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Review article

Interventions used to mitigate muscle fatty degeneration following the repair of massive rotator cuff tears. A systematic review of animal studies

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ABSTRACT

Background: Muscle fatty degeneration following rotator cuff tears has been unequivocally associated with poorer functional outcomes and increased risk for retear following rotator cuff repair. Promising results have emerged from animal studies, with the implementation of various interventions for biologic inhibition of this fatty muscle degeneration. The lack of high quality randomized human evidence on this topic, increases the impact of pooled results from animal literature. The aim of the present study was to systematically review the available published literature for animal studies evaluating the ability of several interventions used to mitigate muscle fatty degeneration following the repair of massive rotator cuff tears.

Patients and methods: A comprehensive search was conducted on Pubmed, Scopus and Google Scholar, covering the period from conception until 16th April 2022. Datasets were stratified based on the type of intervention performed. SYRCLE risk of bias instrument was implemented for quality assessment of the included studies.

Results: Rotator cuff repair augmentation with Adipose derived stem cells (ADSC's), Mesenchymal stem cells (MSC's) and Nandrolone was effective against fatty infiltration, but less effective against muscle atrophy. More beneficial effect was shown by the utilization of Beige adipose tissue – Fibroadipogenic progenitors (BAT-FAP) stimulation, using either Amibregon or BAT-FAPs transplantation. Both provided good results in mitigating muscle atrophy, fatty infiltration and fibrosis.

Discussion: ADSC's, MSC's, Nandrolone and BAT-FAP stimulation may have a role in mitigating muscle fatty degeneration following rotator cuff tears. Large scale human studies are required to further elucidate their role in the clinical setting.

Level of evidence: V; systematic review of pre-clinical studies.

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1. Introduction

Rotator cuff tear (RCT) is a common shoulder disorder, especially in older patients. It affects not only shoulder function but also patients' overall quality of life [1]. Following a massive tear, rotator cuff muscles undergo a variety of changes including fibrosis, atrophy and fatty infiltration which prevent the full recovery of shoulder function even after a successful repair [2]. Atrophy and fatty infiltration of rotator cuff muscles may be attributed to rotator cuff tear itself, through the tendon disuse or in some cases to the simultaneous increased tension on the suprascapular nerve from the retracted cuff musculature [3,4]. Biomechanical and histological studies in animal models have shown that muscle atrophy and fatty

Abbreviations: RCT, Rotator cuff tear; RCR, Rotator cuff repair; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; PROSPERO, Prospective Register of Systematic Reviews; PICO, Population, Intervention or exposure, Comparison, Outcome; BMP, Bone morphogenetic protein; HIF PHD, Hypoxia-inducible factor prolyl 4-hydroxylases; ECM, Extracellular matrix; ADSC, Adipose derived stem cells; MSC, Mesenchymal stem cells; PRP, Platelet Rich Plasma; PSC, Perivascular stem cells; BAT-FAP, Beige adipoge tissue Fibroadipogenic progenitors; FAP, Fibroadipogenic progenitors; FAPB4, Fatty acid-binding protein 4; p38 MAPK, p38 mitogen activated protein kinase; TGF-β, Transforming growth factor beta; SS, Supraspinatus; IS, Infraspinatus; TM, Teres minor; CSA, Cross sectional area.

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infiltration are responsible for the functional impairment of the involved tendons [2,5]. In the clinical setting, both fatty infiltration and muscle atrophy have been associated with poorer functional outcomes and increased risk for retear following rotator cuff repair [6–11].

Recently, scientific interest has arisen for possible methods to prevent, or even reverse the fatty degeneration that follows rotator cuff tears. In vitro studies showed that even though rotator cuff muscle stem cells present reduced myogenic and increased adipogenic differentiation capacity compared to muscle stem cells from other regions of the body [12], they retain sufficient myogenic activity despite fatty infiltration in cases of chronic rotator cuff tears [13]. Simultaneously, promising results have emerged from the use of various substances and interventions for biologic inhibition of muscle degeneration and fatty infiltration in pre-clinical studies [14–18].

The aim of the present study was to systematically investigate the available published animal literature for interventions used to mitigate the development of muscle atrophy, fatty infiltration and fibrosis following the repair of massive rotator cuff tears.

2. Materials and methods

2.1. Guidelines followed

The preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were followed in this systematic review [19]. A completed PRISMA checklist has been submitted as Supplementary Table 1. The present study has been registered in the Prospective Register of Systematic Reviews (PROSPERO) System (ID: CRD42022336063).

2.2. Search strategy

The systematic review was conducted according to Population, Intervention or exposure, Comparison, Outcome (PICO) elements: (i) population: animal model with a full-thickness rotator cuff tear including the supraspinatus, infraspinatus, teres minor or subscapularis; (ii) intervention: stem cells, MSC's, Progenitor cells, scaffolds, PRPs, hormones, growth factors, regulator factors, immunomodulatory agents. If other interventions are identified, these will be also included in the analysis; (iii) comparison group: animal models with a rotator cuff tear and no intervention (e.g., placebo, saline or sham surgery); (iv) outcome: effect of each intervention on fatty infiltration, muscle atrophy and fibrosis. As additional outcomes of interest, muscle force production and performance were both considered.

To identify eligible studies, the main search was applied in the electronic databases Pubmed, Scopus and Google Scholar, covering the period from conception until 16 April 2022 (Supplementary Table 2). The main search was completed independently by three investigators (D.S., A.V., S.S.) who checked all the available articles. Any discrepancies were resolved by consulting a fourth investigator (A.C.).

2.3. Trial selection

Specific inclusion criteria were established prior to the literature search:

- animal studies evaluating the effect of several interventions (in vivo) regarding their ability to ameliorate muscle fatty degeneration following the repair of a rotator cuff tear;
- the animal model must be an otherwise healthy animal;
- muscle atrophy must be evaluated using muscle dry/wet weight, muscle volume using MRI/CT scan or muscle fiber cross sectional area (CSA);
- fibrosis must be evaluated using histologic criteria or chromatography;
- fatty infiltration must be evaluated using histologic criteria, chromatography, CT or MRI.

Studies were excluded if they:

- were in vitro studies;
- evaluated rotator cuff tendon or tendon to bone healing;
- studies not performing rotator cuff repair;
- studies not using a relevant control group;
- studies evaluating other than rotator cuff muscles;
- were written in non-English language.

2.4. Data extraction and synthesis

Two researchers (D.S. and A.V.) reviewed all eligible studies. The following data were extracted and recorded:

- first author;
- year of publication;
- country in which the study was conducted;
- total number of animals used;
- animal model (type, age, sex);
- type of rotator cuff tear;
- type of intervention;
- method of assessment for each outcome of interest.

Alongside the primary outcomes, additional data concerning the secondary outcomes, namely the muscle force production and performance were also extracted and recorded when available.

2.5. Risk of bias assessment

Quality assessment of the included studies was performed independently by the first two authors, using the SYRCLE risk of bias instrument. The latter is an adaptation of the Cochrane risk of bias tool, for animal studies [20]. SYRCLE instrument consists of a fixed set of bias domains, namely randomization; baseline characteristics; allocation concealment; random housing; blinding of caregivers; random outcome assessment; blinding of outcome assessors; incomplete outcome data; selective outcome reporting; other bias. Signaling questions, within each domain, aim to highlight study features prone to the risk of bias. Answering these questions elicits a judgment value regarding the risk of bias for each study. Judgement can be "Low" or "High" risk of bias, or can express "Some concerns".

2.6. Data analysis

Datasets were stratified based on the type of intervention. High heterogeneity regarding animal models (smaller vs larger animals), type and chronicity of rotator cuff tear, method of assessment and report for outcomes of interest between the included studies imbedded the conduction of a meta-analysis. As a result, the outcomes were evaluated qualitatively. The provided results were assembled to identify strengths, weaknesses, and trends suggesting preliminary positive effects from each intervention.

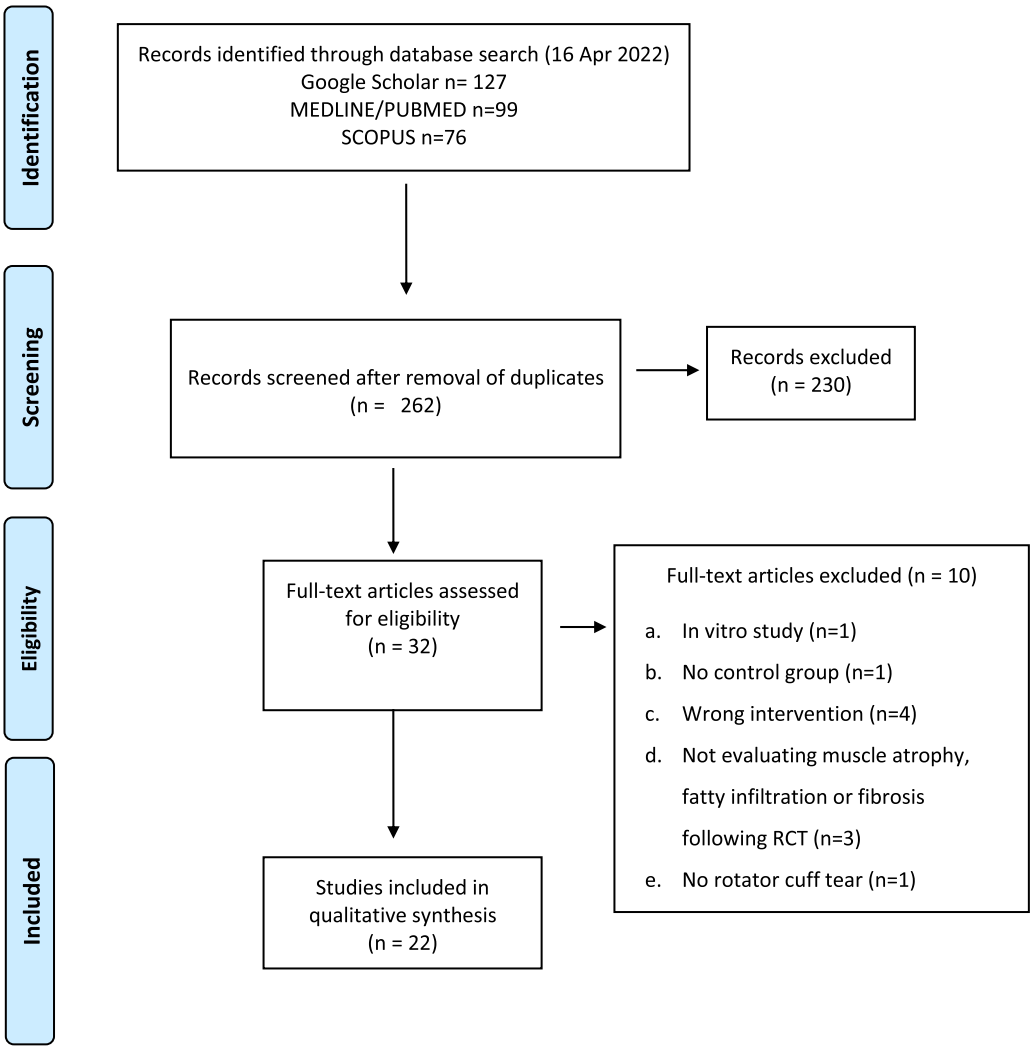

Figure 1. Flow chart diagram.

3. Results

3.1. Study characteristics

Literature search yielded a total of 302 potentially relevant studies. After removal of duplicates ($n = 40$), 262 titles and abstracts were reviewed. Thirty-two studies were assessed as full-text papers, implementing the aforementioned pre-established criteria. The latter resulted in the exclusion of 10 studies, due to the following reasons: (i) one study was in vitro, (ii) one study had no control group, (iii) three studies did not evaluate muscle atrophy, fibrosis or fatty infiltration, (iv) one study evaluated muscle adaptation to Ibuprofen administration (no rotator cuff tear) and (v) four had either no or wrong intervention (eg. evaluating the effect of hypercholesterolemia, TGF-β or RhoA signaling in the development of fatty infiltration). A flow diagram is shown in Figure 1.

The total number of animals used in the included studies were 746. Six studies [18,21–25] used rabbits for their experiments, six studies used sheep [17,26–30] and ten studies evaluated rodents [31–40].

High heterogeneity was spotted during data extraction regarding the type of rotator cuff tear, the chronicity and the simultaneous presence of suprascapular nerve injury. In particular, eight studies evaluated rodents with a single supraspinatus tear and two studies [33,34] evaluated rodents with a combined tendon tear and denervation (suprascapular nerve) of the supraspinatus. All six studies conducted in sheep used only infraspinatus tear, whilst studies conducted in rabbits all evaluated animals with a supraspinatus tear, except one (subscapularis tear). Concerning the chronicity of the tear, in the rodent group it varied from four to sixteen weeks, in the rabbits group from six to twelve weeks and in the sheep group from five to thirty-four weeks. A complete summary of the descriptive characteristics of the included studies is presented in Table 1.

3.2. Risk of bias assessment

All the included studies were pre-clinical animal studies, 15 of which clearly state that randomization took place. RoB was generally unclear across all studies due to limited methodological details, which failed to address several criteria within the SYRCLE RoB tool. The risk of bias assessment results are presented in Supplementary Table 3.

3.3. Interventions

3.3.1. Stem cells and stem cells derivatives

Stem cells and their derivatives were evaluated by seven studies. Two studies, using 75 rabbits in total, evaluated adipose derived stem cells (ADSCs) [18,21]. In both cases, the authors reported significantly less fatty infiltration in the animals of the treat-

Table 1
Descriptive characteristics of the studies included in the analysis.

ID	Study	Country	Number and type of animals		Age	Sex	RCT
1	Oh, 2014 [18]	S.Korea	40	New Zealand white rabbits	24 weeks	Male	SSC
2	Wang C, 2020 [21]	China	35	Rabbits	4 months	Male	SS
3	Güleçyüz,2018 [31]	Germany	112	Lewis rats	12 weeks	Female	SS
4	Gerber C,2011 [23]	Switzerland	20	New Zealand white rabbits	15 weeks		SS
5	Gerber C,2015 [27]	Switzerland	18	Swiss alpine sheep	25 ± 4 m	Female	IS
6	Gilotra, 2015 [24]	USA	14	New Zealand white rabbits			SS
7	Ruoss S, 2018 [28]	Switzerland	18	Swiss alpine sheep		Female	IS
8	Sahin E, 2015 [35]	Turkey	30	Wistar rats	12-14 w		SS
9	Kim H, 2022 [22]	S.Korea	20	New Zealand white rabbits	12 weeks	Male	SS
10	Flück M,2017 [29]	Switzerland	18	Swiss alpine sheep	2 years	Female	IS
11	Wilde J, 2016 [37]	USA	28	Sprague-Dawley rats	6 months	Male	SS
12	Oak NR, 2014 [38]	USA	18	Sprague-Dawley rats	6 months	Male	SS
13	Gumucio, 2017 [39]	USA	30	Sprague-Dawley rats	9 months	Male	SS
14	Huynh T, 2020 [25]	USA	14	New Zealand white rabbits	24 weeks	Male	SS
15	Wang Z, 2020 [33]	USA	70	C57BL/6J mice	3 months	Female	SS + DN
16	Brandão, 2018 [17]	Brazil	6	Santa Inês breed Sheep	2-4 years	Female	IS
17	Gerber C, 2012 [30]	Switzerland	20	Swiss Alpine sheep	23 ± 2 m		IS
18	Gumucio, 2016 [32]	USA	26	Athymic nude rats	4 months	Male	SS
19	Hettrich, 2011 [36]	USA	132	Sprague-Dawley rats		Male	SS
20	Tang X, 2021 [40]	USA	39	Sprague-Dawley rats		Male	SS
21	Flück M, 2021 [26]	Switzerland	14	Swiss Alpine sheep		Female	IS
22	Lee C, 2020 [34]	USA	24	C57BL/6J mice	3 months		SS + DN

SSC: subscapularis; SS: supraspinatus; IS: infraspinatus; DN: denervation (suprascapular nerve); RCT: rotator cuff tear.

ment group. Four studies assessed mesenchymal stem cells (MSCs) [17,22,26,31], using 112 rodents [31] and 40 sheep [17,22,26] overall. None of these studies showed improvement concerning muscle atrophy. Two studies found significantly less fatty infiltration in the MSC group [17,22], whereas the other two [26,31] did not. Interestingly, in the study by Flück et al. [26], although the fatty infiltration observed at 6 weeks after repair was not significantly different between the treated and the respective control group; the alteration in the fat content observed during the six weeks after RCR was significantly less in the treated group (Supplementary Table 4). Stromal vascular stem cells (SVFCs) were evaluated in 26 rats with a supraspinatus tear by one study [32]. Authors reported no improvement regarding muscle atrophy, but also a significant decrease in hydroxyproline content in the treated group. The latter implies a possible positive effect regarding muscle fibrosis. A detailed description regarding the type of intervention and results from studies evaluating stem cells and their derivatives are presented in Table 2.

3.3.2. *Anabolic steroids*

Five studies [23,27–30] evaluated Nandrolone decanoate, using 20 New Zealand white rabbits [23] and 74 Swiss Alpine sheep [27–30]. Authors reported significantly less fatty infiltration in all subgroups when Nandrolone administration started immediately after RCT [23,27–29]. Muscle atrophy was assessed by four studies [23,27,28,30], using infraspinatus (IS) wet muscle mass [23], alterations in IS muscle volume on MRI [27,28] or IS muscle CSA in CT [30]. Except for one subgroup (N6W) in the study by Gerber et al. [27], muscle atrophy was not found to be significantly altered in the treated animals. In the same study [27] authors found a selective increase in the mean CSA of type II muscle fibers (Supplementary Table 4) in the Nandrolone group. A summary of the results from studies evaluating anabolic steroids is depicted in Table 3.

3.3.3. *BAT-FAP stimulation*

Two studies [33,34] examined the ability of BAT-FAP (Beige adipose tissue fibroadipogenic progenitors) stimulation to prevent muscle fatty degeneration following RCR, using 94 C57BL/6J mice with a combined rotator cuff tear and denervation model. In both studies, the authors reported significantly less fatty infiltration in the treated groups. Authors also assessed muscle atrophy, using supraspinatus muscle weight (Table 4) and supraspinatus muscle fiber CSA (Supplementary Table 4). Both were notably higher in the BAT-FAP stimulation groups. Moreover, Lee et al. [34] reported significantly less amount of muscle fibrosis in the treated animals compared to the control group. An overview of the results from studies evaluating BAT-FAP stimulation is presented in Table 4.

3.3.4. *Other interventions*

Intramuscular injection with Botulinum Toxin A was assessed by three studies [24,35,36], using 162 rodents and 14 rabbits. In all cases Botox injections did not improve muscle atrophy and fatty infiltration. Licofelone, p38 mitogen activated protein kinase inhibition (MAPK), hypoxia-inducible factor prolyl 4-hydroxylases inhibition (HIF PHD), ECM (extracellular matrix) and electroconductive nanofibrous matrix were all assessed by one study each. Utilization of SB203580 [37] (p38MAPK-inhibitor) or Licofelone [38] led to a decrease in triglyceride and hydroxyproline content in the supraspinatus muscle of the treated rats. It should be noted though, that neither of these interventions improved muscle maximum isometric force production (Supplementary Table 4). RCR augmentation with the HIF PHD inhibitor GSK1120360A [39] and ECM gel [25] were effective in improving muscle atrophy. GSK1120360A also ameliorated muscle fibrosis, while ECM gel did not show the same results. A detailed summary of the data extracted from the aforementioned studies is presented in Tables 5 and 6.

4. Discussion

This is the first systematic review of the published literature, evaluating the effect of several interventions used to augment rotator cuff repair concerning their ability to ameliorate muscle fatty degeneration.

Rotator cuff tears are identified as the partial or complete detachment of the tendon from its insertion in the upper part of the humerus [1]. In the full-thickness chronic scenario, this injury involves not only the tendon but also the whole bone-tendon-muscle unit [41]. In these cases, the torn tendon retracts medially and its structural and compositional features are altered [42]. In particular, there is an increase in collagen type III, disorientation of

Table 2
Stem cells & stem cells derivatives.

First author, year	Intervention	Muscle atrophy		Fatty infiltration		Muscle fibrosis	
		Assessment method	Results	Assessment method	Results	Assessment method	Results
Oh JH, 2014 [18]	RCR enhanced with ADSC injection, 6 weeks following SSC tear – 6 weeks later muscle evaluation			Histologic assessment (fat/muscle proportion)	30 ± 14% (p = 0.028)		
Wang C, 2020 [21]	RCR enhanced with ADSC derived exosomes injection plus RCR, 6 weeks after RCT –-12 weeks later muscle evaluation			Histologic assessment (area % of FI)	14.01 ± 2.85% (p < 0.001)		
Güleçyüz MF, 2018 [31]	RCT – 4 weeks later, RCR enhanced with MSCs injection – 4 weeks later muscle evaluation	Wet mass (g)	0.2257 ± 0.03443 g (p > 0.05)	Histologic assessment (fat/muscle proportion)	0.5688 ± 1.248% (p > 0.05)		
	RCT – 4 weeks later, RCR enhanced with myocytes injection – 4 weeks later muscle evaluation		0.2322 ± 0.03901 g (p > 0.05)		0.1260 ± 0.2493% (p < 0.05)		
Kim H, 2022 [22]	RCT – 6 weeks later RCR enhanced with injection of EV (derived from MSCs) loaded injectable collagen – 12 weeks later muscle evaluation			Histologic assessment (area % of FI)	1.8 ± 0.6% (p = 0.001)		
Brandão AGM, 2018 [17]	RCT – 60 days later, RCR enhanced with MSC injection – 14 days after RCR, muscle evaluation			Histologic assessment (grade system[b])	Grade 4 (vs. grade 5 in control)		
	RCT – 60 days later, RCR enhanced with MSC injection – 34 days after RCR, muscle evaluation				Grade 1 (vs. grade 4 and 5 in control)		
Gumucio JP, 2016 [32]	RCT – 4 weeks later RCR enhanced with SVFCs injection (dose: 30,000 cells) – 2 weeks later muscle evaluation	Wet mass (mg)	311 ± 6 mg (p > 0.05)			HP content, normalized to dry muscle mass	1.10 ± 0.2 µg/mg[a] (p < 0.05)
	RCT – 4 weeks later RCR enhanced with SVFCs injection (dose: 300,000 cells) – 2 weeks later muscle evaluation		304 ± 15 mg (p > 0.05)				1.12 ± 0.202 µg/mg[a] (p < 0.05)
Flück M, 2021 [26]	RCT – 16 weeks later RCR enhanced with MSC injection – 6 weeks later muscle evaluation	Muscle volume (MRI)	134.3 ± 22.1 mL (p = 0.104)	MRI assessment (fat fraction %)	53.9 ± 10.4% (p = 0.219)		

SSC: Subscapularis; RCT: Rotator cuff tear; RCR: Rotator cuff repair; EV: Extracellular vesicles; MSCs: Mesenchymal stem cells; ADSC: Adipose tissue derived stem cells; SVFCs: Stromal vascular stem cells; FI: Fatty infiltration, HP: Hydroxyproline.

[a] Exact values were calculated through figures in the published study (using the online application graphreader, available from www.graphreader.com).

[b] To evaluate fatty infiltration, authors established groups varying from stage 0 to 5, in which the samples in stage 0 presented with normal morphology. In stage 1, samples presented fatty infiltration that occurred only in the perimysium. In stage 2, samples presented fatty infiltration in the perimysium and a discrete fat infiltration in the endomysium. Stage 3 was characterized by moderate infiltration both in the endomysium and perimysium. In stage 4, infiltration occurred in both leaflets, but it was considered intense only in the perimysium. Finally, at stage 5, fatty infiltration occurred intensely in both the endomysium and perimysium.

collagen fibers, myxoid degeneration, chondroid metaplasia, calcification, and vascular proliferation [43]. These qualitative changes on tendon composition have a detrimental effect on its biomechanical properties. Indeed, a 30% reduction in the tensile strength of the healed tendons has been reported compared to the intact tendons [44]. In addition, bone density in the greater tuberosity is compromised in patients with chronic rotator cuff tears [45].

Chronic rotator cuff tears are also associated with the development of degenerative changes in the affected muscles. These changes are mainly characterized by muscle atrophy, fibrosis and fatty infiltration [7,9,46]. The severity of these changes depends mostly on the extend and the chronicity of the lesion [47]. Although these are likely interrelated processes, each of them has been found to play a detrimental role in tear repairability,

Table 3
Anabolic steroids.

First author, year	Intervention	Muscle atrophy		Fatty infiltration		Muscle fibrosis	
		Assessment method	Results	Assessment method	Results	Assessment method	Results
Gerber C, 2011 [23]	RCT – Immediate RCR, enhanced with weekly nandrolone (local + systemic) injections – 6 weeks later evaluation	Wet mass (g)	8.7 g (95% CI: 6.4,11) ($p > 0.05$)	Histologic assessment (area percentage of FI)	2.2% (range, 0–8%), ($p > 0.05$ vs. pre-status)[a]		
	RCT – Immediate RCR, enhanced with weekly nandrolone (systemic) injections – 6 weeks later evaluation		9.4 g (95% CI: 8.1, 10.7) ($p > 0.05$)		1.0% (range, 0–3.4%), ($p > 0.05$ vs. pre-status)[a]		
Gerber C, 2015 [27]	RCT – 16 weeks later RCR, enhanced with weekly nandrolone injections – 6 weeks later evaluation (N6W group)	Alterations in muscle volume % (MRI)	78 ± 14% ($p = 0.01$ vs. N22 W and $p = 0.02$ vs. control)	Area percentage % of fat using MRI scan	56 ± 12% ($p > 0.05$ vs. control)		
	RCT – weekly Nandrolone injections starting at the time of RCT – 16 weeks later RCR – 6 weeks later evaluation (N22W group)		67 ± 5% ($p > 0.05$ vs. control)		22 ± 7% ($p < 0.05$ vs. N6 W and control)		
Ruoss S, 2018 [28]	weekly injections of 150 µg nandrolone (into gluteus max.), starting after RCT – 16 weeks later repair – 6 weeks later (22 total) muscle evaluation	Alterations in muscle volume (final – initial)	−54.7 ± 19.0cm^3 (P > 0.05)	Alterations in fat volume using MRI scan	-4.6 ± 8.0 cm^3 ($p < 0.001$ vs. control)		
Flück M, 2017 [29]	weekly injections of 150 mg Nandrolone (into Gluteus max.), starting after RCT – 16 weeks later repair – 6 weeks later muscle evaluation (N22 W group)			Histologic assessment (changes in area of FI)	25 ± 15% ($p < 0.05$ vs. control)	Histologic assessment (changes in area of ECM compared to PRE-status)	630 ± 310%[a] ($p > 0.05$)
	RCT – 16 weeks later RCR + weekly injections of 150 mg nandrolone (into Gluteus max.) – 6 weeks later muscle evaluation (N6W group)				1250 ± 650% ($p > 0.05$ vs. control)		260 ± 90%[a] ($p > 0.05$)
Gerber C, 2012 [30]	RCT – 16 weeks later implantation of external lengthening device + local nandrolone injection (150 mg) – 6 weeks later (22 total) repair + local nandrolone injection (150 mg) – 12 weeks later (34 total) muscle evaluation	Muscle CSA (compared to contralateral side), using CT scan	74 ± 6% ($p > 0.05$)	Histologic assessment (fat to muscle proportion)	NS difference between groups		
	RCT – 16 weeks later implantation of external lengthening device + local IGF injection (267 mg, loaded in delayed release PLGA microspheres) – 6 weeks later (22 total) RCR – 12 weeks later (34 total) muscle evaluation		74 ± 10% ($p > 0.05$)		NS difference between groups		

RCT: Rotator cuff tear; RCR: Rotator cuff repair; CSA: Cross Sectional Area; FI: Fatty infiltration; ECM: Extracellular matrix.
[a] Control group had significantly more FI compared to its pre-status.

retear rate and patient's reported outcomes following rotator cuff repair [9,46–48]. Supplementing surgeon's arsenal with interventions capable of improving these degenerative processes would undoubtedly enhance the level of the medical treatment they provide to their patients.

Few clinical studies have evaluated the effect of the augmentation of RCR with stem/progenitor cells or growth factors in human patients with chronic full-thickness rotator cuff tears [49–53]. Most of these studies reported an enhancement in the healing rate and the quality of the repaired surface, but only a slight improvement in postoperative clinical scores. Most importantly, none has evaluated the quality of the muscle nor correlated it with the results. This lack of high quality randomized human evidence on this topic, further increases the impact of pooled results from animal litera-

Table 4
BAT-FAP stimulation.

First author, year	Intervention	Muscle atrophy		Fatty infiltration		Muscle fibrosis	
		Assessment method	Results	Assessment method	Results	Assessment method	Results
Wang Z, 2020 [33]	RCT – amibregon at the time of RCT (dose: 10 mg/kg) through daily intraperitoneal injections for 6 weeks – RCR 6 weeks after RCT – 6 weeks after RCR (12 after RCT) muscle evaluation	Normalized SS muscle weight reduction: ([SS right side–SS left side]/SS left side)%	−8.83 ± 6.82% ($p < 0.05$)[a]	Histologic assessment (area % of FI)	2.74 ± 0.78%[a] ($p < 0.05$)		
	RCT – 6 weeks later RCR + amibregon (dose:10 mg/kg) through daily intraperitoneal injections for 6 weeks – 6 weeks after repair (12 after RCT) muscle evaluation		−10.3 ± 7.83% ($p < 0.05$)[a]		5.36 ± 2.29%[a] ($p < 0.05$)		
Lee C, 2020 [34]	BAT-FAPs transplantation (20 μL of 250,000 BAT-FAPs) + RCR, 2 weeks after RCT – 6 weeks later (8 weeks after RCT) muscle evaluation	Normalized SS muscle weight: SS muscle weight/Total body weight	0.025 ± 0.03 ($p = 0.02$)	Histologic assessment (area % of FI)	3.5 ± 0.6% ($p = 0.001$)	Histologic assessment (area percentage of fibrosis)	6.5 ± 2.1% ($p = 0.001$)
	BAT-FAPs transplantation (20 μL of 250,000 BAT-FAPs) + RCR, 6 weeks after RCT – 6 weeks later (12 weeks after RCT) muscle evaluation		0.022 ± 0.0009 ($p = 0.01$)		8.4 ± 1.6% ($p = 0.004$)		7.8 ± 2.2% ($p = 0.008$)

SS: Supraspinatus; RCT: Rotator cuff tear; RCR: Rotator cuff repair; BAT-FAP: Beige adipose tissue Fibroadipogenic progenitors; FI: Fatty infiltration.
[a] Supplementary material in published study

Table 5
Botox.

First author, year	Intervention	Muscle atrophy		Fatty infiltration		Muscle fibrosis	
		Assessment method	Results	Assessment method	Results	Assessment method	Results
Gilotra M,2015 [24]	RCT – 12 weeks later RCR + Botox (6 U/kg) – 6 weeks later muscle evaluation			Goutalier classification using MRI	Mean grade 3.83 ($p = 0.17$)		
Şahin E, 2015 [35]	RCT and immediate repair + 9 U/kg of BTX-A intramuscularly into the repaired muscle belly – 3 months later muscle evaluation			Authors implemented a custom histopathological evaluation scale to evaluate degeneration, necrosis and neocapillarization	Increased fatty infiltration reported in control group compared to the Botox group		
Hettrich CM, 2011 [36]	RCT and immediate repair + Botox (6 U/kg) – 4/8/24 weeks later muscle evaluation	Wet mass (mg)	24 weeks: 0.50 ± 0.43 mg ($p > 0.05$)				

BTX-A: Botulinum toxin A; SS: Supraspinatus.

ture, as they could offer a valuable insight on the subject and thus upgrade provided medical management for these patients.

Published animal literature support that rodent models (rats and mice) are better suited for biochemical and histological evaluation concerning rotator cuff injury and the subsequent muscle fatty degeneration, whereas rabbits, sheep, and canine models are more suitable for biomechanical testing, rehabilitation, and validation of surgical techniques [54,55]. In our study, authors collectively evaluated 746 animals. As expected most of them were rodents (68,2%), with the rest being rabbits (19,2%) and sheep (12,6%).

In the present systematic review, adipose derived stem cells, mesenchymal stem cells and their derivatives and Nandrolone showed to be effective in ameliorating fatty infiltration, but less effective against muscle atrophy (Tables 2 and 3, Supplementary Table 4). More beneficial effect was shown by BAT-FAP stimulation, using either Amibregon or BAT-FAPs transplantation. Both provided good results in mitigating muscle atrophy, fatty infiltration and fibrosis (Table 4, Supplementary Table 4). Several other interventions were only assessed by one study each, thus extrapolation of their results would be premature. Further studies should be conducted to verify these preliminary results. It is also noteworthy

Table 6
Other Interventions.

First author, year	Intervention	Muscle atrophy		Fatty infiltration		Muscle fibrosis	
		Assessment method	Results	Assessment method	Results	Assessment method	Results
Wilde JM, 2016 [37]	RCT – 30 days later RCR + intraperitoneal injection of SB203580 (p38MAPK-inhibitor) (1 mg/kg) – 14 days after RCR muscle evaluation	Wet mass (mg)	520 ± 70mg[a] ($p > 0.05$)	Triglyceride content evaluation using chromatography	0.44 ± 0.10RU[a] ($p < 0.05$)	Hydroxyproline content, normalized to dry muscle mass	2.40 ± 0.40 μg/mg[a] ($p < 0.05$)
Oak NR, 2014 [38]	RCT – 28 days later RCR + licofelone administration via oral gavage (40 mg/kg) twice daily for 2 weeks – 2 weeks later muscle evaluation	Wet mass (mg)	720.3 ± 35.4 mg ($p = 0.223$)	Triglyceride content evaluation using chromatography	2750 ± 300RU[a] ($p < 0.05$)	Hydroxyproline content, normalized to dry muscle mass	1.90 ± 0.45 μg/mg[a] ($p = 0.009$)
Gumucio JP, 2017 [39]	RCT – 4 weeks later RCR + GSK1120360A (HIF-prolyl 4-hydroxylases inhibitor) administered via oral (3 mg/kg), beginning 3 days before repair – 2 weeks later muscle evaluation	Wet mass (mg)	655 ± 25mg[a] ($p < 0.05$ vs. control, $p > 0.05$ vs. 10 mg/kg group)			Hydroxyproline content, normalized to dry muscle mass	3.00 ± 0.20 μg/mg[a] ($p < 0.05$ vs. control, $p > 0.05$ vs. 10 mg/kg group)
	RCT – 4 weeks later RCR + GSK1120360A administered via oral gavage (10 mg/kg), beginning 3 days before repair – 2 weeks later muscle evaluation		630 ± 20mg[a] ($p < 0.05$ vs. control, $p > 0.05$ vs. 3 mg/kg group)				2.80 ± 0.60 μg/mg[a] ($p < 0.05$ vs. control, $p > 0.05$ vs. 3 mg/kg group)
Huynh T, 2020 [25]	RCT – 12 weeks later RCR + ECM gel injection (10 mg/mL) – 12 weeks later muscle evaluation	Wet mass reduction %	24 ± 3% ($p < 0.05$)	Histologic assessment (area % of FI)	4.1 ± 2.1% ($p = 0.18$)	Histologic assessment (area percentage of col-1 fraction)	2.9 ± 0.8%[a] ($p > 0.05$)
Tang X, 2021 [40]	RCT – Immediate RCR + electroconductive nanofibrous matrix implantation – 6 weeks later muscle evaluation	([SS on right side–SS on left side]/SS on left side) %	7 ± 2.5%[a] ($p > 0.05$)				
	RCT – 6 weeks later RCR + electroconductive nanofibrous matrix implantation – 6 weeks later muscle evaluation		6.75 ± 2.75%[a] ($p > 0.05$)				

SS: Supraspinatus; IS: Infraspinatus; RCT: Rotator cuff tear; RCR: Rotator cuff repair; CSA: Cross Sectional Area; HIF: Hypoxia-inducible factor; ECM: Extracellular matrix; FI: Fatty infiltration.

[a] Exact values were calculated through figures in the published study (using the online application graphreader, available from www.graphreader.com).

that most of the studies (77,2%) were published after 2015, showing an increased scientific interest on this matter. Moreover, studies evaluating other pharmacological substances that could influence the development, growth and repair mechanism of muscle (growth hormones, heparan sulfate, creatine, Vitamins D and E), should also be conducted [27].

Inherent limitations could be recognized in the present study. First, interpretation of the results should be done with caution, as these originate from pre-clinical animal model studies. Additional studies evaluating the exact biochemical mechanism of action and the minimum therapeutically effective dose for these interventions are required, before entering human clinical trials. Moreover, publication bias, which is a common issue in animal research, could compromise the validity of the results. In addition, the type and age of the animal model, the type of rotator cuff tear and its chronicity should also be taken into consideration. In most of the included studies, the authors used relatively young animals with an acute clear cut tear of the rotator cuff tendons, which is not the case in the respective human population. Extrapolation of the results in higher age groups must be done with caution. Furthermore, although no serious side effects were reported in our included studies, safe conclusions concerning the safety of these interventions cannot be made based on the existing literature. Finally, methodological errors during study design or execution were identified in all studies using the SYRCLE's RoB tool. Yet, the major strength of our study is the systematic and comprehensive search of the available animal literature to identify interventions which could assist in mitigating muscle fatty degeneration following rotator cuff tears.

5. Conclusions

Adipose derived stem cells, mesenchymal stem cells, Nandrolone and BAT-FAP stimulation may have a role in mitigating muscle fatty degeneration following repair of rotator cuff tears. Additional studies evaluating the exact biochemical mechanism of action and the minimum therapeutically effective dose for these interventions are required, before entering human clinical trials. Moreover, studies evaluating other pharmacological substances

that could influence the development, growth and repair mechanism of muscle (growth hormones, heparan sulfate, creatine, Vitamins D and E), should also be conducted.

Disclosure of interest

The authors declare that they have no competing interest.

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Authors' contributions

D.S., A.V. and A.C. substantially contributed to the design of the study, data extraction and synthesis, drafting of the article, and approving the final submission of the study. S.S. also contributed to the study conception and design, reviewed the literature and approved the final submission of the study. M.P., L.P., K.P., E.T. and I.S. reviewed the final draft and provided critical scientific input.

Artificial intelligence statement

No artificial intelligence was used for the writing of the submitted work.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.otsr.2023.103723.

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