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REVIEW ARTICLE

Exercise influence on monocarboxylate transporter 1 (MCT1) and 4 (MCT4) in the skeletal muscle: A systematic review

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Abstract

This review aims to systematically analyze the effect of exercise on muscle MCT protein levels and mRNA expression of their respective genes, considering exercise intensity, and duration (single-exercise session and training program) in humans and rodents, to observe whether both models offer aligned results. The review also aims to report methodological aspects that need to be improved in future studies. A systematic search was conducted in the PubMed and Web of Science databases, and the Preferred Reporting Items for Systematic review and Meta-Analyses (PRISMA) checklist was followed. After applying inclusion and exclusion criteria, 41 studies were included and evaluated using the Cochrane collaboration tool for risk of bias assessment. The main findings indicate that exercise is a powerful stimulus to increase MCT1 protein content in human muscle. MCT4 protein level increases can also be observed after a training program, although its responsiveness is lower compared to MCT1. Both transporters seem to change independently of exercise intensity, but the responses that occur with each intensity and each duration need to be better defined. The effect of exercise on muscle mRNA results is less defined, and more research is needed especially in humans. Moreover, results in rodents only agree with human results on the effect of a training program on MCT1 protein levels, indicating increases in both. Finally, we addressed important and feasible methodological aspects to improve the design of future studies.

KEYWORDS

ARNm expression, lactate, lactate shuttle, protein levels, sport, training

José Antonio Benítez-Muñoz and Rocío Cupeiro share first authorship.

1 | INTRODUCTION

The solute carrier 16 (SLC16) gene family has 14 members. It should be noted that only four genes of the human family (*SLC16A1, SLC16A3, SLC16A7*, and *SLC16A8*) have been shown experimentally to encode proteins that transport monocarboxylates (MCT1, MCT4, MCT2, and MCT3, respectively),[1] which play an important role in metabolic communication between cells.[2] They are found in diverse tissues exhibiting different selectivity and affinity for their substrates, with lactate being quantitatively the most important.[3] MCTs 1 to 4 cotransport protons and monocarboxylates passively through the plasma membrane.[1] The direction of transport depends on the gradient of the predominant substrate and protons, and the net rate of transport is determined by the difference between the influx and efflux. In thermodynamic equilibrium, the ratio inside/outside the cell is similar in the concentration of monocarboxylates and protons.[1] Therefore they play a key role in the regulation of pH between cells.[1] MCTs also are capable to influence the redox state of the different cells of the body. Most of the reactions involving monocarboxylates (pyruvate, lactate, β-hydroxybutyrate and acetoacetate) modify the NADH/NAD^+ state inside the cell. Thus, due to the close equilibrium between monocarboxylates and NADH/NAD^+ state, the transport of one of these monocarboxylates from one cell to another through MCTs will modify the redox state of these cells as well.[3] The importance of lactate in the redox balance is reflected in the absence of MCT1 in the beta cells of the pancreas to prevent insulin release triggered by an increase in blood lactate due to exercise.[4]

The distribution of the different MCTs varies among tissues, fitting in part with the different functionality of each member. MCT1 is ubiquitous (except in pancreatic β-cells) and has the most diverse selection, as it transports lactate, pyruvate, ketone bodies, acetate, butyrate, and propionate.[5] MCT2 is mainly present in the brain (neurons), liver, kidney and spermatogonia transporting pyruvate, lactate, and ketone bodies.[5] MCT3 is only found in retinal pigment epithelium transporting lactate.[5] Finally, MCT4 is present in the muscle (white fibers), brain (astrocytes), and white blood cells transporting lactate and ketone bodies.[5] Although MCT1 is ubiquitous, in the skeletal muscle is predominant in the oxidative fibers and the transport direction depends on the metabolic situation of the cell.[6] On the other hand, MCT4 is predominant in the glycolytic fibers of the muscles and is specialized in lactate efflux.[6] MCT4 has a low affinity for pyruvate (MCT4 *Km* for pyruvate is 153 mM) to avoid efflux out of the cell.[3] This is because active white skeletal muscles cells require the conversion of pyruvate to lactate to regenerate cytosolic NADH from NAD^+ to produce energy. At the same time, the low affinity of MCT4 for lactate (MCT4 *Km* for lactate is 28 mM) results in its accumulation inside the cell. This prevents large amounts of H^+ from being expelled out of the cell, which would lower the blood pH and have disastrous consequences.[3] According to the lactate shuttle theory, in high-glycolytic environments (like glycolytic tumor cells or muscle fibers) lactate and protons are released from these glycolytic cells by MCT4.[3,7] Once lactate and protons are out of the cell, they travel through plasma or into erythrocytes. The transport of lactate and protons between plasma and erythrocytes is mediated mainly by MCT1.[8] MCT1 protein is highly expressed in sarcolemma and mitochondrial membranes of type I and type IIA fibers and other oxidative cells and plays a role in cellular lactate uptake and oxidative disposal.[7] These complementary functions between the two transporters play an important role in many scenarios in which the role of lactate is relevant, like intermediary metabolism,[9] glucose homeostasis,[10] or cancer.[7] In fact, the consequences of the partial invalidation of MCT1 have been already described in a knocking mouse for the *SLC16A1*, leading to paramount changes in body composition and energy regulation.[11]

MCT1 and MCT4 protein content seems to be modified in some situations. In some conditions, such as cancer, an overexpression of MCT1 and MCT4 occurs due to the high glycolytic activity of tumor cells (Warburg effect).[12] Additionally, obese patients have a higher MCT4 protein content in the muscles and, interestingly, this content was reduced following weight loss. The higher MCT4 protein content of the muscle in obesity could reflect the need to release greater amounts of lactate from these fibers characterized by a greater dependence on glycolytic metabolism due to the low capillarization causing hypoxia.[13] In fact, hypoxia itself seems to increase *SLC16A3* mRNA mediated by hypoxia-inducible factor 1α (HIF-1 α).[12] In addition to being modified in various diseases, MCTs content may also be modified with training status, being reported a higher MCT1 protein content in well-trained subjects compared to less trained subjects.[14]

It is suggested that exercise would modify MCT1/MCT4 protein levels or *SLC16A1/SLC16A3* mRNA in the muscle. In the literature, there is a wide variety of exercise protocols studied. However, it is well known that the management of the exercise variables will modify the physiological response. Thereby, it would be useful to know in more detail the effect of exercise and its characteristics (such as intensity and duration) on these transporters, to determine which stimulus will provide the most benefit. MCT1 and MCT4 are the most studies related to exercise due to their localization in the muscles and their effect on co-transporting lactate and protons.[6] It is very common to develop this type of studies in rodents, and therefore it is necessary to check if the results in rodents are in line with the results in humans.

There is only one review explaining the effect of exercise on MCT1/MCT4 protein levels or *SLC16A1/SLC16A3*

mRNA[15] carried out several years ago. This study was not a systematic review, and many studies have been published since then. In addition, this previous study did not compare the results in humans with those in animals to see whether the two models provide aligned results. Hence, given the importance of MCT1 and MCT4 in metabolism, exercise physiology, and health, it is necessary to bring together all these findings to get a clear picture of how exercise and its characteristics affect the two main muscle MCTs. Therefore, the aim of this study was to know the effect of exercise considering exercise intensity and duration of the intervention (single session vs. training program) on *SLC16A1* and *SLC16A3* mRNA and MCT1 and MCT4 protein levels in the skeletal muscle, in humans and rodents. The second objective is to observe whether the results of the animal studies follow the same pattern as the human studies. The final aim is to point out methodological aspects of the included studies that deserve to be improved in future studies.

2 | RESULTS

2.1 | Study selection

The initial search identified 1476 articles from the database. After removing duplicates, 1108 manuscripts were screened for eligibility based on their title and abstract. From these, 983 records were excluded after a review of the title and/or abstract, leaving 125 articles remaining. Eighteen additional articles were identified from other sources for eligibility. Also, four additional articles were found for eligibility in the last update. A total of 147 were assessed as full texts, excluding 106 articles based on the exclusion criteria. The flow diagram of the selection criteria is shown in Figure 1. This qualitative analysis review includes 41 studies: 18 articles with a human sample and 23 with samples in rodents. The results of the studies in rodents will be analyzed to compare them with the results in humans to know if the rodent model is useful to infer the human model. In addition, some methodological aspects of the human's studies will be analyzed with the intention to improve future studies on this topic. The main characteristics of the included studies are presented in Tables 1–11. Due to the large variation in study design and outcomes, quantitative analysis was not deemed appropriate and, therefore, the results have been presented in a narrative form.

2.2 | Risks of bias

The risk of bias assessment of each study is presented in Supplementary Table S1. The mean score on the Risk of Bias was 2.77 out of a possible 7 points (range 0–4). This score is explained because: (a) Eight studies were evaluated with a high risk of bias of random sequence generation bias because the study only included one group (exercise group); (b) eight studies were evaluated with a high risk of allocation concealment bias because only included one group; (c) 17 studies were classified as a high risk of blinding participant and personnel bias because exercise intervention cannot be blinded to the participant; (d) 15 studies were evaluated with a high risk of incomplete outcome data bias, one of them reported the data in a graph with an exponential axis making it difficult to extract the data and 14 of them reported the data without a measure of dispersion in the values before exercise.

2.3 | Characteristics of the sample and exercise

All the studies investigating exercise effect on MCT1/MCT4 protein levels or *SLC16A1*/*SLC16A3* mRNA ($n=41$) included a total of 201 humans (10% women) aged between 19 and 62 years, and a total of 572 rodents (no sex specification).

The modulation of high-intensity exercise response on protein levels or *SLC16A1*/*SLC16A3* mRNA comprised of 119 humans (22% women) ($n=12$), and 16 rodents (no sex specification) ($n=2$). The duration of interventions used in human studies was a single session ($n=4$) or a program training ($n=10$), whereas the rodent studies were a single session ($n=1$), or a program exercise ($n=1$).

The studies examining the changes in MCT1/MCT4 protein levels or *SLC16A1*/*SLC16A3* mRNA after low-/moderate-intensity exercise included 30 human volunteers (0% women) ($n=4$) and 379 rodents (no sex specification) ($n=15$). The duration of interventions used in human studies was a single session ($n=1$) or a training program ($n=3$), whereas the rodent studies were a single session ($n=6$), or a training program ($n=9$).

In addition, several studies investigated the effect of other types of exercise on MCT1/MCT4 protein levels or *SLC16A1*/*SLC16A3* mRNA in humans, such as the combination of high- and low-/moderate-intensity exercise in 24 participants ($n=2$) or resistance exercise in 34 humans ($n=1$). In both cases, intervention was conducted as a training program over several weeks. In rodents, the other types of exercise used were electrostimulation in 78 rodents ($n=4$), voluntary physical exercise in 114 rodents ($n=2$) and a combination of low-/moderate-exercise intensity and low physical activity in 40 rodents ($n=1$). These interventions were carried out as a training program except one that was carried out in a single session.

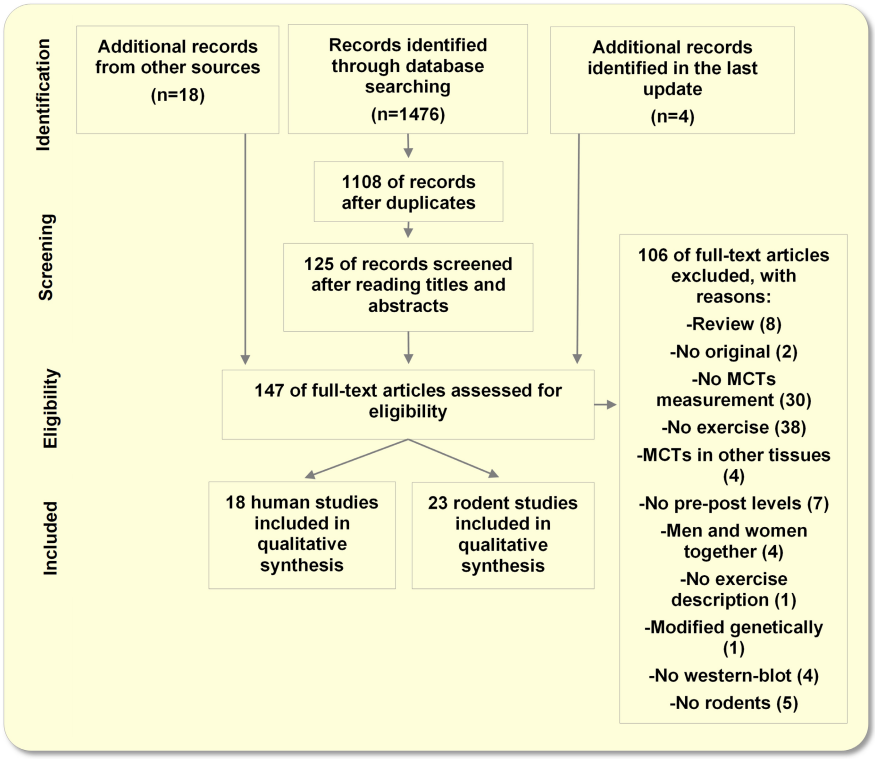

FIGURE 1 Flowchart showing screening process and search results.

2.4 | Characteristics of the study design in human studies

Methodological characteristics of the studies will be reported only for human studies since studies in rodents were used only to observe if their results are in line with human studies. In addition, several methodological differences exist between studies in humans and rodents making impossible to compare them in this aspect. Only five studies included a control group,[21,25–27,48] while the remaining studies were designed with only the experimental group. Control groups among studies were heterogeneous: one study did not extracted a biopsy of the control group[21]; one study trained one leg and used the untrained leg as a control[26]; in one study the experimental and the control group developed an exercise intervention[25]; in another study the experimental group trained in hypoxia and the control group trained without hypoxia, which was used to extract the data[48]; and the control group in one study continued the training as during the period before the study.[27]

2.5 | Characteristics of the biopsy and the measurement of *SLC16A1*/*SLC16A3* mRNA and MCT1/MCT4 protein levels in humans

In humans, all the studies extracted a homogenized sample from the vastus lateralis,[16,17,19–22,24–28,35–38,48] except one study in which the sample origin was not specified.[51] The amount of tissue extracted in the biopsies varied among studies, from 4 to 5 mg dry wt until 150 mg, being the most common 30 mg. More specifically, the amounts extracted in each study were as follows: 4–5 mg dry wt,[27] 10–50 mg,[26] 20 mg,[38] 20–50 mg,[25] 25 mg,[16,17] 30 mg,[19,22–24,51] 30–40 mg,[35] 40 mg,[20] 40–150 mg,[37] 50 mg,[36] 50–80 mg[28] and two studies did not specify the amount of tissue.[21,48] The timing of the biopsy after exercise was highly heterogeneous varying from immediately post exercise until a week after training (Tables 1–11) and it was not clearly specified in four studies.[22,27,28,37]

SLC16A1/*SLC16A3* mRNA was measured with real-time PCR in all the studies.[16,17,48] The control used as a standard was GAPDH,[17] cyclophilin,[48] and β-actin.[16] On the other hand, to measure MCT1/MCT4 protein levels, all the studies included carried out a western blot. The control used as a standard was bovine serum albumin in most of the studies[16,19,20,22–25,27,28,35,37,48,51]; one study used GAPDH,[38] and three studies did not specify the control used.[21,26,36]

SLC16A1/*SLC16A3* mRNA after exercise were expressed relative to mRNA before exercise in two studies[16,17] and relative to cyclophilin proteins in one study.[48] On the other hand, MCT1/MCT4 protein levels after exercise were expressed relative to bovine serum albumin standard in five studies,[19,23,24,48,51] relative to protein levels before exercise in most studies,[16,20–22,25,27,28,35,36,38] relative to the control group in one study[26] and relative to RBC membranes proteins in one study.[37]

TABLE 1 Effect of high-intensity exercise on SLC16A1 and SLC16A3 (MCT1 and MCT4 genes) mRNA expression in humans.

	Study	*N* (women)	Duration	Exercise	Biopsy after exercise	SLC16A1 mRNA		SLC16A3 mRNA	
						PRE	POST	PRE	POST
Single-session intervention	Bickham (2006)[16]	7	Single session	HIE before 6 wks of training (Running: 110% VO2max until exhaustion)	2 h	0.99	0.77 ± 0.34	0.99	0.76 ± 0.9
			Single session	HIE after 6 wks of training (Running: 110% VO2max until exhaustion)	2 h	0.45 ± 0.24	0.58 ± 0.19	0.36 ± 0.36	0.55 ± 0.17
	Nordsborg (2003)[17]	6	Single session	HIE before 5.5 wks of training (Leg extension: 15 × 60 s at 150% VO2max; Rest: 180 s)	0 h	1	1.5 ± 3.8	1	1.8 ± 8.7
					1 h		1.1 ± 4.41		2.2 ± 58.79
					3 h		1.5 ± 2.33		1.5 ± 3.18
					5 h		1.5 ± 1.84		2 ± 5.27
					24 h		0.9 ± 2.82		1.3 ± 3.55
			Single session	HIE after 5.5 wks of training (Leg extension: 15 × 60 s at 150% VO2max; Rest: 180 s)	0 h	1.1 ± 1.59	1 ± 2.57	1.5 ± 2.94	1.8 ± 7.23
					3 h		0.8 ± 1.59		1.3 ± 5.27
Training program intervention	Bickham (2006)[16]	7	6 wks	HIE (Running: 3 s/wk; 4 × (14–30 × 40-100 m; Density: 1:5/3); Rest: 5 min)	48 h	1	**0.24 ± 0.24↓**	1	**0.36 ± 0.36↓**
	Nordsborg (2003)[17]	6	5.5 wks	HIE (Leg extension: 4.2 s/wk; 15 × 60 s at 150% VO2max; Rest: 180 s)	2 h	1	1.1 ± 1.59	1	1.5 ± 2.94

Note: ↓, significant decrease compared to Pre. The values highlighted in bold are of the studies that found differences.

Abbreviations: d, days; HIE, high-intensity exercise; s/wks, sessions/week; wk, week.

TABLE 2 Effect of high-intensity exercise on SLC16A1 and SLC16A3 (MCT1 and MCT4 genes) mRNA expression in rodents.

	Study	*N* per group	Animal	Duration	Exercise	Muscle region	Biopsy after exercise	SLC16A1 mRNA	SLC16A3 mRNA
Single-session intervention	Takimoto (2013)[18]	6	Sprague–Dawley rats	Single session	Control	Epitrochlearis and triceps		0.98 ± 0.23	0.99 ± 0.33
					HIE (swimming: 15 × 20 s 18% body weight)		5 h	**2.04 ± 0.46↑**	1 ± 0.21
							18 h	1.4 ± 0.61	**1.47 ± 0.09↑**

Note: ↑, significant increase compared to the control group. The values highlighted in bold are of the studies that found differences.
Abbreviation: HIE, high-intensity exercise.

2.6 | Reported findings on the effect of high-intensity exercise on *SLC16A1*/*SLC16A3* mRNA and MCT1/MCT4 protein levels

Two studies examined the effect of a single high-intensity session on mRNA in men[16,17] (Table 1). Although they used different types of exercise (leg extension vs. running), none of them reported changes in expression in any of the genes (*SLC16A1* and *SLC16A3)*. In contrast, when a high-intensity ≈6-week intervention is applied in men the results are not conclusive: Bickham et al.[16] observed a decrease in mRNA of both *SLC16A1* and *SLC16A3* using exercise to exhaustion, while Nordsborg et al.[17] found no change with an interval leg-extension exercise training (Table 1). Studies in rodents with high-intensity exercise are scarce, with only one study using a single session as an intervention.[18] They reported increases in the intervention compared to the control group at 5 h for *SLC16A1* mRNA and at 18 h for *SLC16A3* mRNA[18] (Table 2). To date, we have not found any study that analyzes the expression of mRNA after implementing a high-intensity training program in rodents.

The results of protein level changes after a single session of high-intensity training point to different responsiveness of MCT1 compared to MCT4. In men, increases in both proteins have been reported after high-intensity interval training at 79% of the maximal power.[19] However, a higher MCT1 protein content and no changes in MCT4 protein content were reported when the exercise was performed until exhaustion.[16] On the contrary, the only study that included exclusively women in its sample reported a decrease in the levels of both transporters after a high-intensity session[20] (Table 3). If the exercise stimulus is a training program instead of only one session it appears to produce an increase in the level of MCT1, MCT4, or both proteins (7 out of 9 studies observed increases).[16,21–26] MCT1 seems to be slightly more responsive than MCT4, as in four studies[22–25] MCT1 protein levels increase at more time points compared to MCT4. Of the remaining five studies, one found MCT4 protein increases in more timepoints,[21] two found similar increments in both transporters,[16,26] and the other two found no changes for these proteins.[27,28] Again, one of the studies finding no difference is the one carried out by Bishop et al.,[28] where the sample was composed only of women(Table 3). The only study with rodents using a high-intensity training program reported increments for both MCT1 and MCT4 protein contents, 48 h after 6 weeks of training when red gastrocnemius was analyzed, but only for MCT4 when white gastrocnemius was analyzed[29] (Table 4).

TABLE 3 Effect of high-intensity exercise on MCT1 and MCT4 protein content in humans.

	First author	*N* (women)	Duration	Exercise	Biopsy after exercise	MCT1 protein content		MCT4 protein content	
						PRE	POST	PRE	POST
Single-session intervention	McGinley (2016a)[19]	16	Single session	HIE (Cycling: 7 × 120 s at 79% maximal power; Rest: 120 s)	0 h	0.65 ± 0.5	**1.19 ± 0.32↑**	0.81 ± 0.77	**1.00 ± 0.69↑**
					3 h		**1.23 ± 1.4↑**		**1.05 ± 0.88↑**
					9 h		**1.19 ± 1.36↑**		**0.99 ± 0.62↑**
					24 h		**1.52 ± 1.65↑**		**1.05 ± 1↑**
					48 h		**1.56 ± 1.65↑**		**1.05 ± 0.85↑**
					72 h		**1.56 ± 2.48↑**		**1.13 ± 1.35↑**
	Bickham (2006)[16]	7	Single session	HIE before 6 wks of training (Running: 110% VO2max until exhaustion)	2 h	1	**1.5 ± 0.5↑**	1	1.1 ± 0.2
			Single session	HIE after 6 wks of training (Running: 110% VO2max until exhaustion)	2 h	1.52 ± 0.24	1.74 ± 0.84	1.1 ± 0.18	1.23 ± 0.3
	Bishop (2007)[20]	6 (6)	Single session	HIE (Cycling: 45 s at 200% power output at VO2peak)	Immediately after	100	**75.94 ± 6.20↓**	100	**74.08 ± 7.5↓**
Training program intervention	Bickham (2006)[16]	7	6 wks	HIE (Running: 3 s/wk; 4 × (14–30 × 40-100 m; Density: 1:5/3); Rest: 5 min)	48 h	1	**1.52 ± 0.24↑**	1	**1.09 ± 0.18↑**
	Burgomaster (2007)[21]	8	1 wks	HIE (Cycling: 3 s/wk; 4–6 × 30 s; Rest: 240 s)	~72 h	100	157.65 ± 53.67	100	**139.40 ± 26.23↑**
			6 wks				**226.42 ± 162.68↑**		**153.81 ± 39.61↑**
	Juel (2004)[22]	6	2 wks	HIE (Leg extension: 3–5 s/wk; 15 × 60 s at 150% VO2max; Rest: 180 s)	N.S.	100	108 ± 10	100	98 ± 9
			4 wks				138 ± 19		112 ± 7
			7 to 8 wks				**115 ± 5↑**		111 ± 11
	McGinley (2016b)[23]	8	2 wks	HIE (Cycling: 3 s/wk; 5–15 × 120 s at 71% peak power; Rest: 60s)	2–3 days	0,7	**0.87↑**	1.07	1.08
			4 wks		3 days		**1.75↑**		**1.5↑**
		8	2 wks	HIE (Cycling: 3 s/wk; 4–10 × 120 s at 98% peak power; Rest: 60)	2–3 days	0,7	**0.75↑**	1.13	1.19
			4 wks		3 days		**1.43↑**		1.19
	McGinley (2017)[24]	7(7)	4 wks	HIE (Cycling: 3 s/wk; 4–10 × 30 s 121%–186% peak power; Rest: 60s)	3 Days	1.05	**1.25↑**	1.03	1.04
			10 wks				**1.40↑**		0.86
		7(7)	4 wks	HIE (Cycling: 3 s/wk; 4–10 × 30 s 121%–186% peak power; Rest: 300 s)		1.24	**1.15↑**	1.04	1.02
			10 wks				**1.40↑**		0.78
	Mohr (2007)[25]	6	8 wks	HIE (Running: 3–6 s/wk; 15 × 6 s at 95% max speed; Rest: 60s)	End of the test	0	**29.96 ± 22.88↑**	0	10.31 ± 25.26
		7	8 wks	HIE (Running: 3–6 s/wk; 8 × 30 s at 130% VO2max; Rest: 90s)		0	**28.21 ± 33.46↑**	0	12.45 ± 25.22
	Pilegaard (1999)[26]	4	8 wks	Control			100		100
				HIE (Leg extension: 3–5 × 30–60 s at 50–120 N; Rest: 120 s)	48 h		**170 ± 64↑***		**133 ± 20↑***
	Bangsbo (2009)[27]	5	6 to 9 wks	Control		100	95 ± 223.61	100	86 ± 44.72
		8 to 12		HIE (Running: 3–4 s/wk; 8–12 × 30 s at 95% max speed; Rest: 180 s)	N.S.	100	98 ± 37.95	100	90 ± 88.54
	Bishop (2008)[28]	6(6)	5 wks	HIE (Cycling: 3 s/wk; 6–12 × 120 s at 100% VO2max: Rest: 60s)	0 s or 60 s	100	96 ± 12	100	119 ± 21

Note: ↑, significant increase compared to Pre; ↓, significant decrease compared to Pre; ↑*, significant increase compared to control. The values highlighted in bold are of the studies that found differences.

Abbreviations: HIE, high-intensity exercise; N.S., not specified; s/wk, sessions per week; Wks, weeks.

TABLE 4 Effect of high-intensity exercise on MCT1 and MCT4 protein content in rodents.

	Study	*N* per group	Animal	Duration	Exercise	Muscle region	Biopsy after exercise	MCT1 protein content	MCT4 protein content
Training program intervention	Horii (2017)[29]	10	Sprague–Dawley rats	6 wks	Control	Red gastrocnemius		1.01 ± 1.42	0.98 ± 0.49
					HIE (Swimming: 4 s/wk; 14 × 20 s with 16% body weight; Rest: 10s)		48 h	**1.68 ± 0.89↑**	**1.24 ± 0.87↑**
					Control	White gastrocnemius		0.66 ± 0.42	1.26 ± 0.74
					HIE (Swimming: 4 s/wk; 14 × 20 s with 16% body weight; Rest: 10s)		48 h	0.76 ± 0.36	**1.61 ± 0.68↑**

Note: ↑, significant increase compared to the control group. The values highlighted in bold are of the studies that found differences.

Abbreviations: HIE, high-intensity exercise; s/wk, sessions per week; wks, weeks.

2.7 | Reported findings on the effect of low-/moderate-intensity exercise on *SLC16A1*/*SLC16A3* mRNA and MCT1/MCT4 protein levels

No studies investigating the effect of low/moderate intensity on mRNA in humans were included in the present review. In rodents, the use of low/moderate intensity has been more common than high-intensity exercise, observing an increase in *SLC16A1* mRNA at some point in most cases,[18,30–33] except one study.[34] Of the nine exercise sessions (applied by the six studies), five of them produced increases in *SLC16A1* mRNA, and four produced increases in *SLC16A3*. Interestingly, the two studies carrying out a training intervention reported different results depending on fiber composition: an increase in *SLC16A1* mRNA while a decrease in *SLC16A3* mRNA in an oxidative muscle (red gastrocnemius) when compared with the control group[33]; and a rise of *SLC16A3* mRNA plus a reduction of *SLC16A1* mRNA in a glycolytic muscle (white gastrocnemius) when compared with baseline[34] (Table 5).

The effect of low-/moderate-intensity exercise on protein levels in humans has been only studied in men. Only Green et al. investigated the effect of a single session, reporting increases for both proteins after 2, 4, and 6 days of a 5–6 h cycling session at 60% VO2peak[35] (Table 6). The results after a training program showed that MCT1 appeared to be more affected than MCT4 since two of the three studies observed increments only in MCT1 protein content with respect to baseline values.[36,37] The third study observed increases in MCT4, but not in MCT1, compared to baseline values.[38] This is the only one of the three works whose sample is composed of cyclists with extensive training experience (Table 6). In rodents, three studies used what we can consider single-session interventions with low/moderate intensity. One found an increase after 2 h of exercise consisting of 30 min exercise flowed by 30 mi rest, another found no changes in MCT1 levels[39] after running 30 min, whereas Kim et al[40] included exercise until fatigue and reported increases in levels of both proteins in similar quantities: almost doubling its presence after the session (Table 7). For multiple-sessions interventions, similar results as those seen in men were observed in rodents for MCT1 protein content since five of nine training programs found increments when compared with the control group.[33,41–44] Although the percentage of positive results is not as high as in men, for MCT1 the significant results are all positive (increments in MCT1 protein content) and therefore more homogeneous than for MCT4 protein content. Considering the studies investigating MCT4 protein changes after a low-/moderate-intensity training program, three of seven training programs reported a decrease at some point,[33,45,46] two of them increases[42,44] and two found

TABLE 5 Effect of low-/moderate-intensity exercise on SLC16A1 and SLC16A3 (MCT1 and MCT4 genes) mRNA expression in rodents.

	Study	*N* per group	Animal	Duration	Exercise	Muscle region	Biopsy after exercise	SLC16A1 mRNA	SLC16A3 mRNA
Single-session intervention	Coles (2004)[30]	3 to 13	Sprague–Dawley rats	Single session	Baseline	Red gastrocnemius		100	100
					LMIE (running: 30 min of exercise followed by 30 min rest until 2-h of exercise at 21 m/min 15% grade)		0	**154.01↑***	120.92 ± 23.53
							5 h	**167.61 ± 12.28↑***	120.33 ± 74.72
							10 h	**167.02 ± 14.32↑***	**240.89 ± 43↑***
							24 h	**209.57 ± 75.74↑***	**159.92 ± 44.02↑***
					Baseline	White gastrocnemius		100	100
					LMIE (running: 30 min of exercise followed by 30 min rest until 2-h of exercise at 21 m/min 15% grade)		0	**197.75 ± 25.58↑***	84.27
							5 h	134.51 ± 29.68	87.82 ± 20.47
							10 h	142.19 ± 23.55	86.64 ± 24.56
							24 h	**250.94 ± 39.92↑***	116.19 ± 16.38
	de Araujo (2015)[31]	5	C57BL/6J mice	Single session	Control	Red gastrocnemius		1.15 ± 0.19	0.94 ± 0.1
					LMIE (swimming: 25 min at 100% maximal lactate steady state)		Immediately	1.03 ± 0.14	0.89 ± 0.14
							5 h	1.04 ± 0.28	0.96 ± 0.18
							10 h	0.97 ± 0.05	0.88 ± 0.04
					Control	White gastrocnemius		0.35 ± 0.09	0.7 ± 0.19
					LMIE (swimming: 25 min at 100% maximal lactate steady state)		Immediately	**0.62 ± 0.13↑**	0.69 ± 0.19
							5 h	0.23 ± 0.05	0.46 ± 0.16
							10 h	0.24 ± 0.05	0.62 ± 0.175
					Control	Soleus		0.36 ± 0.18	0.52 ± 0.14
					LMIE (swimming: 25 min at 100% maximal lactate steady state)		Immediately	**1.09 ± 0.06↑**	**0.95 ± 0.09↑**
							5 h	**1.18 ± 0.19↑**	0.47 ± 0.07
							10 h	**1.2 ± 0.22↑**	**0.82 ± 0.17↑**

TABLE 5 Continued

Study	*N* per group	Animal	Duration	Exercise	Muscle region	Biopsy after exercise	SLC16A1 mRNA	SLC16A3 mRNA
Forte (2022)[32]	10	Wistar rat	Single session	Control	Gastrocnemius		100 ± 28.28	99.74 ± 38.04
				LMIE (swimming: 37.5 min at 80% of the anaerobic threshold)		4 h	120.32 ± 25.71	115.78 ± 52.31
				LMIE (swimming: 33.3 min at 90% of the anaerobic threshold)			**202.43 ± 133.69↑**	121.8 ± 88.77
				LMIE (swimming: 30 min at 100% of the anaerobic threshold)			160.97 ± 69.41	130.82 ± 53.89
				LMIE (swimming: 27.3 min at 110% of the anaerobic threshold)			186.17 ± 53.99	130.82 ± 31.70
				LMIE (swimming: 25 min at 120% of the anaerobic threshold)			156.91 ± 51.42	119.79 ± 28.53
				Control	Soleus		99.45 ± 32.22	97.29 ± 30.77
				LMIE (swimming: 37.5 min at 80% of the anaerobic threshold)		4 h	97.41 ± 15.46	107.02 ± 112.82
				LMIE (swimming: 33.3 min at 90% of the anaerobic threshold)			96.6 ± 58	237.83 ± 280.33
				LMIE (swimming: 30 min at 100% of the anaerobic threshold)			90.89 ± 20.62	89.72 ± 44.44
				LMIE (swimming: 27.3 min at 110% of the anaerobic threshold)			113.31 ± 25.77	74.59 ± 44.44
				LMIE (swimming: 25 min at 120% of the anaerobic threshold)			100.27 ± 30.93	127.56 ± 88.88
Takimoto (2013)[18]	6	Sprague–Dawley rats	Single session	Control	Epitrochlearis and triceps		0.96 ± 0.3	1.01 ± 0.19
				LMIE (swimming: 6 h in two 3-h sessions separated by 45 min of rest)		5 h	**3 ± 1.94↑**	**1.83 ± 0.44↑**
						18 h	1.56 ± 0.8	1.29 ± 0.37

TABLE 5 Continued

	Study	*N* per group	Animal	Duration	Exercise	Muscle region	Biopsy after exercise	SLC16A1 mRNA	SLC16A3 mRNA
Training program intervention	Saxena (2016)[33]	8	Sprague–Dawley rats	2 wks	Control	Red gastrocnemius		809.08 ± 66.72	4145.5 ± 266.91
					LMIE (Swimming: 6 s/wk; 60 min)		1 day	**7089.89 ± 375.34↑**	**2577.38 ± 158.48↓**
	Scariot (2016)[34]	7 to 10	Wistar rats	Wk 0		White gastrocnemius		100.23 ± 84.11	101.41 ± 31.91
				12 wks	Control			**25.93 ± 10.51↓***	**169.5 ± 31.91↑***
					LMIE (Swimming: 7 s/wk; 40 min at 80% of the anaerobic threshold)		48 h	**34.34 ± 14.71↓***	**185.1 ± 29.78↑***
				Wk 0		Soleus		99.74 ± 111.08	99.22 ± 23.25
				12 wks	Control			152.64 ± 34	71.31 ± 32.55
					LMIE (Swimming: 7 s/wk; 40 min at 80% of the anaerobic threshold)		48 h	189.67 ± 34↑	113.17 ± 51.16

Note: ↑, Significant increase compared to control group; ↓, Significant decrease compared to control group; ↑*, Significant increase compared to baseline; ↓*, Significant decrease compared to baseline. The values highlighted in bold are of the studies that found differences.

Abbreviations: LMIE, low-/moderate-intensity exercise; s/wks, sessions per week; wks, weeks.

no differences[43,47] in all cases compared to control groups (Table 7).

2.8 | Reported findings on the effect of other types of exercise on *SLC16A1*/*SLC16A3* mRNA and MCT1/MCT4 protein levels

This section includes all the studies that use exercise programs that either combine high and moderate intensity, use a strength training protocol (or electrostimulation in the case of rodents), or are programs that cannot be classified in the previous sections. We will try to present the results in a clustered manner, grouping those programs that are similar to each other.

In humans, not many studies investigate the MCT1/MCT4 proteins or *SLC16A1*/*SLC16A3* mRNA responses using other exercises apart from high-intensity or low-/medium-intensity exercises, and all of them use a training program as intervention (no single-session studies). Two of them employed exercise combining high-intensity with low-/medium-intensity exercise, either by merging them in the same session[48] or alternating sessions of each intensity throughout the week.[38] No changes in mRNA or protein content were seen after training program intervention merging both intensities.[48] Only an increase in MCT4 protein levels was reported by Neal et al[38] after a 6 weeks program of polarized training in experienced male cyclists (Table 8–10). The third study applied a 6-week lower limb strength training program in healthy and diabetic older (61–62 years old) men.[51] This intervention resulted in an increase in the levels of both MCT1 and MCT4 protein transporters in the healthy participants, whereas it caused an increase only in MCT1 protein levels in type 2 diabetes participants, in both cases compared to control groups[51] (Table 10).

Four studies investigated the effect of electrostimulation in rodents.[49,52–54] For single-session interventions, we only have the results reported by Tonouchi et al (2002), with MCT1 and MCT4 protein levels decreasing after the session, compared to control groups (Table 11). For longer interventions, either with separate sessions of chronic muscle stimulation (i.e., 24 h/day), results indicate increases in *SLC16A1* mRNA on white and red muscles, as well as a transient decrease in *SLC16A3* mRNA also for both types of muscle (white and red). These lowered mRNA values came back to control levels after 3 weeks of intervention[49] (Table 9). For protein levels, electrostimulation program interventions resulted in increments of MCT1 protein levels in two studies[49,53] and no differences with control in only one study.[54] For MCT4 protein levels,

TABLE 6 Effect of low/moderate-intensity exercise on MCT1 and MCT4 protein content in humans.

	Study	*N* (women)	Duration	Exercise	Biopsy after exercise	MCT1 protein content		MCT4 protein content	
						PRE	POST	PRE	POST
Single-session intervention	Green (2002)[35]	8	Single session	LMIE (Cycling: 300–360 min at 60%VO2max)	2 days	100	**121 ± 17.54**↑	100	**120 ± 23.48**↑
					4 days		**143 ± 31.11**↑		**137 ± 39.6**↑
					6 days		**114 ± 26.30**↑		**114 ± 27.72**↑
Training program intervention	Bonen (1998)[36]	7	1 wk	LMIE (Cycling: 7 s/wk; 120 min at 65% VO2max)	1 day	100	**117.87 ± 23.17**↑		
	Dubouchaud (2000)[37]	9	9 wks	LMIE (Cycling: 6 s/wk; 50–60 min at HR corresponding to 75% VO2peak	N.S.	6.86 ± 1.81	**13.17 ± 2.36**↑	5.12 ± 3.15	7.21 ± 5.43
	Neal (2013)[38]	6	6 wks	LMIE (Cycling: 5–6 s/wk; 60 min at power output half-way between the LT and the LTP [3 s/wk]; ≈240 min/wk < lactate threshold)	Week after training	100	110 ± 13	100	**180 ± 41**↑

Note: ↑, Significant increase compared to PRE. The values highlighted in bold are of the studies that found differences.

Abbreviations: LMIE, low-/moderate-intensity exercise; N.S., not specified; s/wk, sessions per week; wk, week.

results are scarce and inconclusive, finding increases in one study[54] and no changes in the other[49] (Table 11).

Finally, studies applying a voluntary running program (i.e., exercise ad libitum) found increases in *SLC16A1* mRNA in gastrocnemius[50] (Table 9) and MCT1 protein levels in plantaris and anterior tibialis muscles, but only after 6 weeks[55] (Table 11). Moreover, the only study recording the level of physical activity reported no changes in protein levels, of even a decrease in MCT4 protein levels when low physical levels were combined with a low-/moderate-intensity exercise program[56] (Table 11).

3 | DISCUSSION

This study systematically reviews the scientific literature on the impact of exercise on MCT1 and MCT4 protein content and mRNA expression of their respective genes in muscle tissue, to know: (1) the effect of exercise considering its intensity and duration of the intervention (single session vs. training program), (2) including human and rodent studies to observe whether both models provide aligned results, and (3) mentioning the methodological aspects that should be improved in future studies. Our main results are that physical exercise is a stimulus that modifies protein levels in skeletal muscle in humans. Concretely, MCT1 protein content increases both after a single exercise session and after a training program in humans. Increases in MCT4 protein content can be observed after a training program in humans. Protein content responsiveness is higher for MCT1 than for MCT4, and most of the results indicate the same tendency regardless of exercise characteristics. However, it still remains to be better defined what responses occur with each intensity and duration. On the other hand, the effect of exercise on mRNA results is less defined, and more research is needed in this aspect in humans. In this line, the present review has pointed out that this new research should be developed with more robust designs and higher levels of clinical evidence since high-quality studies in this area are sparse. Moreover, results in animals only agree with humans' results on the observed increase in MCT1 levels after a training program.

3.1 | Effect of the methodological characteristics of human studies in the results and future methodological considerations

After performing the systematic review and reading the included studies in depth, we have observed methodological and design weaknesses, some of which have made

TABLE 7 Effect of low-/moderate-intensity exercise on MCT1 and MCT4 protein content in animals.

	Study	*N* per group	Animal	Duration	Exercise	Muscle region	Biopsy after exercise	MCT1 protein content	MCT4 protein content
Single-session intervention	Coles (2004)[30]	3 to 13	Sprague–Dawley rats	Single session	Baseline	Soleus		100	100
					LMIE (running: 30 min of exercise followed by 30 min rest until 2-h of exercise at 21 m/min 15% grade)		0	122.48 ± 44.48	**198.97 ± 68.09↑***
							5 h	137.91 ± 35.92	**332.53 ± 188.58↑***
							10 h	**178.18 ± 22.23↑***	**422.94 ± 172.88↑***
							24 h	**154.69 ± 41.04↑***	**325.34 ± 133.56↑***
					Baseline	Red gastrocnemius		100	100
					LMIE (running: 30 min of exercise followed by 30 min rest until 2-h of exercise at 21 m/min 15% grade)		0	**161.4 ± 58.17↑***	**142.46↑***
							5 h	**250 ± 171.09↑***	**198.97 ± 62.87↑***
							10 h	**258.05 ± 68.42↑***	**231.84 ± 34.06↑***
							24 h	118.45 ± 63.30	**207.19 ± 62.84↑***
					Baseline	White gastrocnemius		100	100
					LMIE (running: 30 min of exercise followed by 30 min rest until 2-h of exercise at 21 m/min 15% grade)		0	**154.69 ± 42.78↑***	107.53
							5 h	**276.84 ± 41.07↑***	96.23
							10 h	**293.62 ± 87.26↑***	109.58
							24 h	**201 ± 53.05↑***	109.58
	Eydoux (2000)[39]	10	Wistar rat	Single session	Baseline	Soleus		52.57 ± 7.63	
					LMIE (Running: 30 min at 25 m/min with 8% grade)		N.S.	55.75 ± 10.04	
					Control	Red tibialis anterior		30.45 ± 6.02	
					LMIE (Running: 30 min at 25 m/min with 8% grade)		N.S.	33.18 ± 6.41	
					Control	White gastrocnemius		11.96 ± 8.04	
					LMIE (Running: 30 min at 25 m/min with 8% grade)		N.S.	10.6 ± 5.22	
	Kim (2019)[40]	10	Sprague–Dawley rats	Single session	Control	Gastrocnemius		1	1
					LMIE (Swimming: 10% body weight until fatigue)		N.S.	**1.82 ± 0.1↑**	**1.87 ± 0.18↑**

TABLE 7 Continued

	Study	*N* per group	Animal	Duration	Exercise	Muscle region	Biopsy after exercise	MCT1 protein content	MCT4 protein content
Training program intervention	Baker (1998)[41]	4 to 5	Sprague–Dawley rats	Control		Soleus		100	
				0 wks	LMIE (Running: 5 s/wk; 60 min at 21 m/min with 8% grade)		N.S.	100.55 ± 23.6	
				1 wks				101.11 ± 4.96	
				2 wks				98.33 ± 14.9	
				3 wks				102.77 ± 16.14	
				Control		Red gastrocnemius		100	
				0 wks	LMIE (Running: 5 s/wk; 60 min at 21 m/min with 8% grade)		N.S.	102.22 ± 26.08	
				1 wks				98.33 ± 9.93	
				2 wks				111.11 ± 13.66	
				3 wks				110.55 ± 14.90	
				Control		Extensor digitorum longus		100	
				0 wks	LMIE (Running: 5 s/wk; 60 min at 21 m/min with 8% grade)		N.S.	99.32 ± 17.32	
				1 wks				91.02 ± 22.27	
				2 wks				105.96 ± 16.08	
				3 wks				104.3 ± 9.89	
				Control		White gastrocnemius		100	
				0 wks	LMIE (Running: 5 s/wk; 60 min at 21 m/min with 8% grade)		N.S.	100.43 ± 16.08	
				1 wks				91.02 ± 24.74	
				2 wks				106.52 ± 13.61	
				3 wks				**112.608↑**	
				Control		Soleus		100	
				0 wks	LMIE (Running: 5 s/wk; 60 min at 31 m/min with 15% grade)		N.S.	100.55 ± 23.6	
				1 wks				**130.55 ± 17.39↑**	
				2 wks				**147.22 ± 9.93↑**	
				3 wks				**171.66 ± 29.81↑**	
				Control		Red gastrocnemius		100	
				0 wks	LMIE (Running: 5 s/wk; 60 min at 31 m/min with 15% grade)		N.S.	102.22 ± 26.08	
				1 wks				**134.44 ± 18.63↑**	
				2 wks				**183.33 ± 19.87↑**	
				3 wks				**197.22 ± 23.6↑**	
				Control		Extensor digitorum longus		100	
				0 wks	LMIE (Running: 5 s/wk; 60 min at 31 m/min with 15% grade)		N.S.	99.32 ± 17.32	
				1 wks				97.66 ± 12.37	
				2 wks				102.09 ± 12.37	
				3 wks				100.43 ± 12.37	
				Control		White gastrocnemius		100	
				0 wks	LMIE (Running: 5 s/wk; 60 min at 31 m/min with 15% grade)		N.S.	100.43 ± 16.08	
				1 wks				98.22 ± 55.68	
				2 wks				98.22 ± 37.12	
				3 wks				103.2 ± 35.88	

TABLE 7 Continued

Study	*N* per group	Animal	Duration	Exercise	Muscle region	Biopsy after exercise	MCT1 protein content	MCT4 protein content
Kim (2011)[42]	8	Goto-Kakizaki rats (diabetes)	6 wks	Control	Soleus		100.38	99.61
				LMIE (Running: 5 s/wk; 50 min at 21 m/min)		N.S.	**137.93 ± 6.5↑**	**142.52 ± 21.67↑**
				Control	Plantaris		100.38	99.61
				LMIE (Running: 5 s/wk; 50 min at 21 m/min)		N.S.	**131.55 ± 6.45↑**	113.3 ± 4.3
Saxena (2016)[33]	8	Sprague–Dawley rats	2 wks	Control	Red gastrocnemius		925.61 ± 52.59	2424.49 ± 126.22
				LMIE (Swimming: 6 s/wk; 60 min)		1 day	**4675.43 ± 378.66↑**	**830.95 ± 47.33↓**
Takahashi (2019)[43]	7 to 9	ICR mice	3 wks	Control	Soleus		0.65 ± 0.17	0.65 ± 0.19
				LMIE (running: 7 s/wk; 60 min at 20 m/min)		24 h	0.68 ± 0.23	0.73 ± 0.23
				Control	Plantaris		0.64 ± 0.11	0.65 ± 0.1
				LMIE (running: 7 s/wk; 60 min at 20 m/min)		24 h	**0.74 ± 0.12↑**	0.62 ± 0.12
Takahashi (2022)[44]	10	Mice	5 wks	Control	Soleus		0.97 ± 0.27	0.97 ± 0.56
				LMIE (Running: 5 s/wk; 60 min at 15–20 m/min)		24 h	0.95 ± 0.26	**1.36 ± 0.6↑**
				Control	Plantaris		0.98 ± 0.26	0.98 ± 0.12
				LMIE (Running: 5 s/wk; 60 min at 15–20 m/min)		24 h	**1.38 ± 4.75↑**	0.97 ± 0.15
Metz (2005)[45]	8	Male Wistar rats	10 wks	Control	Soleus		99.62 ± 27.75	98.8 ± 19.81
		Male Zucker fa/fa rats (insulin resistance)				N.S.	89.66 ± 46.68	57.81 ± 39.63
		Male Zucker fa/fa rats (insulin resistance)		LMIE (Running: 5 s/wk; 60 min at 25 m/min with 5% grade)			108.84 ± 22.29	72.87 ± 22.29
		Male Wistar rats		Control	Red tibialis anterior		99.62 ± 39.11	99.32 ± 32.2
		Male Zucker fa/fa rats (insulin resistance)				N.S.	**62 ± 21.44↓**	**56.23 ± 22.79↓**
		Male Zucker fa/fa rats (insulin resistance)		LMIE (Running: 5 s/wk; 60 min at 25 m/min with 5% grade)			73.01 ± 24.81	**65.51 ± 8.42↓**
		Male Wistar rats		Control	White tibialis anterior		99.77 ± 23.55	98.27 ± 16.84
		Male Zucker fa/fa rats (insulin resistance)				N.S.	**34.2 ± 32.38↓**	**64.29 ± 11.89↓**
		Male Zucker fa/fa rats (insulin resistance)		LMIE (Running: 5 s/wk; 60 min at 25 m/min with 5% grade)			47.43 ± 62.24	**64.29 ± 8.42↓**

TABLE 7 Continued

Study	*N* per group	Animal	Duration	Exercise	Muscle region	Biopsy after exercise	MCT1 protein content	MCT4 protein content
Takeda (2022)[46]	7	C57BL6/J mice	6 wks	Control	Gastrocnemius		0.98 ± 0.4	0.96 ± 0.16
				LMIE (Running: 5 s/wk; 30 min at 20-25 m/min)		24 h	1.01 ± 0.26	**0.82 ± 0.19↓**
				Control	Soleus		0.98 ± 0.27	0.97 ± 0.19
				LMIE (Running: 5 s/wk; 30 min at 20-25 m/min)		24 h	0.85 ± 0.22	**0.79 ± 0.2↓**
				Control	Plantaris		0.98 ± 0.45	0.93 ± 0.28
				LMIE (Running: 5 s/wk; 30 min at 20-25 m/min)		24 h	1.01 ± 0.38	0.83 ± 0.24
Suzuki (2022)[47]	11 to 12	MCH(ICR)/jcl mice	4 wks	Control	Soleus		Percentile 25th:0.83/50th:0.99/75th:1.15	Percentile 25th:0.85/50th:0.89/75th:1.11
				LMIE (Running: 6 s/wk; 75 min at 18 m/min with 5 (π/180) incline increasing 1 m/min every 3 days)		48 h	Percentile 25th:0.88/50th:1.08/75th:1.28	Percentile 25th:0.64/50th:0.75/75th:1.61
				Control	Red gastrocnemius		Percentile 25th:0.56/50th:0.9/75th:1.35	Percentile 25th:0.98/50th:1.02/75th:1.78
				LMIE (Running: 6 s/wk; 75 min at 18 m/min with 5 (π/180) incline increasing 1 m/min every 3 days)		48 h	Percentile 25th:0.53/50th:0.69/75th:0.99	Percentile 25th:0.86/50th:0.87/75th:1.06
				Control	White gastrocnemius		Percentile 25th:1.09/50th:1.33/75th:1.54	Percentile 25th:0.5/50th:0.76/75th:1.45
				LMIE (Running: 6 s/wk; 75 min at 18 m/min with 5 (π/180) incline increasing 1 m/min every 3 days)		48 h	Percentile 25th:1.41/50th:1.61/75th:1.82	Percentile 25th:0.58/50th:0.85/75th:1.58
				Control	Plantaris		Percentile 25th:0.79/50th:0.98/75th:1.22	Percentile 25th:0.75/50th:0.8/75th:1.22
				LMIE (Running: 6 s/wk; 75 min at 18 m/min with 5 (π/180) incline increasing 1 m/min every 3 days)		48 h	Percentile 25th:1.11/50th:1.25/75th:1.35	Percentile 25th:0.83/50th:0.88/75th:1.08

Note: ↑, significant increase compared to control; ↓, significant decrease compared to control; ↑*, significant increase compared to baseline. The values highlighted in bold are of the studies that found differences.
Abbreviations: LMIE, low-/moderate-intensity exercise; N.S., not specified; s/wk, sessions per week; wk, week.

TABLE 8 Effect of other types of exercise on SLC16A1 and SLC16A3 (MCT1 and MCT4 genes) mRNA expression in humans.

	Study	*N* (women)	Duration	Exercise	Biopsy after exercise	SLC16A1 mRNA		SLC16A3 mRNA	
						PRE	POST	PRE	POST
Training program intervention	Millet (2014)[48]	18	3 wk	HIE plus LMIE (Cycling: 5 s/wk; 60 min at 60% VO2peak and 3 × (2 × 120 s at 100% peak power); Rest: 120 s)	Week after training	0.37 ± 0.22	0.72 ± 0.44	0.004 ± 0.007	0.007 ± 0.005

Note: ↓, significant decrease compared to PRE. The values highlighted in bold are of the studies that found differences.

Abbreviations: HIE, high-intensity exercise; LMIE, low-/moderate-intensity exercise; N.S., not specified; s/wk, sessions per week; wk, week.

TABLE 9 Effect of other types of exercise on SLC16A1 and SLC16A3 (MCT1 and MCT4 genes) mRNA expression in rodents.

	Study	*N* per group	Animal	Duration	Exercise	Muscle region	Biopsy after exercise	SLC16A1 mRNA	SLC16A3 mRNA
Training program intervention	Bonen (2000)[49]	3 to 10	Sprague–Dawley rats		Control	Red tibialis anterior		163.2 ± 15.67	164.36 ± 10.68
				1 wks	Electrostimulation (24 h, 10 Hz, 50 μs duration)		N.S.	161.6 ± 8.31	**137.45 ± 11.33↓**
				3 wks				**196.8 ± 36.02↑**	164.36 ± 6.29
					Control	White tibialis anterior		102.4 ± 15.67	165.09 ± 8.9
				1 wks	Electrostimulation (24 h, 10 Hz, 50 μs duration)		N.S.	**136.8 ± 13.85↑**	**143.27 ± 35.27↓**
				3 wks				**116 ± 15.24↑**	164.36 ± 8.81
	Lima (2020)[50]	18	Male Fischer rats	4 wks	Control	Gastrocnemius		0.71 ± 0.16	
					VPE (Running: 8090.45 ± 2203,03 min/4 wks)		48 h	**1.29 ± 0.47↑**	
			Male Fischer rats (hypertension)		Control			0.89 ± 0.12	
					VPE (Running: 8090.45 ± 2203,03 min/4 wks)		48 h	**1.32 ± 0.5↑**	

Note: ↑, significant increase compared to control group; ↓, significant decrease compared to control group; ↑*, significant increase compared to baseline; ↓*, significant decrease compared to baseline. The values highlighted in bold are of the studies that found differences.

Abbreviations: N.S., not specified; s/wk, sessions per week; VPE, voluntary physical exercise; wk, week.

TABLE 10 Effect of other types of exercise on MCT1 and MCT4 protein content in humans.

	Study	*N* (women)	Duration	Exercise	Biopsy after exercise	MCT1 protein content		MCT4 protein content	
						PRE	POST	PRE	POST
Training program intervention	Millet (2014)[48]	18	3 wks	HIE plus LMIE (Cycling: 5 s/w; 60 min at 60% VO2peak and 3 × (2 × 120 s at 100% peak power); Rest: 120 s)	Week after training	2.28 ± 0.62	2.38 ± 0.63	1.55 ± 0.56	1.32 ± 0.61
	Neal (2013)[38]	6	6 wks	HIE and LMIE (Cycling: HIE = 3 s/wk; 6 × 240 s at 5–10% above lactate turnpoint; Rest: 120 s; LMIE = ≈290 min/wk < lactate threshold)	Week after training	100	112 ± 13	100	**233 ± 56↑**
	Juel (2004)[51]	10	6 wks	Control			100 ± 31.61		100 ± 34.98
		10		Strength (Leg press, knee extension, hamstring curl: 3 s/w; 3–4 sets of 10–12 reps at 50%–80% RM; Rest: 90s)	16 h		**149.16 ± 58.13↑***		**132.20 ± 47.53↑***
		7 (Diabetes)		Control			65.52 ± 35.35		93.9 ± 60.03
		7 (Diabetes)		Strength (Leg press, knee extension, hamstring curl: 3 s/w; 3–4 sets of 10–12 reps at 50%–80% RM; Rest: 90s)	16 h		**114.09 ± 43.88↑***		99.66 ± 47.17

Note: ↑, significant increase compared to PRE; ↓, significant decrease compared to PRE; ↑*, significant increase compared to control group; ↓*, significant decrease compared to control group. The values highlighted in bold are of the studies that found differences.

Abbreviations: HIE, high-intensity exercise; LMIE, low-/moderate-intensity exercise; s/w: sessions/week; wk, week.

TABLE 11 Effect of other types of exercise on MCT1 and MCT4 protein content in animals.

	Study	*N* per group	Animal	Duration	Exercise	Muscle region	Biopsy after exercise	MCT1 protein content	MCT4 protein content
Single-session intervention	Tonouchi (2002)[52]	13	Sprague–Dawley rats	Single session	Control	N.S. (muscle giant vesicle)		100	100
					Electrostimulation (2 × 5 (50-60 V, stimulation rate 100 Hz, train delay<0.01 ms, train duration 200 ms, pulse duration 100 μs) interrupted by a 1 min rest)		N.S.	**81.44 ± 22.3↓**	**60.05 ± 26.94↓**
					Control	N.S. (muscle sarcolemma giant vesicle)		100	100
					Electrostimulation (2 × 5 (50-60 V, stimulation rate 100 Hz, train delay<0,01 ms, train duration 200 ms, pulse duration 100 μs) interrupted by a 1 min rest)		N.S.	99.69 ± 8.16	**79.75 ± 12.68↓**
Training program intervention	Bonen (2000)[49]	3 to 10	Sprague–Dawley rats	Control		Red tibialis anterior		460.64 ± 73.44	549.19 ± 113.88
				1 wks	Electrostimulation (24 h, 10 Hz, 50 μs duration)		N.S.	**816.77 ± 174.32↑**	522.18 ± 31.18
				3 wks				**983.22 ± 441.44↑**	535.69 ± 171.12
				Control		White tibialis anterior		201.29 ± 61.2	571.7 ± 99.64
				1 wks	Electrostimulation (24 h, 10 Hz, 50 μs duration)		N.S.	**584.51 ± 216.39↑**	495.17 ± 70.46
				3 wks				**298.06 ± 51.93↑**	531.18 ± 80.52
	McCullagh (1997)[53]	6	Sprague–Dawley rats	1 wks	Control	Red tibialis anterior		44.82 ± 7.11	
					Electrostimulation (10 Hz, 50 micros, 24 h/d during 7d)		N.S.	**68.23 ± 10.22↑**	
					Control	White tibialis anterior		19.23 ± 5.77	
					Electrostimulation (10 Hz, 50 micros, 24 h/d during 7d)		N.S.	**55.89 ± 7.55↑**	
					Control	Extensor digitorum longus		42.1 ± 6.22	
					Electrostimulation (10 Hz, 50 micros, 24 h/d during 7d)		N.S.	**81.85 ± 12.44↑**	
	Kitaoka (2015)[54]	5	Sprague–Dawley rats	4 wks	Control	Gastrocnemius		100.66 ± 20.07	100.22 ± 18.92
					Electrostimulation (5 sets of 10 × 3 s (30 V and 100 Hz); Rest: 7 s between contractions)		48 h	109.57 ± 4.98	**124.72 ± 16.93↑**

TABLE 11 Continued

Study	*N* per group	Animal	Duration	Exercise	Muscle region	Biopsy after exercise	MCT1 protein content	MCT4 protein content
Yoshida (2004)[55]	6 to 7	ICR mice	1 wks	Control	Plantaris		100 ± 48.98	98.55 ± 49.69
			1 wks	VPE (Mice ran freely in the wheel)		N.S.	106.31 ± 41.25	121.73 ± 30.76
			3 wks	Control			100 ± 51.56	99.51 ± 54.43
			3 wks	VPE (Mice ran freely in the wheel)		N.S.	102.1 ± 41.25	68.59 ± 21.29
			6 wks	Control			100 ± 38.67	98.55 ± 16.56
			6 wks	VPE (Mice ran freely in the wheel)		N.S.	**148.42 ± 20.62↑**	101.44 ± 21.29
			1 wks	Control	Tibialis anterior		100 ± 54.14	96.61 ± 35.49
			1 wks	VPE (Mice ran freely in the wheel)		N.S.	128.42 ± 54.14	122.7 ± 30.76
			3 wks	Control			100 ± 46.41	98.55 ± 52.06
			3 wks	VPE (Mice ran freely in the wheel)		N.S.	116.84 ± 33.51	141.06 ± 82.83
			6 wks	Control			100 ± 41.25	96.61 ± 21.29
			6 wks	VPE (Mice ran freely in the wheel)		N.S.	**144.21 ± 51.56↑**	113.04 ± 18.93
			1 wks	Control	Soleus		100 ± 70.35	
			1 wks	VPE (Mice ran freely in the wheel)		N.S.	125.53 ± 45.6	
			3 wks	Control			100 ± 39.08	
			3 wks	VPE (Mice ran freely in the wheel)		N.S.	96.8 ± 13.02	
			6 wks	Control			100 ± 39.08	
			6 wks	VPE (Mice ran freely in the wheel)		N.S.	79.78 ± 15.63	
Scariot (2022)[56]	10	C57BL/6J mice	8 wks	Low physically active	Soleus		0.038 ± 0.033	0.043 ± 0.013
				Low physically active+LMIE (5 s/w; 40 min at 80% critical velocity)		48 h	0.049 ± 0.031	0.052 ± 0.02
				High physically active			0.037 ± 0.024	0.048 ± 0.01
				Low physically active+LMIE (5 s/w; 40 min at 80% critical velocity)		48 h	0.044 ± 0.03	**0.006 ± 0.006↓**

Note: ↑, significant increase compared to control group; ↓, significant decrease compared to control group. The values highlighted in bold are of the studies that found differences.

Abbreviations: HIE, high-intensity exercise; LMIE, low-/moderate-intensity exercise; N.S., not specified; s/w, sessions/week; VPE, voluntary Physical Exercise; wk, week.

impossible to perform a quantitative analysis (i.e., meta-analysis), as well as hindering the drawing of robust conclusions. Furthermore, practical comments and recommendations will be made in order to improve future research. Firstly, most of the selected studies did not include a control group (75%). The absence of a control group in most of the studies prevented to perform a quantitative analysis in this systematic review. In this sense, the ideal study to test the effects of a single-session stimulus would be a randomized parallel design with two groups, one group performing exercise and other group performing a control situation. Moreover, studies that want to observe the effect of an exercise program should perform a randomized control trial with an intervention group and a control group. Measurements should be performed in both groups, which did not occur in one of the included studies, in which only the experimental group was measured.[21] Moreover, and contrary to some studies in which both the control and experimental groups performed an exercise intervention,[25,27,48] we consider the control group should perform an intervention that does not provoke metabolic changes in the muscle, ideally not performing any type of physical activity. Other types of designs, like the one which opted to exercise one leg and take the other non-exercising leg as a control[26] are certainly not the best design. This is because the exercising leg causes systemic changes that likely affect the non-exercising leg. For example, the increase in blood lactate concentration caused by the exercising leg could affect the MCT1 response of the non-exercising leg.[15]

Timing of the biopsies in the included studies was very heterogeneous, varying from 0 min to a week after the end of the exercise. As already pointed out, this is one of the key aspects,[57] since the kinetics of *SLC16A1*/*SLC16A3* mRNA and MCT1/MCT4 protein levels seems to change over time after exercise. McGinley & Bishop reported that both *SLC16A1* and *SLC16A3* mRNA peaked 9 h after exercise, whereas MCT proteins behaved differently from each other. More specifically, MCT1 protein levels were greater at 24-72 h compared with the first 9 h after exercise, contrary to MCT4 protein which levels did not change over the 72 h measurement period.[19] Hence, to investigate the effect of a single exercise session on MCTs response, we suggest extracting several biopsies after exercise from 0 min up to 72 h after exercise, instead of performing only a single biopsy. The kinetics of the response of these two parameters (mRNA expression and protein level change) is a process that is not momentary but extends over time, so only one biopsy after exercise may proportionate a wrong picture of the whole process. On the other hand, if the purpose is to investigate the effect of a training program, it is recommended to extract the biopsy far after the last exercise session, to avoid interferences from this last session. It has been previously suggested to measure at least 24 h after exercise and at several time points.[19] However, if the effects of the last exercise session can last up to 72 h as shown above, we recommended to perform at least one measurement from 72 h onwards.

Another important consideration is the way the results are reported, the most common being the presentation of post-exercise results relative to pre-exercise values (65% of the studies).[16,17,20–22,25,27,28,35,36,38] However, those studies expressing the response relative to the value before exercise did not report any measure of variability in the value before exercise, what leads to two problems. On the one hand, artificially reducing the dispersion of the pre-value increases the likelihood of finding significant differences between two means, what could misrepresent the actual results. On the other hand, the lack of a measure of variability in the pre-exercise value was another reason why it was impossible for us to carry out a quantitative analysis. We therefore propose to present the results relative to an internal control, as several studies have already done.[19,23,24,48,51] In case of mRNA expression, we consider that the internal control should be a stable mRNA housekeeping expression. On the other hand, in case of protein level, we consider that the internal control should be an internal standard loaded in each gel, and each lane should be normalized to this value.

Last but not least, we consider it imperative to highlight the fact that less than 15% of the sample was composed by female participants. Such an excessive decompensation implies that the data available so far are only applicable to males. Sadly, this is in line with the publication trends in Sport Sciences, where females are still underrepresented.[58,59] Thus, we encourage to follow the warnings made by some experts in various publications on the need to extend the studies to females,[60,61] even more when we already have data available indicating a possible dysmorphism in the response of monocarboxylate transporters, since sex hormones influence MCTs levels in rat skeletal muscle.[62] Moreover, this consideration is especially important in the case of muscle MCTs, since they are dependent on the type of muscle fiber and the proportion of muscle fibers is different according to sex.[63]

Therefore, although some methodological aspects have been properly carried out in the studies up to date, such as the homogeneity of the techniques used to measure protein levels and mRNA or the maintenance of the biopsy location, others should be considered to potentially alleviate the limitations described above. All of these recommendations have been already conducted by previous studies meaning that, although challenging, their implementation is feasible. In brief, these recommendations are: the inclusion of a control group with a non-effect intervention on mRNA or protein levels; the measurement at several

time points (i.e., several biopsies), far from the last session when studying the effect of a training program, as in[19]; reporting the values relative to an internal control instead of relative to pre values, as in[64]; and the inclusion of more females as participants in future investigations, as in the study cited herein.[24]

3.2 | Effect of exercise on *SLC16A1*/*SLC16A3* mRNA and MCT1/MCT4 protein levels

Exercise is a complex stimulus, composed of several characteristics that model the final load of the intervention. Therefore, to thoroughly understand the effect of it, researchers should separately analyze the effect of each factor and then combining that knowledge to comprehend the responses that a particular intervention will elicit. From the existing literature reviewed here, the characteristics that we considered most relevant in order to determine the response were the intensity (low/moderate vs. high intensity) and the duration of the intervention (single session vs. training program).

3.2.1 | Intensity influence

Since only two studies with high intensity[16,17] and no studies with low/moderate intensity have been performed in humans, it is complicated to draw a pattern for mRNAs expression according to exercise intensity, regardless of the duration of the intervention. However, data available to date suggest that high-intensity exercise in human males does not appear to affect mRNA expression in muscle MCT genes. The data in rodents are hardly comparable to humans, since the vast majority have implemented low-/moderate-exercise intensity. Nonetheless, in rodent, the behavior seems to be more responsiveness of *SLC16A1* compared to *SLC16A3*, in addition to a fiber-specific response, which fits the distribution of the related proteins (i.e., MCT1 in more oxidative and MCT4 in more glycolytic fibers). Nevertheless, the discussion of the effect of intensity on mRNAs responses is conditioned by the fact already mentioned, that all the works in humans employed high-intensity exercise, whereas in rodents the majority uses low-/moderate-intensity exercise. Therefore, the present review reveals the lack of diversity in exercise protocol design among studies, which leads to a biased knowledge of the response to exercise of mRNA of muscle *SLC16As*. At this point, we strongly encourage the researchers to apply and compare a greater diversity of training and exercise characteristics in their future studies, in order to fulfill this gap in knowledge.

Regardless of intervention duration, the percentage of studies finding a significant increase in MCT1 protein content after high-intensity exercise is very similar to the percentage of low-/moderate-intensity exercise studies (around 70% in both cases). Therefore, the current data seem to indicate that, in the case of aiming to increase MCT1 protein levels, both low-/moderate- and high-intensity exercise could be a good strategy, even if only a single exercise session is applied. Regarding MCT4 protein content, the percentage of studies performing low-/moderate-intensity exercise observing increases in MCT4 protein content is similar to the percentage of studies performing high-intensity exercise (around 50% in both cases). Even gathering interventions by exercise intensity, the responsiveness of the MCT4 protein content appears to remain lower than MCT1. Therefore, and contrary to what is generally believed (i.e., that high intensity is required to increase MCT4 protein content), changes in MCT4 protein content are similar between low-/moderate- and high-intensity exercise. Traditionally, we have assumed that MCT1 protein levels increased with both low-/moderate- and high-intensity exercise, while MCT4 protein levels increased only with high-intensity exercise. This assumption is probably because MCT1 is more present in type I fibers (presumably activated by both moderate- and high-intensity exercise), whereas MCT4 is more present in type II fibers (presumably activated only at high intensity). Our review shows results in line with the fact that MCT1 protein levels increase with both intensities. However, when we compiled all the studies in the literature, we found that MCT4 protein levels do not necessarily increase with high-intensity exercise exclusively, since we found studies that observed an increase in MCT4 protein content after a low-/moderate-intensity training program.[37] Our main hypothesis is that MCT4-mediated lactate release occurs at both intensities and that an increase in MCT4 levels may be caused by this demand. Actually, in a previous excellent review aligned results were found.[15]

The only two studies combining low-/moderate- and high-intensity exercise[38,48] reported no differences. Although we cannot propose any explanation for their findings because they may be conditioned by the timing of the biopsy (week after training) or the training status of the participants (active/trained); we believe that this finding should be mentioned.

On the other hand, most of the studies in rodents involving low-/moderate-intensity exercise reported a very heterogeneous response and only one study performed high-intensity exercise showed an increase.[29] Hence, it is difficult to establish a pattern according to exercise intensity in rodents. With respect to the comparison between humans and rodents, as with studies investigating mRNA, most human studies use high-intensity exercise while

most rodent studies use low-/moderate-intensity exercise. So, it is important to take into account the knowledge bias that has been previously mentioned.

3.2.2 | Influence of the exercise duration

Although based on scarce studies, single-session interventions with high-intensity do not appear to be sufficient stimulus to generate changes in mRNA for any of the muscle *SLC16A1* or *SLC16A3* in male humans (no human study utilize low-/moderate-intensity exercise).[16,17] On the contrary, the four interventions in rodents with single-session interventions show increases at some point both in *SLC16A1*[18,30–32] and *SLC16A3* mRNA.[18,30,31] The discrepancies between humans and animals could be due to several reasons, like the training status of the sample (training status is not usually evaluated in rodents) or the setting of the exercise intensity (relative intensity in humans vs. absolute intensity in rodents). Furthermore, the way the muscle samples were taken could also affect, since in humans were extracted by muscle biopsies while in rodents were extracted after sacrifice. In addition, biopsies in humans were always taken from the same muscle (vastus lateralis), while different muscles with different fiber compositions were analyzed in rodents. Finally, an intra-subject study design was carried out in most of the studies in humans, while an inter-subject study design is used in rodents. With only 6 investigations conducted so far and with substantial methodological differences, it is not prudent to draw conclusions. However, preliminary data suggest that the mRNA response to a training session is different between humans and rodents, the latter being more responsive.

The three studies in men reviewed in this section do not indicate a definite trend for either *SLC16A1* or *SLC16A3* mRNA after a training program, since only Bickham et al.[16] reported changes (i.e., decrease in expression) in both mRNAs after 6 weeks of training. Maybe the other two investigations[17,48] did not reach a sufficient stimulus to generate changes, but further research is needed anyway. In rodents, the data are also insufficient to establish a clear response. However, the analysis of muscles with different fibrillar compositions hints at a possible different adaptation of mRNA depending on the abundance of fiber types: in more oxidative muscles (i.e., soleus and red gastrocnemius) an increase in *SLC16A1* and a decrease in *SLC16A3* mRNA are observed, while in more glycolytic muscles (i.e., white gastrocnemius) *SLC16A1* mRNA decreases and *SLC16A3* mRNA increases. Hence, the data available to date do not indicate a homogeneous response, although it is true that the amount of knowledge in this regard is still scarce. It may be necessary for future studies to take into account other factors, such as the comparison of muscles with different fibrillar compositions, the use of a greater training stimulus that generates measurable responses, or the selection of a homogeneous sample in terms of fitness status, since the latter is key to determining the response to a training program.

Regarding protein levels, only Green et al. investigated the effect of a single session at low-/moderate-intensity exercise in humans and reported increases in both proteins after 2, 4 and 6 days of a 5-6-h cycle at 60% VO2peak. This suggests that low-/moderate-intensity exercise is a plausible strategy to increase MCTs protein levels after a single exercise session. On the other hand, it seems that the response of MCT1 and MCT4 protein abundance after a high-intensity session in humans is heterogeneous. We can highlight some interesting details. For instance, the only study with one session in women is the only one reporting decreases,[20] implying a possible sexual dimorphism in the MCTs response. Moreover, the biopsy in this case was taken immediately post-exercise, as in the study by McGinley et al[19] The difference between the study by Bishop et al[20] and the study by McGinley et al.[19] is not only the sex of participants (women and men, respectively), but also the exercise intensity, which was considerably higher in Bishop et al. investigation (i.e., 200% of the power output at VO2peak) than in the other work extracting the biopsy just after exercise. Finally, when exercised until exhaustion, a higher protein content of MCT1 and no changes in the protein content of MCT4 were reported,[16] suggesting that fatigue could affect differently to both transporters. In rodents, the effect of a single exercise session was studied only through low-/moderate-intensity exercise in three studies, where Eydoux et al. observed an increase in MCT1 protein content swimming until fatigue,[39] Kim et al. found no change after running for 30 min[40] and Coles et al. observed an increased after 2 h of exercise composed by 30 min exercise and 30 min rest.[30] The different type of exercise and duration of the exercise session are possibly influencing the different response between studies. Contrary, the only study performing electrostimulation showed a reduced protein level content of both transporters after a single session.

With multi-session programs in humans, most of the studies reported a significant increase in MCT1 protein content after a training intervention involving different types of training. Even the only study using a strength-training-based program found an increase in both proteins.[51] These results are in line with the higher MCT1 protein content observed in well-trained subjects compared to less trained subjects.[14] It is important to mention that the lack of differences in MCT1 responses reported in some of the included studies could be due to methodological aspects already discussed, like the timing of

biopsy. For example, two of the works which failed to find an increase in MCT1 protein content[38,48] are the only studies performing the biopsy a week after the end of the training. This may have implied a too-long period of time and therefore diluting the possible effects achieved with training. Similar results are found in rodents since most of the studies observed a higher MCT1 protein content in the training groups compared to control groups. Thus, the existing data suggest an increase in muscle MCT1 protein content with regular and periodized exercise, which hints that the increase in this protein is an adaptation to training. This seems to be one of the common adaptations to training, as increased MCT1 protein levels have been linked to improved fatigue index and lactate clearance in humans.[14] In addition, inhibition of MCT1 has recently been shown to reduce performance in rodents[65] suggesting this protein is clearly related to performance. Regarding MCT4 protein content, about half of the studies in humans included in the present review showed an increase in this protein with different training programs involving different exercise characteristics, suggesting a less pronounce response compared to MCT1. Results in rodents are elusive on MCT4 protein content because different responses are found. This could indicate the MCT4 protein content response is more diverse in rodents compared to humans.

Although the pathways responsible for regulating MCT1 and MCT4 remain to be determined, the current review supports they respond to different stimuli, as previously suggested.[24] In this sense, we observe that MCT1 seems to be more responder compared to MCT4 protein content after a training program independently of exercise characteristics. The higher frequency of increases observed in MCT1 protein content points out a greater plasticity of this carrier, which is consistent with its broader localization and greater number of functions.[3] Since it is found in most of the tissues and transports a wide spectrum of monocarboxylates,[5] a great variety of stimulus could trigger the increase in MCT1 protein content. In addition, the fact that MCT1 can transport lactate and H^+ in both directions (uptake and release) whereas MCT4 is specialized only in lactate/H^+ release implies per se a situation of higher demand for MCT1.[5] In this sense, the different exercise characteristics represent different stimulus that increase MCT1 protein content supporting a putative greater plasticity of this carrier. In contrast, the MCT4 response is less frequent in the studies reviewed. This could be due to, among others, a greater specificity in the stimuli that trigger its change, responding only to more specific exercise characteristics; that the change occurs only in some muscle fibers, given that MCT4 is more present in glycolytic fibers[3]; and/or that its changes are more genetically determined.

3.3 | Regulatory mechanisms of mRNA expression and protein content that could be influenced by exercise

The changes reported by the articles included in this systematic review are driven by regulatory mechanisms that are likely to occur at all steps of the expression pathway, that is, transcriptional, post-transcriptional, translational, and/or post-translational mechanisms. Nowadays, data regarding these regulation mechanisms are scarce, but we believe it helpful to summarize below the different steps where exercise could have an impact in order to have a general idea of how exercise influences these mechanisms of SLC16A1/SLC16A3 mRNA expression and MCT1/MCT4 protein levels.

Transcriptional regulation: Exercise can stimulate the transcription of SLC16A1/SLC16A3 genes. Transcription factors activated during exercise may bind to specific regulatory regions in the DNA, promoting gene expression.[66,67]

Post-transcriptional regulation: Exercise may influence the stability of SLC16A1/SLC16A3 mRNA. Certain RNA-binding proteins or non-coding RNAs can affect the degradation or stabilization of mRNA molecules.[67]

Translational regulation: We hypothesized exercise may modulate the initiation of translation, influencing the rate at which mRNA is translated into protein. Signaling pathways activated during exercise may impact the assembly of the translation initiation complex. To the best of our knowledge, we have not found any studies on this issue, opening the door for future studies to address this possibility.

Protein Synthesis: Acute exercise, especially resistance or high-intensity exercise, can stimulate protein synthesis,[68] being MCTs one of the potential proteins synthesized by exercise.

Protein Degradation: Some studies suggest that acute exercise may influence protein degradation pathways,[68] potentially preventing degradation of MCTs protein content.

Translocation to the Membrane: Translocation of MCT proteins to the membrane is a crucial step in their functional activation.[69] Exercise may influence the translocation process, allowing MCTs to facilitate lactate transport more effectively.

3.4 | Considerations for future studies

It is worthwhile to mention that the increase in MCT1 protein levels after a training program observed in most of the studies in humans is not preceded by an increase in SLC16A1 mRNA after a single exercise session or a training program, which would be expected as the most likely causal event.[70] Therefore, it cannot be considered that an increase

in SLC16A1 mRNA predicts an increase in MCT1 protein levels from the studies included in the present review. Moreover, there is still controversy about whether changes in mRNA with exercise will affect protein abundance.[57] In addition, mRNA response is usually a more transient increase over time compared to protein content, which is more stable[57] so results about protein content would be more consistent and should be the main outcome when analyzing training adaptation in humans. In this line, mRNA changes would be a desirable measurement when the focus of research is to unveil the mechanism behind these protein changes.[71] The lack of relationship between changes in mRNA and protein seen in our results in humans suggests that post-transcriptional mechanisms are playing a role in the increase in protein content after a training program. A possible mechanism is that MCT1 is continuously demanded by the cell, since transports the greatest variety of monocarboxylates.[5] Hence, *SLC16A1* might be expressed continuously and MCT1 protein is formed from the SLC16A1 mRNA only when the environment is favorable. In this case, exercise could create a favorable situation for the generation of MCT1 protein (i.e., presence of facilitators for translation of mRNA to upregulate protein content). It is interesting to notice that our results in animals do support a greater match between mRNA and protein changes. The higher SLC16A1 mRNA after exercise observed in most of the studies in animals (whether as a single session or as part of a training program) fits with the increase in MCT1 protein that we observed after most of the training programs. With these results, it is speculative but tempting to suggest different MCT1 regulation mechanisms between humans and rodents.

An important consideration when interpreting the effect of a training program is the suppressing phenomenon in the transcription responses induced by exercise of genes after training. The result of this phenomenon is a gradual decrease in the exercise-induced transcriptional response after a period of training, which has already been demonstrated in other studies.[64] This phenomenon could have occurred in the studies of the present review investigating the effect of exercise at the same absolute intensity on mRNA and protein content before and after a training program. A possible explanation is that adaptation to training cause a lower transcription-inducing signaling pathway (lower homeostatic perturbation, sensor activation, transcription factors, and transcription coregulators) by the same exercise session reducing transcription and the subsequent protein content.

Also, future studies could consider the protein extraction methods for western-blotting (whole lysate vs. membrane extraction). Whole lysate extraction may provide a snapshot of the total protein content, while membrane extraction specifically captures membrane-bound proteins. A previous study compared the effect of a training program (9 weeks of leg cycle endurance training at 75% VO_{2peak}) on MCT1 and MCT4 protein content in total muscle homogenates and sarcolemma-enriched fractions.[37] Their results showed that MCT1 protein content increased after training in both protein extraction methods, while MCT4 protein content only increased in sarcolemma-enriched fractions but not total muscle homogenates. These results suggest that the choice of protein extraction method in western-blotting can significantly impact the results.

Finally, it is interesting to note that the only results coinciding between humans and rodents are when analyzing the effect of a training program on MCT1 protein levels. In this case, the response observed in most studies is an increase in both species, but in the other comparisons, no common pattern is observed. Throughout this review, we have noticed some aspects that might explain the differences found between human and rodent studies that are worth summarizing. First, training status is different between humans and rodents, in fact, training status of rodents is not usually reported. Exercise intensity setting is another aspect of controversy, since relative intensity is usually performed in humans and absolute intensity is used in rodents. Furthermore, muscle sample measurement is completely different, while a biopsy is extracted in humans, rodents are always sacrificed. In addition, biopsies in humans were always taken from the same muscle (vastus lateralis), while different muscles with different fiber compositions were analyzed in rodents. Finally, an intra-subject study design was developed in most of the studies in humans, while an inter-subject study design is used in rodents without reporting the sex and the litter.

4 | MATERIALS AND METHODS

4.1 | Design

The methodological process was based on the recommendations indicated by the guidelines of the Preferred Reported Items for Systematic Reviews and Meta-Analysis (PRISMA).[72] The eligibility criteria were established by the authors. The study was preregistered in the International Prospective Register of Systematic Review (PROSPERO) with the following registered number: CRD42021238997.

4.2 | Data sources and searches

A comprehensive database search was systematically conducted (PubMed and Web of Science) up to January 13, 2023 and performed independently by two authors (RCC

and JAB) obtaining the same results. The following combination terms were used: "MCT" OR "monocarboxylate transporter" OR "monocarboxylic acid transport" OR "SLC16A1" OR "muscle lactate transport". The Boolean operator "AND" was used to combine these descriptors with: "Exercise" OR "train" OR "training" OR "sport" OR "physical activity". The search results were downloaded and imported into Reference Manager EndNote (version X7, Clarivate Analytics, Philadelphia, PA, USA).

4.3 | Selection criteria

Two authors (RCC and JAB) carried out the study selection independently. Disparities found were discussed by the authors to reach a consensus. Research studies were included if (1) studies examined the effect of single exercise session or training program on MCT1/MCT4 protein levels or *SLC16A1/SLC16A3* mRNA; (2) humans or rodents were analyzed; (3) studies were published in English, Spanish or Portuguese; and (4) an exercise intervention was carried out. Research studies were excluded if (1) it was a review; (2) it was not an original investigation; (3) the study was in vitro; (4) information about pre-post protein levels or mRNA was lacking; (5) for human studies, the sample population was not between 18 and 65 years of age; (6) for human studies, men and women were mixed for the analysis or the sex of the sample was not specified; (7) training characteristics (volume, intensity, frequency, type of exercise, etc.) were not properly specified; (8) protein or mRNA measurements were not properly specified; (9) rodents were genetically modified to alter the MCTs protein content or the mRNA expression of their respective genes; (10) MCT proteins were not measured with western-blot; (11) studies in animals that were not rodents; and (12) an hypoxia stimulus was included.

4.4 | Outcome variables

The main outcome variables of the present study were MCT1 protein levels, MCT4 protein levels, *SLC16A1* mRNA expression, and *SLC16A3* mRNA expression. MCT1 and MCT4 protein levels were assessed because they are the two main muscle transporters of lactate and protons during exercise. On the other hand, *SLC16A1* and *SLC16A3* mRNA were evaluated because they are usually used to predict changes in MCT1 and MCT4 protein levels.

4.5 | Study selection and data extraction

Two authors (R.C.C. and J.A.B.) independently extracted data from the included studies in a spreadsheet. The following information was extracted: (1) study (authors, title, year, design and duration of the intervention [single exercise session or training program]); (2) sample (size, age, weight, height, training experience and disease); (3) training (duration of intervention, type of training, type of exercise, training frequency, session characteristics (intensity, duration, rests, etc.)); (4) biopsy (timing, type of tissue, analysis method and amount of tissue); (5) MCT1/MCT4 proteins levels and *SLC16A1*/*SCL16A3* mRNA. If insufficient information was reported, the corresponding authors of the included studies were contacted to obtain missing information. In case results were reported in figures, values were extracted from the studies' figures using an online software (WebPlotDigitizer 4.6, California, USA).

4.6 | Risks of bias assessment

The articles involving human sample of this review were evaluated with the Cochrane collaboration tool for risk of bias assessment.[73] The following criteria were assessed: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessment; (5) incomplete outcome data and 6) selective reporting. For each study, each source of bias was described as having either a low risk of bias, an unclear risk of bias, or a high risk of bias. Each item evaluated as "High" was scored with 1 point. The score for each study was calculated by adding the score for each item. A punctuation lower than 3 was classified as low, between 3 and 4 as medium and higher than 4 as high.

5 | CONCLUSION

We have provided an extensive review of the current knowledge regarding SLC16A1 and SLC16A3 mRNA and MCT1 and MCT4 protein content in response to single exercise session and training program of different intensities. The studies summarized in this systematic review demonstrate that exercise represents a powerful stimulus to increase MCT1 protein content in humans, regardless of whether a single session or a training program is used. In addition, MCT4 protein level increases can also be observed after a training program, although its responsiveness is lower compared to MCT1. This adaptation (i.e., increments) of both transporters is observed independently of the exercise intensity used, again with increases in MCT1 reported in a greater number of studies than for MCT4. Regarding mRNA changes, increases in MCT1 protein levels observed in humans are not preceded by increases in SLC16A1 mRNA indicating that a SLC16A1 mRNA increment may not predict an increase in MCT1 protein levels. This, together with the absence of changes

in *SLC16A3* mRNA following interventions that do report changes in MCT4 levels, points to the existence of regulatory factors that we have not analyzed so far. At this point, and although it could sound cliché, we want to highlight the need for more studies that compare the effect of different intensities and types of exercise, considering all the methodological recommendations mentioned above.

When comparing the results of humans and rodents, they only coincide for the effect of a training program on MCT1 protein levels, reporting increments in both. Some aspects that may explain these differences could be training status, exercise intensity setting (relative vs. absolute), location of the biopsy, or the study design.

Finally, conducting the systematic review, we have noticed some important methodological aspects that we deem are worth considering to improve the design of future studies. All of them have already been implemented in previous studies, which confirms their feasibility, and comprises the inclusion of a control group with a non-effect intervention, the measurement at several time points and far from the last session in case of a training program, reporting the values relative to an internal control instead of relative to pre-values and the inclusion of more female participants. It would be desirable that the future studies needed apply these considerations. Thus, the results and conclusions obtained will be more robust and a simple tool such as exercise will be safely used to modify MCTs, whose role is becoming increasingly crucial in clinical practice and in health in general.

AUTHOR CONTRIBUTIONS

José Antonio Benítez-Muñoz: Conceptualization; investigation; writing – original draft; methodology; writing – review and editing; formal analysis; data curation; visualization. **Rocío Cupeiro:** Conceptualization; investigation; writing – original draft; methodology; writing – review and editing; formal analysis; data curation; visualization; supervision. **Jacobo Á. Rubio-Arias:** Investigation; methodology; writing – review and editing; formal analysis; data curation. **Teresa Amigo:** Conceptualization; investigation; methodology; writing – review and editing; data curation. **Domingo González-Lamuño:** Conceptualization; investigation; visualization; writing – review and editing; supervision; methodology.

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CONFLICT OF INTEREST STATEMENT

José Antonio Benítez-Muñoz, Rocío Cupeiro, Jacobo Á. Rubio-Arias, Teresa Amigo and Domingo González-Lamuño declare that they have no competing interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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