REVIEW ARTICLE

Systematic review of the synergist muscle ablation model for compensatory hypertrophy

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Summary

Objective: The aim was to evaluate the effectiveness of the experimental synergists muscle ablation model to promote muscle hypertrophy, determine the period of greatest hypertrophy and its influence on muscle fiber types and determine differences in bilateral and unilateral removal to reduce the number of animals used in this model.
Method: Following the application of the eligibility criteria for the mechanical overload of the plantar muscle in rats, nineteen papers were included in the review.
Results: The results reveal a greatest hypertrophy occurring between days 12 and 15, and based on the findings, synergist muscle ablation is an efficient model for achieving rapid hypertrophy and the contralateral limb can be used as there was no difference between unilateral and bilateral surgery, which reduces the number of animals used in this model.
Conclusion: This model differs from other overload models (exercise and training) regarding the characteristics involved in the hypertrophy process (acute) and result in a chronic muscle adaptation with selective regulation and modification of fast-twitch fibers in skeletal muscle. This is an efficient and rapid model for compensatory hypertrophy.

Keywords: ablation of synergists, compensatory hypertrophy, experimental models, muscle mass, skeletal muscle cross-sectional area.

Introduction

Skeletal muscle is highly adaptive and has a self-regulating capacity.[1-3] Hypertrophy is an example of this plasticity and refers to the increase in muscle mass necessary to enable the muscle to optimize its response to the demands of sustaining and generating force.[1,2,4-6]

Skeletal muscle mass is regulated by a variety of stimuli, the best known of which is mechanical overload. The muscle adaptation process can be induced by stretching/immobilization,[44,46] compensatory mechanisms (chronic).[1,2-6,8,9,12,14,18-20,61-65] and exercise/training.[33,46] Evidence of this is derived from a large number of studies demonstrating that overload leads to an increase in muscle mass and cross-sectional area of the muscle fibers and induces chronic changes in the balance between the synthesis and degradation of proteins.[2,7-9] Compensatory hypertrophy through the ablation of synergists of plantar flexion is one of the ways to produce chronic overload experimentally.[3,7,12,13,20,59] The ablation of synergists for compensatory hypertrophy consists of the surgical removal of all or part of synergistic muscles, which can be either unilateral or bilateral, to generate chronic functional overload that causes hypertrophy.[3,7,12,13,20,59] According to Parvaresh et al.,[1] complete muscle removal can compromise the neurovascular supply, which increases edema and the recovery of the animal in the postoperative period. Thus, the removal of only the distal portion of synergist muscle is recommended (Figure 1).

The synergist muscle ablation model induces muscle hypertrophy in only a few days, thereby facilitating the study of adaptive responses.[2,3,7,10-20] The most studied muscles are plantar flexors in the rear paw of rats. As

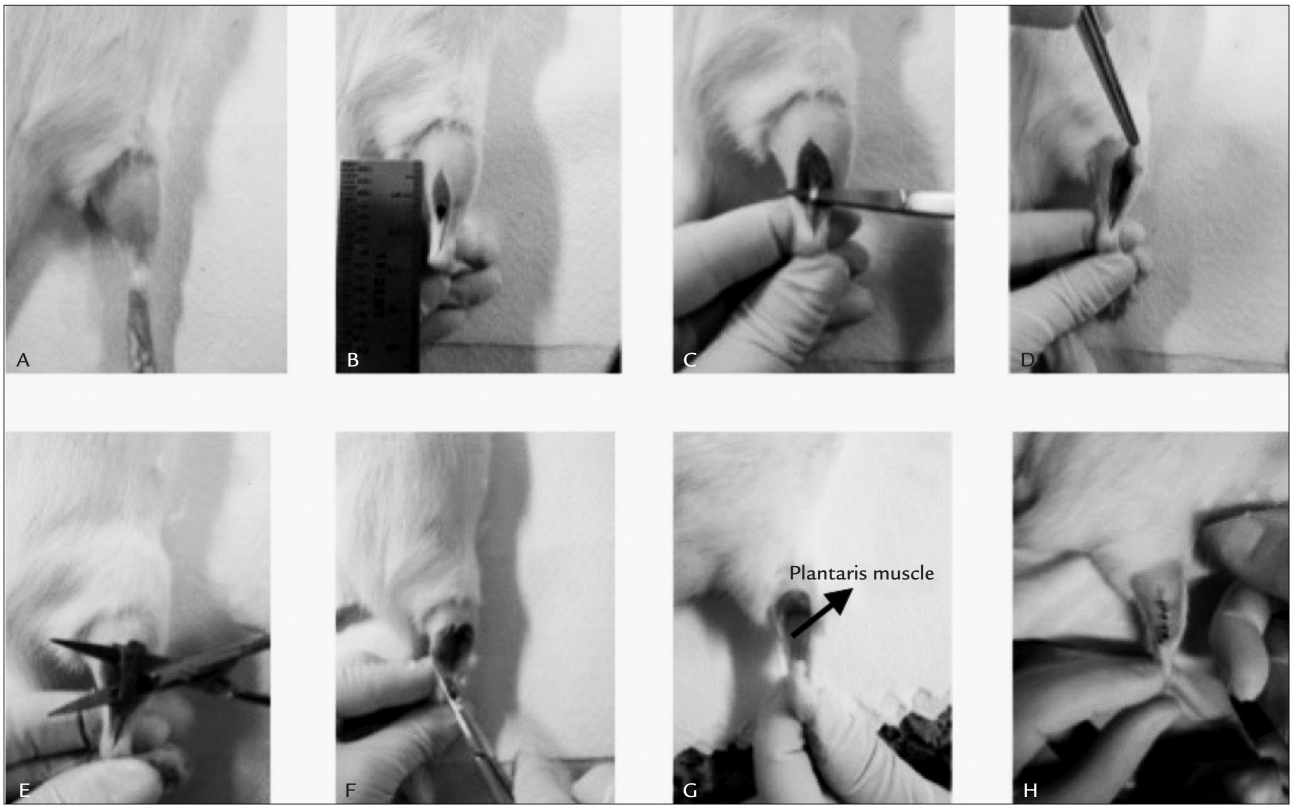

FIGURE 1 Synergist ablation surgery of plantaris muscle. A. Shaving the back of the hind leg. B. Incision of 2 cm. C. Tendon of gastrocnemius muscle. D. Partial removal of the lateral gastrocnemius muscle. E. Soleus muscle – total removal. F. Partial removal of the medial gastrocnemius muscle. G. The plantaris muscle is isolated. H. Suture with seven points.

skeletal muscle has different types of fibers (type I [slow--twitch] and type II [fast-twitch – IIa, IIb, IIx/IId]),[21] a number of authors justify the choice of the plantaris muscle due to its diversity of fiber types (type I: 8 ± 2%; type IIA: 19 ± 3%; type IIB/D: 74 ± 4%) and its different adaptation possibilities.[9] Compensatory hypertrophy induced by the functional elimination of synergistic muscles results in an increase in muscle fiber diameter and muscle mass as well as the regulation of protein synthesis in different types of muscle fibers.

The present systematic review of the literature discusses the results found in studies using this experimental model to cause overload in the plantar muscle of rats, comparing the findings with regard to the percentage increase in the mass of the plantar muscle, the period of greatest muscle mass gain and differences between unilateral and bilateral surgery. The aim of this review was to evaluate the effectiveness of the experimental synergist muscle ablation model to promote muscle hypertrophy in different overload models, to determine the period of greatest hypertrophy and its influence on muscle fiber types, and to determine differences in bilateral and unilateral removal to reduce the number of animals used in this model, thereby facilitating its reproduction and its choice among different chronic hypertrophy models.

METHOD

The methods were based on PRISMA guidelines. Searches were performed in the PubMed, ScienceDirect, MEDLINE and CAPES Portal databases for articles published between January 1999 and July 2013 using the keywords "compensatory hypertrophy" AND "mechanical overload" OR "ablation of synergists" AND "compensatory hypertrophy" AND "experimental models" OR "skeletal muscle cross-sectional area." The following criteria were used for the selection of papers: (1) the use of a rat model; (2) the use of synergist ablation to overload the plantaris muscle; (3) bilateral or unilateral muscle removal; and (4) determination of the cross-sectional area of muscle fibers or muscle mass. Review articles were excluded, as well as other experimental models and in vitro studies. Articles that used overload in another muscle and did not report on their studies the cross-sectional area (CSA) or muscle mass were also excluded.

A total of 63 articles were retrieved using combinations of the keywords. Twenty-four papers were review articles;[7,9,21-42] eight studies used a model other than the ablation of synergists to cause hypertrophy;[43-50] and six were in vitro studies.[51-56] All these studies were excluded. Among the remaining 25 studies, seven did not compare the cross-sectional area of the muscle and/or muscle mass to a control group and were excluded.[3,13,15,48,57,59,60] Thus, 19 studies met the inclusion criteria and were selected for the present review (Figure 2).

Statistical analysis

The data from graphs were grouped based on collection time and percentage of increase in mass of the plantaris muscle with error propagation. A scatter plot was created to show the distribution of muscle mass gain in function of the number of days following the ablation procedure. Two regressions were employed: one for less than 15 days of data and another for more than 15 days of data. A slope of the regression line coefficient of $0.042 \pm 0.002\%$ and linear coefficient of $0.095 \pm 0.021\%$ was used for this calculation (slope of the regression line coefficient + x linear coefficient, in which x is the number of days). R^2 values demonstrate how the data approaches the progression and form a straight line ($R^2 = 0.52$ in the first 15 days following the ablation of synergist muscles and $R^2 = 0.06$, 15 days after surgery). Values greater than 50% demonstrate that the linear fit is adequate. Chebyshev's inequality test was used to compare muscle mass following unilateral or bilateral removal. This test makes no assumptions regarding the normality of the data distribution and only requires the means and standard errors as inputs. Only periods of 14 and 28 days were compared, which were the periods used by most authors. The results were $p=0.2996$ for 14 days and $p=0.2584$ for 28 days.

Results

Table 1 summarizes the findings of the 19 articles analyzed in the present systematic review. Considerable variation was found in the analysis period following the ablation of synergists. Increases in muscle mass (g) and

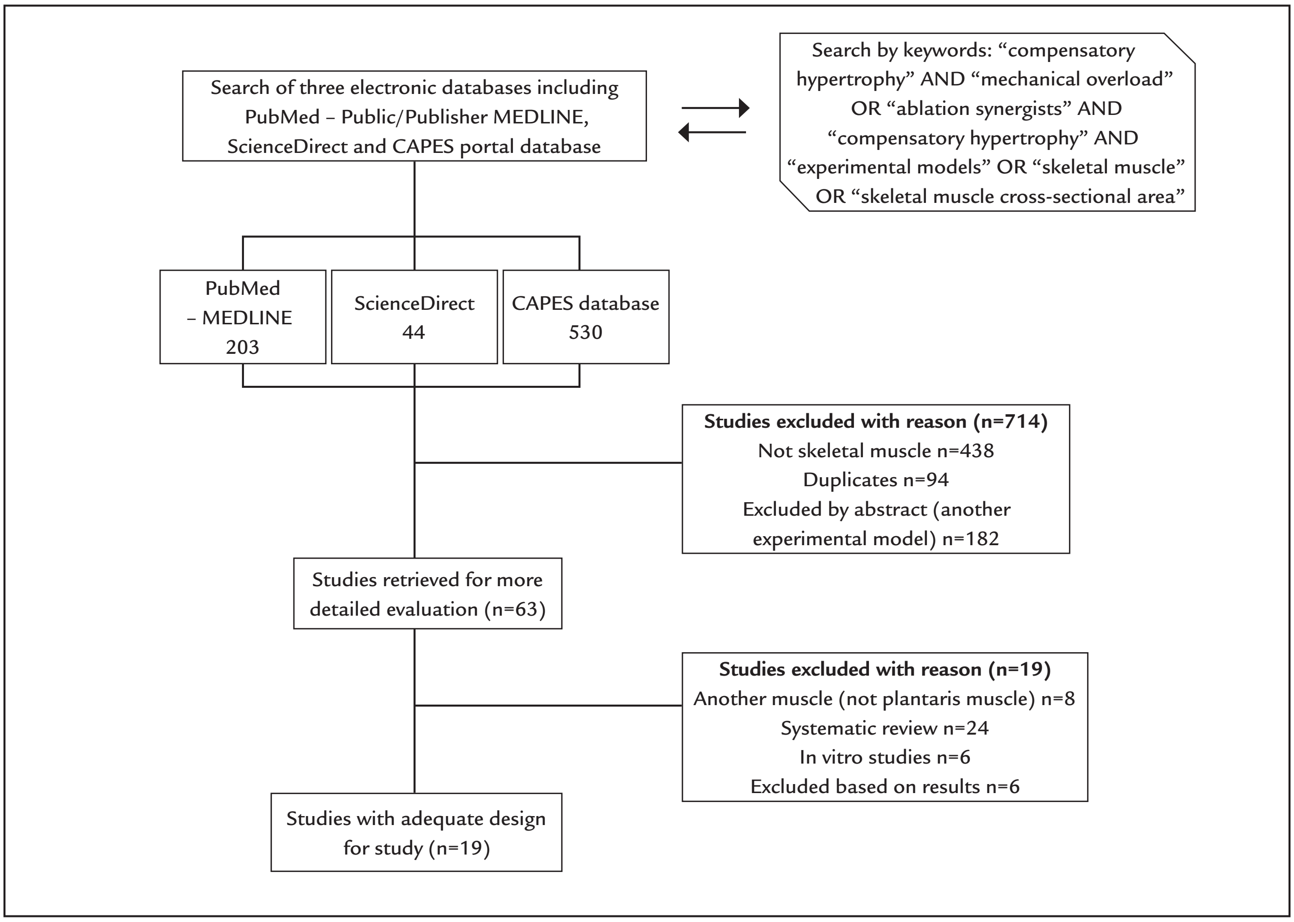

FIGURE 2 Flowchart of the selection process of literature according to the PRISMA guidelines.

fiber cross-sectional area (μm^2) of the plantar muscle were reported in all studies evaluated, demonstrating compensatory hypertrophy.

The data were grouped based on collection time and percentage of increase in mass of the plantar muscle with error propagation. The trend line revealed linear progression up to 15 days, with stabilization of the data after this period. The method of least squares was used, including the error of the data reported by the authors. For studies that did not provide such information, the mean error was used. The trend line in Figure 3 shows the percentage (± error) of increase in muscle mass according to days after surgery as follows: 13.6 ± 2.1% one day after ablation, 38.7 ± 2.6% seven days after ablation and 68.0 ± 3.6% 14 days after ablation.

Only periods of 14 and 28 days were compared, which were the periods used by most authors. Both groups presented a large effect size (1.15 and 1.39 for 14 and 28 days, respectively) but since the authors made no assumptions regarding the data's distribution, the p-values were higher than the significance level (p=0.2996 for 14 days and p=0.2584 for 28 days), thus no significant differences were found between unilateral and bilateral surgery in the two periods. At 28 days, there is an overlap between both 95% confidence intervals ([68%, 85%] and [45%, 61%] for unilateral and bilateral, respectively) but no overlap was found at 14 days ([38%, 55%] and [45%, 61%] for unilateral and bilateral, respectively). By not assuming the normality of the data's distribution, the authors guarantee the probability of the type I error at $\alpha = 0.05$ at the expenses of an increased probability of the type II error. Therefore, despite the lack of statistical significance, the power of the test was low due to the limited data in the literature on unilateral synergist ablation reporting the percentage gain in plantaris muscle mass.

All data were grouped based on the period after the ablation of synergists (Figure 4). Greatest hypertrophy occurred between 12 and 15 days postoperatively. The increase in the cross-sectional area of the muscle and muscle fibers was studied using histological techniques.[1,7-9,60] The mean increase in cross-sectional area in comparison to the control was 66 ± 4% at day 14, demonstrating that compensatory hypertrophy is an effective model for increasing muscle mass.

Discussion

Compensatory hypertrophy occurs in response to a sustained increase in the mechanical load of skeletal muscle. Although the mechanisms involved in compensatory hypertrophy are not yet fully understood, this is an intense topic of research, which includes the definition, measuring, loading stimulus parameters, acute responses, hyperplasia, experimental models, adaptations of muscle fiber types, the involvement of satellite cells and endocrinology. The purpose of the present systematic review was to gather results reported by researchers who have used the standard ablation of synergists (gastrocnemius and soleus muscles) model to determine the induction of hypertrophy in the plantar muscle of rats, comparing the percentage of muscle gain to facilitate and standardize the use of this model for the study of muscle plasticity following functional overload. Increasing interest in the molecular and cellular mechanisms responsible for hypertrophy in recent years[1,6-9] underscores the need for a reliable and easily reproducible model. Rats are often used due to their considerable activity and their larger size in comparison to mice. The mean weight of the animals used in the studies analyzed was 220 ± 12 g.[1-5,7,14-16,18]

Among the models described in the literature for changes in muscle demand, different protocols of mechanical loading have been used: resistance training (RT) and compensatory hypertrophy after ablation and tenotomy.[2,3,5-7,13,18,65] Current theories suggest differences between mechanisms that induce hypertrophy through exercise and compensatory hypertrophy. Both methods cause changes in the muscle, but the molecular signaling pathways seem to be different.[26,49] Compensatory hypertrophy due to the ablation of synergists and tenotomy differ in terms of phases. The former has two distinct phases: an inflammatory phase, followed by the response of the muscle to the demand for a functional increase. Tenotomy has the disadvantage of the rapid reconnection of the cut tendon, which limits functionality.[65]

Most commonly studied muscles

Compensatory hypertrophy by the ablation of synergists is an efficient model for studies on muscle hypertrophy,[2,3,7,10-20] as the fast increase in muscle mass reduces the duration of the experiment. In recent years, changes have occurred in the standard of surgery (bilateral or unilateral) and the relationship between the number of days and increase in muscle mass, which justifies this systematic review.

In rats, the most commonly studied muscles are the tibial anterior, digitorum longus, soleus and plantar muscles.[1-5,7,14-16,18] In the 1980s and 1990s, the model most often employed was the entire removal of the tibialis anterior to generate overload of the digitorum longus.[15] Currently, the most used muscles in such models are the soleus and plantar muscle and compensatory hypertrophy commonly involves the removal of the distal portion of

TABLE 1 Studies selected for review using the synergist ablation model for compensatory hypertrophy.

Article	Ablation of synergists	Study design	Data collection	Outcomes (compared to control)
Adams et al.[4]	Unilateral	Plantar mass Rat body mass	6, 12, 24 and 48 h 3, 7 and 12 days	**12 d** Body mass (g) (226 ± 5 to 257 ± 6) Muscle mass (mg/g) (1.07 ± 0.02 to 1.73 ± 0.18)
Dunn et al.[64]	Bilateral	Cross-sectional area of muscle	7, 14 and 28 days	**28 d** Cross-sectional area increased 75% compared to control
Bodine et al[5]	Bilateral	Muscle mass	7, 14 and 30 days	**7 d** Muscle mass increased by 25% **14 d** Muscle mass increased by 38%
Adams et al.[65]	Bilateral	Cross-sectional area	6 and 24 h 3, 7, 15 and 90 days	**90 d** 46% increase in cross-sectional area of muscle fibers
Lee et al.[62]	Bilateral	Muscle mass	1, 3, 7 and 21 days	**1 d** Increased by 10% **3 d** Increased by 31% **21 d** Increased by 21%
Yamaguchi et al.[12]	Unilateral	Cross-sectional area	3 and 14 days	**14 d** Increased by 43.3 ± 3.8%
Sakuma et al.[63]	Unilateral	Muscle mass	1, 2, 3, 4, 6, 8, 10, 14 and 28 days	**1 d** Increased by 56% **3 d** Increased by 40,9% **6 d** Increased by 31.3 % **10 d** Increased by 44.8 % **14 d** Increased by 46.8% **28 d** Increased by 76.2%
Pehme et al.[14]	Bilateral	Muscle mass	14 days	**14 d** Increased by 40%
DiPasquale et al.[1]	Bilateral	Cross-sectional area	1, 3, 5 and 14 days	**3 d** Increase in peak edema No statistical difference in cross-sectional area of muscle in 3 days
Marino et al.[6]	Bilateral	Cross-sectional area Peak edema	3, 7 and 14 days	**3 d** Statistical difference in cross-sectional area of muscle Retention of 90% water **7 d** 5% Increase in cross-sectional area of muscle Retention of 70% water **14 d** 21% increase in cross-sectional area of muscle Retention of 45% water
Novack et al.[18]	Bilateral	Plantar mass Peak edema	1, 3, 5 and 14 days	**14 d** 80% increase in muscle mass Peak edema in 5 days
Huey et al.[19]	Bilateral	Relative and absolute plantaris muscle	12 h, 1, 2, 3 and 7 days	**7 d** Relative mass increased by 15% Absolute mass increased by 21%
Pavaresh et al.[2]	Bilateral	Absolute and relative mass	3 and 7 days	**3 d** Absolute mass increased by 10% Relative mass increased by 18% **7 d** Absolute mass increased by 21% Relative mass increased by 20%
Goodman et al.[7]	Bilateral	Cross-sectional area	7 and 14 days	**14 d** Increased by 30%
Schuenke et al.[9]	Bilateral	Cross-sectional area	28 days	**28 d** Increased by 35% in young rats Increased by 21% in older rats
Goodman et al.[8]	Bilateral	Cross-sectional area	10 days	**10 d** 1,000 ± 60 vs. 2,000 ± 200 (μm^2)
Gordon et al.[20]	Bilateral	Muscle mass	1 and 3 days	**1 d** Increased by 48 ± 9% (m±SD) **3 d** Increased by 73 ± 17% (m±SD)
Bentzinger et al.[61]	Unilateral	Muscle mass	7 and 28 days	**7 d** Increased by 90% **28 d** Increased by 120%

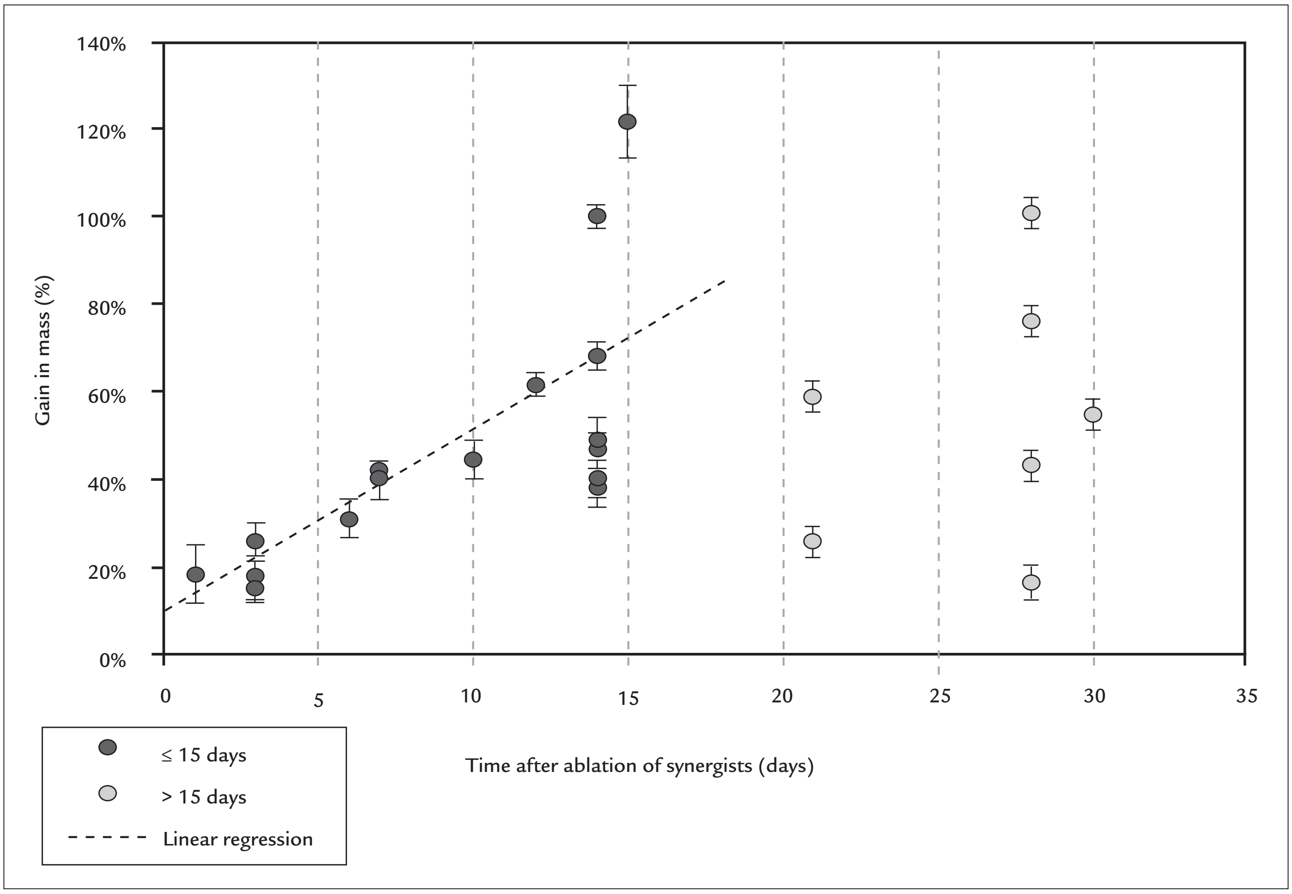

FIGURE 3 Distribution of plantaris muscle hypertrophy according to number of days after ablation of synergists. Dark gray dots represent data collected in less than 15 days after ablation. Light gray dots represent data collected 15 days after ablation of synergists. The trend line demonstrates linear progression up to 15 days, with stabilization thereafter.

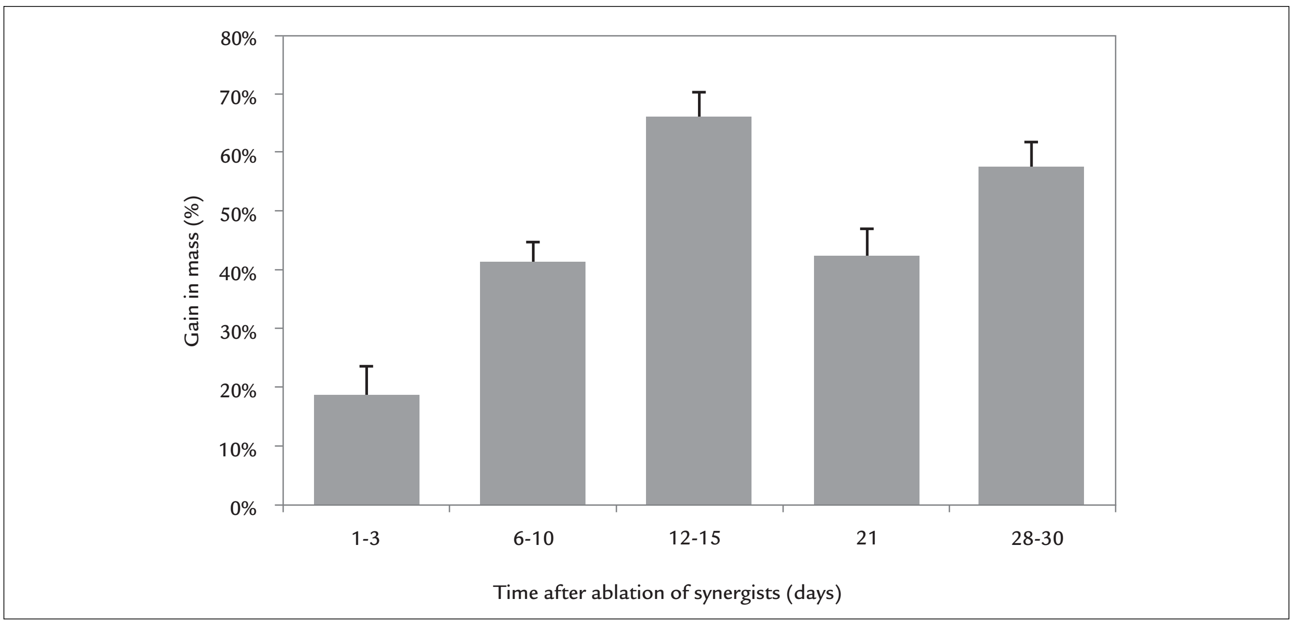

FIGURE 4 Mean gain in muscle mass according to time after the ablation of synergists based on the literature.

the gastrocnemius. Despite displaying anatomical proximity in rats, these muscles are distinct in their architecture and biochemistry.[6,9,16,19,58]

Considering the different types of muscle fiber (slow--twitch [type I] and fast-twitch [type IIa, IIb, IIx and IId]),[21] a number of authors justify the choice of the plantar muscle for studies on adaptation due to its composition of different fiber types. The plantar muscle is predominantly composed of fibers IId and therefore has a smaller amount of mitochondria as such fibers use the glycolytic pathway for a faster response during gait. Authors attribute this adaptation feature of the plantar muscle to its constant activation during the stance phase and weight bearing in quadrupeds, which use this muscle to resume ambulation.[9]

Unilateral vs. bilateral surgery

Based on the data analyzed, both unilateral and bilateral synergist ablation lead to an increase in muscle mass, with no statistically significant difference between the two types of surgery. Researchers working with unilateral surgery report a mean increase in muscle mass of 46.8 ± 2.6% 14 days following synergist ablation,[4,12,61,63] whereas those working with bilateral surgery report an increase of 52.3 ± 3.1% in the same period.[4,12,61,63] Although the number of studies involving unilateral ablation (n=4) was smaller than the number involving bilateral ablation (n=14), the similar increase in muscle mass demonstrates the benefits of unilateral surgery, which reduces the number of animals used in experiments and is in line with the goals of the International Council for Laboratory Animal Sciences.

Expected time for hypertrophy

The data collection period varied considerably among the studies analyzed. Moreover, it is important to determine how the data are distributed for adequate visualization of the period of greatest hypertrophy. The synergist ablation model led to an increase in muscle mass in the first three days due to inflammation and edema caused by the surgical procedure.[1,2,6,20,62,63] This disadvantage in the compensatory hypertrophy model by synergist ablation is due to the inflammation process that occurs after surgery. However, Novack et al.[18] demonstrated that components of the acute inflammatory response are required in the muscle repair and remodeling process and the intensity of the inflammatory response is related to the magnitude of hypertrophy. With synergist ablation, the increase in prostaglandin-endoperoxide synthase 2 (COX-2) seems to be related to the considerable increase in muscle mass that occurs in this model and the inflammatory response enables and facilitates the activity of extracellular proteases, the accumulation of macrophages and cell proliferation, including the activation and proliferation of satellite cells, which seems to exert an influence on the greater hypertrophy achieved with this model in comparison to exercise-induced hypertrophy.

According to Marino et al.,[6] no statistically significant difference in the cross-sectional area of the muscle fibers was found in the first three days following ablation. At 3 to 5 days, the edema is reduced, followed by an increase in the cross-sectional area of the muscle fibers as well as enzyme activity and protein synthesis, which constitute hypertrophy as an adaptation to the new condition of chronic overload.[1,6,18,61,63] The period of 12 to 15 days was identified as that with the greatest percentage increase in muscle mass in comparison to the control (Figure 3), demonstrating a linear progression (i.e., a progressive gain in muscle mass over the first 15 days after ablation). At 28 days, the authors found no further increase in gene expression related to increased muscle mass,[9,64,65] as demonstrated by the cessation of linear progression and stabilization of the data (Figure 2). Thus, peak hypertrophy (greatest increase in muscle mass and cross-sectional area of the muscle fibers) occurs between the second and third week following synergist ablation. Concentrating studies on this period is fundamental to determining the impact of novel therapies and interventions designed either to diminish or potentiate the effects of compensatory muscle hypertrophy.

Cross-sectional area and types of muscle fiber

The increase in the cross-sectional area of the muscle and muscle fibers was studied using histological techniques.[1,7-9,61] The mean increase in cross-sectional area in comparison to the control was 18.66% in 14 days, demonstrating that compensatory hypertrophy is an effective model for increasing muscle mass. The trend line in Figure 2 shows the percentage increase in muscle mass according to days following surgery: approximately 10% one day after ablation, 38% seven days after ablation and 68% 14 days after ablation.

The increase in the cross-sectional area of muscle is related to protein synthesis of the muscle fibers and the activation of satellite cells. Studies suggest that satellite cells are responsible for both the growth of muscle fibers and the regulation of the muscle fiber phenotype.[8,14,19,20,37,46] At the onset of compensatory hypertrophy, the muscle fiber alters its response. The relationship among the cross--sectional area, hypertrophy and fiber type[37] indicates that chronic overload induces changes in the expression of heavy chain myosin.

Goodman et al.[8] demonstrated a significant increase in protein synthesis in four types of muscle fiber (slow--twitch [type I] and fast-twitch [type IIa, IIb and IIx]) in the plantaris muscle in rats submitted to synergist ablation. Type IIb fibers exhibited the least amount of protein synthesis, whereas IIa fibers exhibited the most amount of protein synthesis, which did not differ significantly from that found in type I fibers. In the cross-sectional area, type IIb fibers were shorter than IIa fibers, which also exceeded the area found in type I fibers. These findings suggest that this model results in the selective regulation and modification of fast-twitch fibers in skeletal muscle.

Conclusion

Based on the findings of the present systematic review, the following conclusions may be drawn: 1. the synergist ablation model differs from other overload models regarding the characteristics involved in the hypertrophy process; 2. 12 to 15 days following ablation is the period of greatest muscle hypertrophy; 3. the lack of a significant difference in the gain in muscle mass between unilateral and bilateral ablation demonstrates that contralateral limb can be used as the control, which reduces the number of animals used in this model; and 4. synergist muscle ablation is an efficient reproducible model for achieving rapid hypertrophy and results in the selective regulation and modification of fast-twitch fibers in skeletal muscle.

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Conflict of interest

The authors declare no conflict of interest.

Resumo

Revisão sistemática do modelo de ablação dos músculos sinérgicos na hipertrofia compensatória

Objetivo: Avaliar a eficácia do modelo experimental de ablação dos sinergistas para promover a hipertrofia muscular, determinar o período de maior hipertrofia, sua influência sobre os tipos de fibras musculares e determinar diferenças na remoção unilateral ou bilateral para reduzir o número de animais utilizados nesse modelo.

Método: Após a aplicação dos critérios de elegibilidade para sobrecarga mecânica do músculo plantar em ratos, 19 artigos foram incluídos na revisão.

Resultados: Ocorre maior hipertrofia entre os dias 12 e 15, o que torna o modelo eficiente para alcançar a hipertrofia rapidamente. O membro contralateral também pode ser usado, pois não houve diferença entre a cirurgia unilateral e bilateral, o que reduz o número de animais usados no experimento.

Conclusão: O modelo difere de outros modelos de sobrecarga (exercício e treinamento) em razão das características envolvidas no processo de sobrecarga imposta (aguda), resultando em uma adaptação crônica muscular com modificação de fibras de contração rápida do músculo esquelético. É um modelo rápido e eficiente para se estudar hipertrofia compensatória.

Palavras-chave: ablação dos sinergistas, hipertrofia compensatória, modelos experimentais, massa muscular, área de secção transversa do músculo esquelético.

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