC1                           | ↑ 105% (p < 0.05)       |                                        |                                                                     |
| LAMB1                            | ↑ 79% (p < 0.05)        |                                        |                                                                     |
| THBS4                            | ↑ 144% (p < 0.05)       |                                        |                                                                     |
| PXDN                             | ↑ 81% (p < 0.05)        |                                        |                                                                     |
| **Protein expression**           |                         |                                        |                                                                     |
| **Glycoproteins**                |                         |                                        |                                                                     |
| Agrin                            |                      |                                        |                                                                     |
| Slow fibres: ↑ 147% (NS)         |                      |                                        |                                                                     |
| Fast fibres: ↑ 460% (p < 0.001)  |                      |                                        |                                                                     |
| Whole muscle: ↑ 130% (NS)        |                      |                                        |                                                                     |
| Thrombospondin 4                 |                      |                                        |                                                                     |
| Slow fibres: ↑ 240% (NS)         |                      |                                        |                                                                     |
| Fast fibres: ↑ 360% (p = 0.015)  |                      |                                        |                                                                     |
| Whole muscle: N/A                |                      |                                        |                                                                     |
| Peroxidasin                      |                      |                                        |                                                                     |
| Slow fibres: ↑ 320% (p = 0.0017) |                      |                                        |                                                                     |
| Fast fibres: ↑ 300% (NS)         |                      |                                        |                                                                     |
| Whole muscle: ↑ 360% (p = 0.0017) |                      |                                        |                                                                     |
| Dermatopontin                    |                      |                                        |                                                                     |
| Slow fibres: ↓ 70% (NS)          |                      |                                        |                                                                     |
| Fast fibres: ↓ 85% (NS)          |                      |                                        |                                                                     |
| Whole muscle: ↓ 16% (p = 0.0046) |                      |                                        |                                                                     |
| **Deshmukh et al., 2021 [25]**   |                         |                                        |                                                                     |
| Fibrillin-1                      |                      |                                        |                                                                     |
| Slow fibres: ↓ 100% (NS)         |                      |                                        |                                                                     |
| Fast fibres: ↓ 82% (NS)          |                      |                                        |                                                                     |
| Whole muscle: ↑ 280% (p = 0.0063)|                      |                                        |                                                                     |
| Irisin precursor, fibronectin type III |              |                                        |                                                                     |
| Slow fibres: ↑ 108% (NS)         |                      |                                        |                                                                     |
| Fast fibres: ↓ 90% (NS)          |                      |                                        |                                                                     |
| Whole muscle: ↓ 70% (p = 0.025)  |                      |                                        |                                                                     |
| IGFN1 (Immunoglobulin-like and fibronectin type III domain containing) | | | |
| Slow fibres: ↑ 790% (p = 0.0028) |                      |                                        |                                                                     |
| Fast fibres: ↑ 560% (p = 0.011)  |                      |                                        |                                                                     |
| Whole muscle: ↑ 225% (NS)        |                      |                                        |                                                                     |
| Laminin subunit alpha-1          |                      |                                        |                                                                     |
| Slow fibres: N/A                 |                      |                                        |                                                                     |
| Fast fibres: N/A                 |                      |                                        |                                                                     |
| Whole muscle: ↑ 370% (p = 0.0415)|                      |                                        |                                                                     |
| Laminin subunit alpha 4          |                      |                                        |                                                                     |
| Slow fibres: ↑ 160% (p = 0.0119) |                      |                                        |                                                                     |
| Fast fibres: ↑ 143% (NS)         |                      |                                        |                                                                     |
Laminin subunit alpha 5  
Whole muscle: ↓ 93% (NS)  
Slow fibres: ↑ 119% (NS)  
Fast fibres: ↑ 99% (NS)  
Whole muscle: ↑ 60% (p = 0.0431)

Microfibrillar-associated protein 4  
Slow fibres: ↓ 90% (NS)  
Fast fibres: ↓ 39% (p = 0.043)  
Whole muscle: ↑ 137% (NS)

Microfibrillar-associated protein 5  
Slow fibres: ↑ 440% (p = 0.0197)  
Fast fibres: ↓ 62% (NS)  
Whole muscle: ↑ 162% (NS)

Picachurin (EGFLAM)  
Slow fibres: ↓ 90% (NS)  
Fast fibres: ↓ 39% (p = 0.043)  
Whole muscle: ↑ 330% (p = 0.0008)

Circulating markers (serum)  
P3NP vs. LBM (r = 0.422, p = 0.045)

C-terminal agrin fragment (CAF)  
Exercise: ↑ 10.4% (NS)  
Control: ↑ 0.3% (NS)  
CAF vs. VL CSA (r = 0.542, p = 0.008)

N-terminal peptide of procollagen type III (P3NP)  
Exercise: ↑ 7.9% (NS)  
Control: ↑ 1.9% (NS)  
CAF vs. muscle strength/quality (NS)

mRNA expression  
Collagens  
COL1A1 ↑ 140% (p < 0.001)  
COL1A2 ↑ 80% (p < 0.001)  
COL3A1 ↑ 140% (p < 0.001)  
COL4A1 ↑ 140% (p < 0.001)  
COL4A2 ↑ 120% (p < 0.001)  
COL5A1 ↑ 50% (p < 0.001)  
COL5A2 ↑ 60% (p < 0.001)  
COL6A6 ↑ 100% (p < 0.001)  
COL14A1 ↑ 80% (p < 0.001)  
COL15A1 ↑ 50% (p < 0.001)  
COL18A1 ↑ 50% (p < 0.001)  

Hjorth et al., 2015 [26]  
N/A

Proteoglycans  
ASPN ↑ 80% (p < 0.001)  
BGN ↑ 110% (p < 0.001)  
HSPG2 ↑ 50% (p < 0.001)  
OGN ↑ 110% (p < 0.001)  
OMD ↑ 80% (p < 0.001)  
ECM2 ↑ 60% (p < 0.001)  
LUM ↑ 50% (p < 0.001)  

GPC4 ↓ N/A (p < 0.001)
| Glycoproteins | CHAD | ↓ 52% \( (p < 0.001) \) |
|--------------|------|--------------------------|
| CSPG4        | ↑ 50% \( (p < 0.001) \) |

| Proteoglycans | AGRN | ↑ 60% \( (p < 0.001) \) |
|--------------|------|--------------------------|
| LAMA4        | ↑ 70% \( (p < 0.001) \) |
| LAMB1        | ↑ 70% \( (p < 0.001) \) |
| LAMB3        | ↓ 56% \( (p < 0.001) \) |
| LAMC3        | ↑ 70% \( (p < 0.001) \) |
| THBS1        | ↑ 60% \( (p < 0.001) \) |
| THBS4        | ↑ 220% \( (p < 0.001) \) |
| NID1         | ↑ 60% \( (p < 0.001) \) |
| NID2         | ↑ 70% \( (p < 0.001) \) |
| PXDN         | ↑ 200% \( (p < 0.001) \) |
| ELN          | ↑ 50% \( (p < 0.001) \) |
| EMILIN3      | ↑ 60% \( (p < 0.001) \) |
| SPARC        | ↑ 80% \( (p < 0.001) \) |
| CTHRC1       | ↑ 70% \( (p < 0.001) \) |

**mRNA expression**

**Proteoglycans**

| Kanzleiter et al., 2014 [27] | DCN | Healthy: ↑ \( (p < 0.05) \) |
|------------------------------|-----|--------------------------|
|                              |     | Pre-diabetes: ↓ \( (NS) \) |

**Collagens**

| Karlsen et al., 2020 [28] | COL1A1 | Young: (NS) |
|----------------------------|---------|-------------|
|                            |         | Older: ↑ \( (values not reported) \) \( (p < 0.05) \) |

**Collagens**

| Kern et al., 2014 [29] | COL1 | ↑ \( (p < 0.005) \) |
|------------------------|------|---------------------|
|                        | COL3 | ↑ \( (p < 0.005) \) |
|                        | COL6 | ↑ \( (p < 0.005) \) |

**Circulating markers (serum)**

| Kim et al., 2015 [44] | Irisin | Exercise: ↑ 22.5% \( (p < 0.05) \) | Irisin vs. grip strength \( (r = 0.526, p = 0.002) \) |
|                       |        | Control: NS            | Irisin vs. leg strength \( (r = 0.414, p = 0.003) \) |

**mRNA expression**

**Collagens**

| Makhnovskii et al., 2020 [30] | COL1A1 | ↑ 1060% \( (p < 0.05) \) |
|--------------------------------|--------|--------------------------|
|                               | COL1A2 | ↑ 440% \( (p < 0.05) \) |
|                               | COL3A1 | ↑ 656% \( (p < 0.05) \) |
|                               | COL4A2 | ↑ 439% \( (p < 0.05) \) |
|                               | COL6A1 | ↑ 196% \( (p < 0.05) \) |
|                               | COL6A2 | ↑ 232% \( (p < 0.05) \) |
|                               | COL6A3 | ↑ 273% \( (p < 0.05) \) |
|                               | COL14A1| ↑ 608% \( (p < 0.05) \) |
|                               | COL15A1| ↑ 271% \( (p < 0.05) \) |

**Proteoglycans**

| ASPN | ↑ 359% \( (p < 0.05) \) |
| BGN  | ↑ 435% \( (p < 0.05) \) |

\( \Delta \) Decorin expression vs. \( \Delta \)Leg press strength \( (kg) \) \( (r = 0.56, p = 0.047) \)

\( r \) correlation coefficient, \( p \) significance level
| Glycoproteins       |   |   |
|--------------------|---|---|
| HSPG2              | ↑ 204% (p < 0.05) |
| OGN                | ↑ 421% (p < 0.05) |
| LUM                | ↑ 447% (p < 0.05) |
| DCN                | ↑ (NS) |
| PRELP              | ↑ (NS) |

| Protein expression |   |   |
|--------------------|---|---|
| Glycoproteins      |   |   |
| LAMC1              | ↑ 175% (p < 0.05) |
| Gypnotin           | ↑ 118% (p < 0.05) |

**mRNA expression (using SAGE)**

| Collagens          |   |   |
|--------------------|---|---|
| Nishida et al., 2010 [31] |   |   |
| COL1A2             | ↑ 1200% (p < 0.05) |

| Collagens          |   |   |
|--------------------|---|---|
| Norheim et al., 2011 [32] |   |   |
| COL1A1             |   |   |
| M. VL: ↑ 520 (p < 0.05) |
| M. TRAP: ↑ 4340% (p < 0.05) |

| Proteoglycans      |   |   |
|--------------------|---|---|
| LUM                |   |   |
| M. VL: ↑ 250 (p < 0.05) |
| M. TRAP: ↑ 430 (p < 0.05) |

| Glycoproteins      |   |   |
|--------------------|---|---|
| FN1                |   |   |
| M. VL: ↑ 180 (p < 0.05) |
| M. TRAP: ↑ 250 (p < 0.05) |

| FNDC5 (Irisin)     |   |   |
|--------------------|---|---|
| Norheim et al., 2014 [33] |   |   |
| Healthy: ↑ 40% (p < 0.05) |
| Pre-diabetes: ↑ 100% (p < 0.01) |

| Collagens          |   |   |
|--------------------|---|---|
| Radom-Aizak et al., 2005 [35] |   |   |
| COL3A1             | ↑ 111% (p = 0.0178) |

| Collagens          |   |   |
|--------------------|---|---|
| Raue et al., 2012 [36] |   |   |
| mRNA expression    |   |   |
| Pooled mRNA expression of COL4α2 vs. 1-RM (r = -0.418) |   |   |
### Collagens

| Protein   | Young: | Older: | Expression Change | Pearson Correlation |
|-----------|--------|--------|-------------------|---------------------|
| COL1A1    | N/A    | ↑ 220–300% | Pooled mRNA expression of COL4α3 vs. 1-RM (r = −0.344–(−0.486)) |
| COL1A2    | N/A    | ↑ 150–200% | Pooled mRNA expression of COL4α4 vs. 1-RM (r = −0.540–(0.623)) |
| COL3A1    | N/A    | ↑ 260–210% | Pooled mRNA expression of COL4α3 vs. 1-RM (r = −0.547) Pooled mRNA expression of COLQ vs. 1-RM (r = 0.652) |
| COL4A1    | ↑ 190–200% | N/A | Pooled mRNA expression of COL28α1 vs. CSA (r = −0.345–(−0.462)) |
| COL4A2    | ↑ 170% | ↑ 220% | Pooled mRNA expression of COL4α3 vs. CSA (r = −0.405) |
| COL5A1    | N/A    | ↑ 290% | Pooled mRNA expression of COL4α4 vs. CSA (r = −0.461–(0.486)) |
| COL5A2    | N/A    | ↑ 180% | Pooled mRNA expression of COL4α5 vs. CSA (r = −0.406) |
| COL5A3    | N/A    | ↑ 170–180% | Pooled mRNA expression of COLQ vs. CSA (r = 0.540) |
| COL15A1   | N/A    | ↑ 150% | Pooled mRNA expression of COL27α1 vs. CSA (r = −0.348) |

### Proteoglycans

| Protein | Young: | Older: | Expression Change | Pearson Correlation |
|---------|--------|--------|-------------------|---------------------|
| ASPN    | N/A    | ↑ 150% | 200%              |                     |

### Glycoproteins

| Protein | Young: | Older: | Expression Change | Pearson Correlation |
|---------|--------|--------|-------------------|---------------------|
| LAMA4   | N/A    | ↑ 174% |                   |                     |
| LAMB1   | N/A    | ↑ 165% |                   |                     |
| NID1    | N/A    | ↑ 160–200% |                   |                     |
| NID2    | N/A    | ↑ 194% |                   |                     |
| SPARC   | N/A    | ↑ 150–160% |                   |                     |
| THBS4   | N/A    | ↑ 168% |                   |                     |
| CTHRC1  | N/A    | ↑ 200% |                   |                     |
| Number of tags per 100,000 SAGE tags |
|-------------------------------------|
| **Collagens**                        |
| Riedl et al., 2010 [37]              |
| COL3A1                              | ↑ 14 |
| COL4A1                              | ↑ 15 |
| **Glycoproteins**                    |
| SPARC                               | ↑ 20 |

| mRNA expression                      |
|-------------------------------------|
| **Collagens**                        |
| COL4A1                              |
| HIIT young: ↑ 217% (p ≤ 0.05)         |
| HIIT older: ↑ 361% (p ≤ 0.05)         |
| RET young: ↑ 267% (p ≤ 0.05)          |
| RET older: ↑ 236% (p ≤ 0.05)          |
| CT young: ↑ 185% (p ≤ 0.05)           |
| CT older: ↑ 197% (p ≤ 0.05)           |
| COL4A2                              |
| HIIT young: ↑ 188% (p ≤ 0.05)         |
| HIIT older: ↑ 303% (p ≤ 0.05)         |
| RET young: ↑ 219% (p ≤ 0.05)          |
| RET older: ↑ 202% (p ≤ 0.05)          |
| CT young: ↑ 172% (p ≤ 0.05)           |
| CT older: ↑ 182% (p ≤ 0.05)           |
| COL14A1                             |
| HIIT young: (NS)                     |
| HIIT older: ↑ 165% (p ≤ 0.05)         |
| RET young: (NS)                      |
| RET older: (NS)                      |

| **Proteoglycans**                    |
| ASPN                                |
| HIIT young: ↑ 174% (p ≤ 0.05)        |
| HIIT older: ↑ 232% (p ≤ 0.05)        |
| RET young: ↑ 187% (p ≤ 0.05)         |
| RET older: ↑ 243% (p ≤ 0.05)         |
| CT young: ↑ 158% (p ≤ 0.05)          |
| CT older: ↑ 177% (p ≤ 0.05)          |

| Robinson et al., 2017 [38]          |
| LUM                                 |
| HIIT young: (NS)                     |
| HIIT older: ↑ 156% (p ≤ 0.05)        |
| RET young: (NS)                      |
| RET older: (NS)                      |
| CT young: (NS)                       |
| CT older: (NS)                       |

| **ECM2**                             |
| HIIT young: ↑ 175% (p ≤ 0.05)         |
| HIIT older: ↑ 180% (p ≤ 0.05)         |
| RET young: ↑ 161% (p ≤ 0.05)          |
| RET older: ↑ 173% (p ≤ 0.05)          |
| CT young: (NS)                        |
| CT older: (NS)                        |

| **Glycoproteins**                    |
| LAMB1                                |
| HIIT young: ↑ 171% (p ≤ 0.05)         |
| HIIT older: ↑ 170% (p ≤ 0.05)         |
| RET young: ↑ 154% (p ≤ 0.05)          |
| RET older: (NS)                       |
| CT young: (NS)                        |
| CT older: ↑ 160% (p ≤ 0.05)           |

| NID1                                 |
| HIIT young: ↑ 160% (p ≤ 0.05)         |
| HIIT older: ↑ 205% (p ≤ 0.05)         |
RET young: ↑ 152% (p ≤ 0.05)
RET older: ↑ 157% (p ≤ 0.05)
CT young: ↑ 155% (p ≤ 0.05)
CT older: ↑ 156% (p ≤ 0.05)

PXDN
HIIT young: ↑ 196% (p ≤ 0.05)
HIIT older: ↑ 266% (p ≤ 0.05)
RET young: ↑ 234% (p ≤ 0.05)
RET older: ↑ 209% (p ≤ 0.05)
CT young: ↑ 162% (p ≤ 0.05)
CT older: ↑ 166% (p ≤ 0.05)

SPARC
HIIT young: ↑ 188% (p ≤ 0.05)
HIIT older: ↑ 224% (p ≤ 0.05)
RET young: ↑ 170% (p ≤ 0.05)
RET older: ↑ 179% (p ≤ 0.05)
CT young: (NS)
CT older: ↑ 165% (p ≤ 0.05)

ELN
HIIT young: (NS)
HIIT older: ↑ 181% (p ≤ 0.05)
RET young: (NS)
RET older: (NS)
CT young: (NS)
CT older: (NS)

POSTN
HIIT young: (NS)
HIIT older: ↑ 167% (p ≤ 0.05)
RET young: (NS)
RET older: (NS)
CT young: (NS)
CT older: (NS)

mRNA expression

Collagens

| Name      | Expression  |
|-----------|-------------|
| COL1A1    | ↑ 370–510%  |
| COL1A2    | ↑ 90–550%   |
| COL3A1    | ↑ 80–540%   |
| COL4A1    | ↑ 350–430%  |
| COL4A2    | ↑ 280–350%  |
| COL5A1    | ↑ 240–270%  |
| COL5A2    | ↑ 250–290%  |
| COL5A3    | ↑ 50%       |
| COL6A1    | ↑ 70%       |
| COL6A2    | ↑ 210%      |
| COL6A3    | ↑ 230%      |
| COL8A1    | ↑ 260%      |
| COL12A1   | ↑ 50%       |
| COL14A1   | ↑ 250%      |
| COL15A1   | ↑ 80%       |
| COL18A1   | ↑ 60%       |
| PLOD2     | ↑ 60%       |

Proteoglycans

| Name      | Expression  |
|-----------|-------------|
| ASPN      | ↑ 220–290%  |
| BGN       | ↑ 250–560%  |
| CSPG2     | ↑ 170–590%  |
| HSPG2     | ↑ 90%       |
| LUM       | ↑ 270%      |

Timmons et al., 2010 [39]

N/A
OGN  \(\uparrow 420–500\%\)  

**Glycoproteins**

- AGRN  \(\uparrow 60–80\%\)
- LAMA4  \(\uparrow 240\%\)
- LAMB1  \(\uparrow 250–270\%\)
- LAMC1  \(\uparrow 50\%\)
- SPARC  \(\uparrow 50–250\%\)
- NID1  \(\uparrow 80\%\)
- NID2  \(\uparrow 290\%\)
- FBN1  \(\uparrow 50–730\%\)
- FN1  \(\uparrow 60–90\%\)
- TNC  \(\uparrow 430–530\%\)
- THBS4  \(\uparrow 280\%\)
- POSTN  \(\uparrow 390\%\)
- PXDN  \(\uparrow 220–250\%\)
- FNDC1  \(\uparrow 300\%\)
- CTHRC1  \(\uparrow 340\%\)

Valdivierzo et al., 2017 [40]

**Protein expression**

| Glycoproteins | Valdivierzo et al., 2017 [40] |
|---------------|-------------------------------|
| Tenascin C    |                                |
| A/A alleles:  | \(\uparrow 138\% \) \(p < 0.05\) | Capillary/fibre \(\uparrow\) |
| A/T alleles:  | \(\uparrow 77\% \) \(p < 0.05\)  | Capillary/fibre \(\uparrow\) |
| T/T alleles:  | \(=\)                       | Capillary/fibre \(15\%\) |

Walton et al., 2019 [41]

**mRNA expression**

| Glycoproteins | Walton et al., 2019 [41] |
|---------------|--------------------------|
| COL5A1        | \(\uparrow 53.6\% \) \(p = 0.013\) | SPARC expression \(r = 0.63\) \(p = 0.007\) |
| COL6A1        | \(\uparrow 29.5\% \) \(p = 0.009\)  | M2 macrophages/fibre vs. |

Alghadir et al., 2016 [42]

**Circulating markers (serum)**

| Glycoproteins | Alghadir et al., 2016 [42] |
|---------------|----------------------------|
| Cellular Fibronectin (or cFN) | Exercise: \(\downarrow 53\% \) \(p < 0.001\) |
|                | Control: \(\downarrow 2.1\% \) \(p < 0.001\) |

Olstad et al., 2020 [34]

**mRNA expression**

| Glycoproteins | Olstad et al., 2020 [34] |
|---------------|--------------------------|
| DCN           | Healthy: N/A              |
|               | Osteoporotic: \(\uparrow 129.4\%\) | N/A                      |

**Proteoglycans**

| Glycoproteins | Olstad et al., 2020 [34] |
|---------------|--------------------------|
| SPARC         | Healthy: N/A              |
|               | Osteoporotic: \(\uparrow 141.6\%\) |
The last two entries are from clinical populations. Data are presented as mean ± SD (or SEM *); lean body mass (LBM); cross sectional area (CSA); increase (↑); decrease (↓); not significant (NS); not available (N/A); change (Δ); serial analysis of gene expression tags (SAGE tags); resistance exercise training (RET); combined training (CT); high intensity interval training (HIIT); vastus lateralis muscle (MVL); trapezius muscle (MTRAP).

### Figure 2.
Venn diagrams of the upregulated collagens, proteoglycans and glycoproteins ECMs transcriptomes in healthy young and old participants when exercise training lasted less than or more than 9 weeks.

3.4. ECM Adaptation Associated with Muscle Structure and Stability

ECMs play a crucial role in muscle structure. They stabilise muscle cells by modifying the mechanical properties of the tissue, decreasing its stress and making it more load resistant. The failure of ECMs to maintain this structure results in increased susceptibility to mechanical stress and muscular fibre necrosis. Collagen fibrils provide mechanical stability to the skeletal muscle and regulate cell adhesion and differentiation. They confer tensile strength, rigidity, and compliance to the muscle [11,45]. Among the collagen superfamily, collagen I and III are present in the form of fibrils and they account for the 75% of the total skeletal muscle collagen. Exercise training promoted a widespread increase in mRNA expression of various types of collagen including COL1, COL3, COL4, COL5, COL6, COL8, COL12, COL14, COL15, and COL18 and PLOD2 in both age groups [29,30,37,39]. The increase in collagens is also shown at protein level [30], demonstrating an increase in posttranscriptional and translation events. The studies comparing younger to older participants [36,38] demonstrated a higher fold change in ECMs from older participants, which was dependent on the type of exercise modality. Robinson et al. found that older participants present greater induction of the transcriptomes for collagen IV,
collagen XIV, lumican, elastin and periostin after HIIT training, but not after RT and CT [38], whereas Raue et al. demonstrate that RT induces a greater fold change of collagens, proteoglycans and glycoproteins in older participants compared to young [36].

The collagen types XV and XVIII have structural features of both collagens and proteoglycans [46]. These collagens are known to be associated with the stability of microvessels to muscle cells [47] and they were transcriptionally upregulated mainly in older subjects after CT or RET [26,36] and in young after AET [30,39].

Type IV collagen is the major constituent of the basement membrane supporting the ECM niche for satellite cells. Collagen IV forms a complex network tethering other ECM proteins, including laminins and proteoglycans, as well as growth factors and cellular receptors, as reviewed elsewhere [48]. COL4 mRNA expression was increased after all types of exercise training and in subjects of all ages at mRNA and protein level [24,26,30,36–38], including after shorter durations of AET [37]. Interestingly, HIIT induced a more than 60% increase in COL4 in older participants compared to young [38].

Among the glycoproteins, the laminin subunits were significantly increased across all the population tested at the level of mRNA [25,26,30,36,38,39] and protein [24]. Laminins are heterodimers constituted by association of three different gene products, the α, β and γ chains. LAMA4, LAMB1, LAMC1 and LAMC3 transcriptomes were upregulated after exercise, but LAMβ3 chain was decreased in older subjects after CT [26]. At the basement membrane, laminin serves as a ligand for the sarcolemma receptors of the dystrophin-associated glycoprotein complex and the α7β1 integrin. In addition to its central role in the architecture and stability of the basement membrane, laminins control and trigger cellular functions by interacting with cell surface components and trapping growth factors [49]. Nidogens also contribute to the structural support of the muscle by promoting the interactions between laminin and collagens [48]. All types of exercise training significantly induced upregulation in the mRNA expression of nidogen 1 and 2, irrespective of participants’ age [26,36,38,39].

Perlecán (HSPG2) is a pericellular proteoglycan found at the basement membrane and it was reportedly increased in two studies investigating young participants after AET [30,39] and in one study in older adults after CT [26]. Proteoglycans interact with elastic fibres providing tissue extensibility and resilience [50]. At transcriptional level, CT and HIIT increased elastin and elasticity-associated emilin-3 in older participants [26,38].

### 3.5. ECMs Associated with Myogenic Regeneration and Repair

A similar number of glycoproteins were identified to be upregulated in both age groups after exercise training. However, fibronectin, tenasin C and fibrillin were only reported in the young group [33,39,40]. The adhesive properties of these glycoproteins are crucial to satellite cell function promoting muscle repair and regeneration. It is unknown why the retrieved studies did not report these glycoproteins in the muscle of older participants. One of the studies measuring serum fibronectin in older diabetic patients (48.8 ± 14.6 years old) found a 50% reduction of this protein in response to moderate aerobic training [44].

Osteonectin (SPARC) was one of the most frequently reported glycoproteins in the retrieved studies. SPARC was increased after all types of exercise stimuli, duration and age groups [26,32,34,36–39,41]. This matricellular protein is essential to tissue regeneration by contributing to myofiber metabolic homeostasis, reduction in inflammation, extracellular matrix remodelling and collagen maturation [51].

Proteoglycans are also involved in the process of skeletal muscle regeneration [52] and are upregulated after skeletal muscle damage in newly formed myotubes [53]. The mRNA expression of the small leucine-rich repeat proteoglycans (SLRPs), biglycan, asporin, osteoglycin (or mimecan), lumican, was upregulated in all age groups after various exercise interventions and durations [26,30,33,36,38,39]. At protein level, AET increased the expression of asporin, lumican and prolargin in young participants [30]. Decorin is the most abundant proteoglycan in the skeletal muscle and was reported in
both age groups after training. However, in young participants, decorin was either unchanged or downregulated upon the stimulus of AET [30,31], whereas in older participants it was upregulated following a CT intervention [27] and RET in osteoporotic women [34]. The proteoglycans perlecain (HSPG2) and ECM2 were reported to be upregulated independent of age or intervention type [26,30,38,39]. Aggrecan (CSPG4) was reported to be increased when measured after CT in older participants [26]. Versican (CSPG2) was reportedly increased only after AET in young participants [39].

Glypican 4 and chondroadherin are proteoglycans reported only in the older group and were among the few ECMs downregulated after exercise training [26], while in the same study, osteomodulin and phosphacan/receptor-type protein phosphatase β (CSPG4) [26] were induced by CT exercise in old participants. The cell surface proteoglycan CSPG4 interacts with neurons and neural cell-adhesion molecules (N-CAM) in addition to blocking N-CAM and tenascin growth-promoting ability [46].

3.6. Angiogenesis

Increased capillarisation to muscle fibre ratio was seen after exercise training across age groups and a range of body mass indexes (BMI) [4,6,54]. Adhesive glycoproteins such as thrombospondins are involved in angiogenesis [55]. Combined exercise training enhanced the mRNA expression of both the anti-angiogenic thrombospondin 1 (THBS1) and the pro-angiogenic thrombospondin 4 (THBS4), but the THBS4/THBS1 fold change ratio was 1.4 [26]. Although tenasin C is upregulated as consequence of injured muscle fibre [56] and damaging eccentric contraction [57], Valdivieso et al. [40] testing young participants after AET demonstrated that A/A genotype has superior gain in muscle capillarization postexercise, as compared to the T/T genotype Tenasin C (Tn-C). In addition, exercise training upregulated perlecain in both age groups [26,30,39], indicating a pro-angiogenic effect in muscle, as this proteoglycan is known to modulate pro-angiogenic factors such as fibroblast growth factor 2 (FGF2), vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) reviewed by Iozzo et al. [46].

4. Discussion

In this review, evidence from 21 studies including 402 participants was analysed to investigate the effect of exercise training on intramuscular ECM composition and whether these ECMs are involved in the events of muscle adaptation and remodelling. There was a widespread increase in the expression of ECM molecules in response to exercise training stimulus. Intramuscular ECMs were altered after training interventions at the transcriptional and translational level. All types of exercise training significantly upregulated similar numbers of collagens, glycoproteins, proteoglycans. Structural ECMs are likely to be widely increased supporting muscle remodelling. While it became evident that ECMs participate in muscle adaptation, the current evidence on the role of ECMs orchestrating particular events during remodelling was limited by lack of controlled trials incorporating mechanistic outcome measures into adequately sized human exercise training trials.

All studies demonstrated that repetitive bouts of exercise over time (training) promotes changes in muscle architecture, capillarisation and myogenesis in younger and older participants, consistent with other studies [4,13,17,54,58]. Despite the variability regarding participant sex, age and exercise type/duration, muscle remodelling was accompanied by ECM adaptation. This was mostly evident in seven studies, which associated ECM changes to specific muscle remodelling events including CSA, muscle strength, angiogenesis, as well as the level of physical activity [27,36,40–44].

Exercise is known to affect muscle in young and old adults differently. Our findings revealed that similar ECMs are increased in both age groups after exercise training. Only two studies compared the exercise training-induced ECM response in younger and older participants [36,38]. Their results were in agreement, showing that change in ECMs is towards the same direction in young and older participants. Although the fold change may be different among age groups and exercise training applied, the ECM responses are
towards a similar direction. In agreement, it was observed that ECMs upregulated in early training sessions are also upregulated at later sessions. [36]. Thus, the findings indicate that in healthy adults, exercise training leads to similar ECM transcriptomes independently of age group and number of training sessions, demonstrating similar regulation in both age groups.

The ECM response is resultant of a force–time integral among the interventions tested, which may have affected the fold change of individual genes, but resulted in similar transcriptomes [59]. Further understanding of how different types of exercise cause changes in intramuscular ECMs was limited by the number of studies comparing exercise modalities [38], as AET and HIIT were mostly prescribed to younger populations and CT and RET to the older age groups. Likewise, rat skeletal muscle presented similarly increased ECM transcriptomes in response to isometric and concentric exercise training, but greater fold change was observed in response to higher mechanical stimulus [60]. Considering that the changes in gene expression after exercise in the elderly are delayed compared to younger participants [59], the tendency of applying longer training protocols to the elderly may have contributed to the observed similar ECM outcomes. In agreement with our findings, the study on acute RET bouts demonstrated that ECMs, including COL1A1, COL7A7, ADAMTS1, are upregulated in participants from both age groups [61]. Importantly, all exercise types upregulated collagen IV and laminin in both age groups. These ECMs provide critical scaffolding for the basement membrane, offering stability for the sarcolemma and myofiber cytoskeletal integrity, and the lateral transfer of mechanical force from the muscle cell to surrounding stroma ECM during contraction. The observed ECM remodelling at the basement membrane, in addition to facilitating myofiber repair, will allow the healthy expansion of intramuscular ECM to accommodate muscle fibre growth. Therefore, this systematic review demonstrates that adequate training interventions in terms of duration and intensity were applied according to age groups, and ECM adaptation accompanied muscle phenotypic remodelling [27,36,42,43].

Quiescent satellite cells which reside beneath the basal lamina can respond to mechanical stimuli and damage, becoming activated, differentiating into myoblasts that can fuse together to regenerate lost tissue or fuse with existing fibres to allow for myofiber repair [62]. This process depends on ECM composition, stiffness, topography and porosity [20]. The observed balanced composition of ECMs between age groups highlights the importance of ECMs’ function not only as a supportive scaffold, but also integrating both biochemical and mechanical signalling in the stem cell niche [63]. Therefore, ECMs play a role regulating cell behaviour, dictating tissue repair, remodelling and overall function [20]. At the early stages of muscle regeneration and repair, laminin and collagen type I are downregulated. In contrast, hyaluronic acid, tenascin and fibronectin are upregulated, forming a provisional matrix, enabling mitotic satellite cell adhesion, fusion and muscle regeneration [9].

Fibronectin, the preferred adhesive substrate for satellite cells, was reportedly increased only in young participants. Further studies on the effect of exercise training on the expression of fibronectin in the older population will be necessary to understand the importance of this glycoprotein to myogenesis. It is noteworthy that loss of muscle fibronectin in aged mice leads to ineffective muscle remodelling [64]. As satellite cells fail to adhere to fibronectin, the cells die by anoikis, demonstrating that ECM composition controls remodelling. The study also demonstrated that overexpression of fibronectin leads to rejuvenation of the skeletal muscle. In addition, fibronectin has been shown to prevent myostatin-mediated inhibition of myoblast proliferation [65,66]. Decorin is another ECM upregulated after exercise training, which is capable of inhibiting myostatin [27,34]. Myostatin regulates myogenesis and inhibits muscle mass by maintaining satellite cell quiescence. Recently, the group of Barreiro demonstrated that sarcopenic muscle from COPD patients is characterised by increased levels of myostatin compared to non-sarcopenic controls [58]. However, the levels of decorin and fibronectin in sarcopenic muscle after exercise training is not known.
Endothelial cell adhesion is mediated by the counterbalancing properties of fibronectin and tenascin-C [67]. The antiadhesive tenascin C, previously associated with muscle damage, is shown in this review to be crucial to increased capillarisation in young participants after AET postexercise training [40]. The authors concluded that the A/A genotype for tenascin C is more permissive of structural rearrangements of capillaries with respect to muscle fibres by relieving cells from the mechanical constraints of contact inhibition. For individuals carrying the T/T genotype, angiogenesis remained unchanged, suggesting that genotyping of tenascin C affects the exercise-induced level of capillarization [40].

Glypican-4 and chondroadherin are proteoglycans reported only in the older group and were among the few ECMS downregulated after exercise training [26]. The heparan sulphate proteoglycans, such as glypican-4, agrin and perlecan, are intimately associated with the plasma membrane of satellite cells functioning as major modifiers of growth factors such as FGF and VEGF. Glypican-4 also functions as an adipokine, which is associated with metabolic disease [68]. The downregulation of glypican-4 in an older group [26] is herein another supportive finding on the effect of ECM regulating muscle metabolism [68]. Increased levels of glypican-4 are associated with risk of type 2 diabetes and the prevalence of insulin resistance in these patients [69].

None of the studies compiled in this analysis included participants presenting muscle and nerve pathologies, sarcopenia, cachexia, dystrophic muscle repair, fibrosis or abnormal muscle remodelling. Nor were any damaging exercise interventions included. Thus, we can conclude that the that the observed widespread increase in ECMS reflects a physiological ECM response and adaptation to exercise training in all age groups tested.

Strength and Limitations

To the best of our knowledge, this is the first systematic review on the effect of exercise training-induced ECM adaptations in human skeletal muscle. Only training exercise interventions which displayed a balanced insight of the post-training adaptations and repair of the muscle tissue were retained in this review. The effect of an acute bout of exercise was not the topic of this review, as that would reflect momentarily changes in ECM which may not be representative of a physiological muscle tissue adaptation, especially when considering the variability in human response. Importantly, only data from healthy adults were analysed, allowing direct translation of this research into understanding the benefits of exercise training improving muscle health. However, due to the different methodological approaches used in the studies, further data analyses were restricted. Future research on exercise training should be focused on addressing how the skeletal muscle ECM of a specific population group (e.g., sex and age) responds to a specific exercise training intervention. Deciphering the mechanisms that underlie ECM-induced skeletal muscle adaptation will support the discovery of biomarkers of ECM adaptation, which can present itself as a novel therapeutic target, contributing to the understanding of muscle remodelling myogenic processes and supporting the use of exercise training as medicine.

5. Conclusions

The importance of exercise training conditioning muscle has long been recognised for its therapeutic effect in healthy adults and counteracting muscle wasting [2,58]. Recently, advances have supported better understanding of the potential of exercise training for maintaining muscle mass, strength and function during ageing. Our findings demonstrate that exercise training affects ECM composition and, consequently, adaptation and regeneration after exercise. The intramuscular ECMS, consisting of collagens, proteoglycans and glycoproteins, have a well-defined role in three-dimensional scaffolding and are also essential for effective muscle contraction and force transmission. This systematic review also points to the involvement of ECMS in myogenic and angiogenic physiological processes, and it is clear that the ECM, by interacting with various cells, can regulate exercise-induced muscle adaptation, regeneration and repair. Further studies on the effect of exercise training modifying ECMS in different age groups are necessary to better
understand the crucial role of these molecules on ageing muscle. New findings on the role of ECMs will support the development of effective therapeutic approaches to support and treat muscle wasting.

**Supplementary Materials:** The systematic review search strategy for PUBMED (Table S1), and results on the changes in ECM-related molecules after exercise training intervention (Table S2) are available online at www.mdpi.com/2073-4409/10/5/1022/s1.

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