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SYSTEMATIC REVIEW AND META-ANALYSIS ABOUT THE EFFECTS OF ENDURANCE TRAINING AND WHEY PROTEIN SUPPLEMENTATION ON GENE EXPRESSION OF MTOR, MURF-1, MAFBX

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ABSTRACT

Aim: Systematic review and meta-analysis about the effects of endurance training and Whey Protein supplementation on the gene expression of MTOR, MURF-1, MAFBX. Materials and methods: To this systematic review was used the concepts of systematic review and meta-analysis proposed by Thomas, Nelson, Silverman (2012), and Berwanger et al., (2007), and the search followed procedures proposed by Navarro and Navarro (2012), and for the criteria of evaluation of the technical and scientific quality of the texts was used the scale proposed by Galna et al., (2009). Results and discursion: From 724 eligible studies, the sample was 4 original articles where we inferred that the models of endurance training adopted in the experiments, are, the following: Jump in liquid environment, motorized treadmill, and, in squatting apparatus for electric stimulation in the base and that in terms of experimental study in relation to the dose of the supplement, the prescribed was recommended by manuals; and about the gene expression of MTOR, MURF-1, MAFBX, although had been verified it does not occurred due the endurance training and the Whey Protein supplementation and, therefore, absent. Conclusion: In terms of experimentation, it's not found studies enough to compose the adequate procedure for a meta-analysis, even after a systematic review about the effects of endurance training and Whey Protein supplementation on the gene expression of MTOR, protein synthesis and the gene expression of MURF-1, MAFBx of protein degradation in wistar rats.

Key words: Endurance training. Whey Proteins. MTOR. MURF-1. MAFBX.

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RESUMO

Revisão sistemática e meta-análise sobre os efeitos do treinamento de endurance e da suplementação de whey protein sobre a expressão gênica de MTOR, MURF-1, MAFBX

Objetivo: Revisão sistemática e meta-análise sobre os efeitos do treinamento de resistência e suplementação de Whey Protein na expressão gênica de MTOR, MURF-1, MAFBX. Materiais e métodos: Para esta revisão sistemática foram utilizados os conceitos de revisão sistemática e metanálise propostos por Thomas, Nelson, Silverman (2012), e Berwanger et al., (2007), e a busca seguiu os procedimentos propostos por Navarro e Navarro (2012), e para os critérios de avaliação da qualidade técnica e científica dos textos foi utilizada a escala proposta por Galna et al., (2009). Resultados e discussão: A partir de 724 estudos elegíveis, a amostra foi de 4 artigos originais onde inferimos que os modelos de treinamento de endurance adotados nos experimentos, são, os seguintes: Salto em meio líquido, esteira motorizada, e, em agachamento aparelho para eletroestimulação na base e que em termos de estudo experimental em relação à dose do suplemento, o prescrito foi recomendado por manuais; e sobre a expressão gênica de MTOR, MURF-1, MAFBX, embora tenha sido verificado não ocorreu devido ao treinamento de resistência e à suplementação de Whey Protein e, portanto, ausente. Conclusão: Em termos de experimentação, não foram encontrados estudos suficientes para compor o procedimento adequado para uma meta-análise, mesmo após uma revisão sistemática sobre os efeitos do treinamento de resistência e da suplementação de Whey Protein na expressão gênica de MTOR, síntese protéica e no gene expressão de MURF-1, MAFBx de degradação de proteínas em ratos wistar.

Palavras-chave: Treinamento de resistência. Whey Protein. MTOR. MURF-1. MAFBX.

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INTRODUCTION

Endurance training is characterized by repeated series of contractions against a resistance, that results in a fast recruitment of type 2 muscle fiber, it's also a strong stimulus to the skeletal muscle protein synthesis (Phillips, 2009).

However, the increase of skeletal muscle mass depends on the temporal relation between muscle protein synthesis and degradation of the muscle protein.

The synthesis and degradation of proteins are dynamically regulated process and acting together to control the alterations of gain and loss of muscle mass.

Due to this, muscle hypertrophy occurs when the synthesis rate exceeds the degradation rate, or inversely the muscle atrophy occurs under conditions in which the synthesis rate is lower in relation to the degradation (Gordon et al., 2013).

Furthermore, the major intracellular pathway that coordinates signals in regulation of the muscle protein synthesis is the Mammalian target of rapamycin (MTOR) (Drummond et al., 2008).

This pathway regulates the protein synthesis through the action of three proteins known as ribosomal S6 kinase (p70), eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) and eukaryotic initiation factor 4G (eIF4G) (Laplante, Sabatini, 2009).

The degradation pathway known as Ubiquitin proteasome is the main regulator of skeletal muscle atrophy. From ubiquitin ligase, the Muscle Ring Finger (MURF-1) and Muscle Atrophy F-Box (MAFBX) are known as E3 ligase of the Ubiquitin Proteasome System and they are related to the signaling of protein degradation and auto phagocytosis (Rom, Reznick, 2016; Bondine et al., 2001) and are important markers of protein degradation.

Thus, the mechanical stimulus promoted by endurance training influences the MTOR pathway (protein synthesis) through growth factors such as insulin-like growth factor 1 (IGF-1), AKT that stimulate MTORC-1 (Guertin and Sabatini, 2007).

In addition, MURF-1 and MAFBX (protein degradation) present promoter regions controlled by transcription factor from Forkhead Box O Transcrition Factors family (FOXO) that can be phosphorylated by AKT (protein kinase B-AKT), preventing them of translocating to the core.

In addition, protein supplements, such as, Whey Proteins that have high amino acids concentration represent a strong signal that positively regulates MTORC1 and especially leucine, which is an essential amino acid and necessary for the activation o of MTORC1 (Laplante and Sabatini, 2013).

Thus, the investigation of these pathways is of great importance for the study of skeletal muscle hypertrophy. Studies performed with laboratory animals such as rats or mice have great relevance due to some characteristics, for example, greater homogeneity of the samples, and greater ease in the control of variables such as training load and mainly on caloric intake.

In the scientific literature there are several models of acute and chronic exercise performed with rats and mice, in addition to supplementation by different sources of protein, with the objective of evaluating the behavior of these pathways for the regulation of protein synthesis and degradation.

In this sense, the objective of this systematic review and meta-analysis was on the effects of endurance training and the supplementation of whey proteins on the gene expression of MTOR, MURF-1, MAFBX.

MATERIALS AND METHODS

Conceptualization

For this systematic review and meta-analysis, the concepts of revision proposed by Thomas, Nelson and Silverman, (2012) and by Berwanger et al., (2007) were used, and the search followed the procedures proposed by Navarro and Navarro, (2012) and for the criteria of evaluation of the technical and scientific quality of the texts was used the scale proposed by Galna et al., (2009).

Procedures

For this review of the scientific literature, the following databases and their respective electronic addresses were used: the Capes Newspapers portal (www.periodicos.capes.gov.br); Bireme Library: Medline and Lilacs (bvsalud.org); PubMed (http://www.ncbi.nlm.nih.gov/pubmed); Scielo.org (http://scielo.org); Scielo.br

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(http://scielo.br/); Redib (http://redib.org); Dialnet https://dialnet.unirioja.es/).

For this study, the scientific production accessed, from the search result in each database was used from the combination of two and three terms contained in the Descriptors in Health Sciences (DeCS) of the Virtual Health Library (VHL). From this, a total of 754 possible documents to be considered, therefore eligible, were found. And in relation to the quantitative result of the search terms, found for each combination, are described in chart 1.

Chart 1 - Quantitative result, in two or three, of the search words.

Search Words	Periódicos Capes	Bireme/ Mediline	Bireme/ Lilacs	Pubmed	Scielo. org	Scielo.br	Redib	Dialnet
Power Training / Whey proteins	2	17	0	137	0	0	2	2
Resisted Training / Whey proteins	3	0	0	133	0	0	0	0
Anaerobic Training / Whey proteins	1	1	0	10	0	0	0	0
Power Training / MTOR	2	8	2	109	2	0	1	1
Resisted Training / MTOR	3	0	0	101	0	0	0	0
Anaerobic Training / MTOR	0	0	0	0	0	0	0	0
Power Training / MURF-1	0	1	0	25	0	0	0	56
Resisted Training / MURF-1	0	0	0	29	0	0	0	22
Anaerobic Training / MURF-1	0	0	0	1	0	0	0	5
Power Training / MAFBX	0	1	0	19	0	0	0	0
Resisted Training / MAFBX	0	0	0	16	0	0	0	0
Anaerobic Training / MAFBX	0	0	0	0	0	0	0	0
Power Training / Whey proteins / MTOR	3	1	0	13	0	0	0	0
Resisted Training / Whey proteins/ MTOR	2	0	0	13	0	0	0	0
Anaerobic Training / Whey proteins / MTOR	0	0	0	0	0	0	0	0
Power Training / Whey proteins / MURF-1	0	0	0	3	0	0	0	0
Resisted Training / Whey proteins / MURF-1	0	0	0	3	0	0	0	0
Anaerobic Training / Whey proteins / MURF-1	0	0	0	0	0	0	0	0
Power Training / Whey proteins / MAFBx	0	0	0	2	0	0	0	0

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Resisted Training / Whey proteins / MAFBX	0	0	0	2	0	0	0	0
Anaerobic Training / Whey proteins / MAFBX	0	0	0	0	0	0	0	0
Partial Total by Database	16	29	2	616	2	0	3	86
Total	754							

Subtitle: MTOR: Mammalian Target of Rapamycin; MURF-1: Muscle Ring Finger; MAFBX: Muscle Atrophy F-Box.

From the initial quantification and transfer of the digital files to the systematization of the reading procedures, the inclusion and exclusion criteria were applied and then the quality of the scientific texts was evaluated according to the Galna scale for later observations of the variables to be considered in scientific publications for the purpose of this systematic review and meta-analysis.

Inclusion Criteria

The pre-determined inclusion criteria for this systematic review and meta-analysis are: electronic access, free access, full text available, written in Portuguese and/or English, which have prescribed supplementation of whey proteins and resistance training, and that when assessed on the basis of the Galna scale, it achieved a score of 8.0 or higher.

The evaluation items of the Galna scale are as follows: 1) Clarity of the study objective; 2) Detail of the participants; 3) Description of the sample selection; 4) Detail of inclusion and exclusion criteria; 5) Control of Co-variables; 6) Clarity in the description of the main results; 7) Adequacy of the methodology for the reproduction of the study; 8) Capacity of the methodology to answer the questions of the study; 9) Reliability of the methodology; 10) Internal validity of the methodology; 11) Answer the research questions in the discussion; 12) Main findings supported in the results; 13) Logical interpretation of the results with support in the scientific literature.

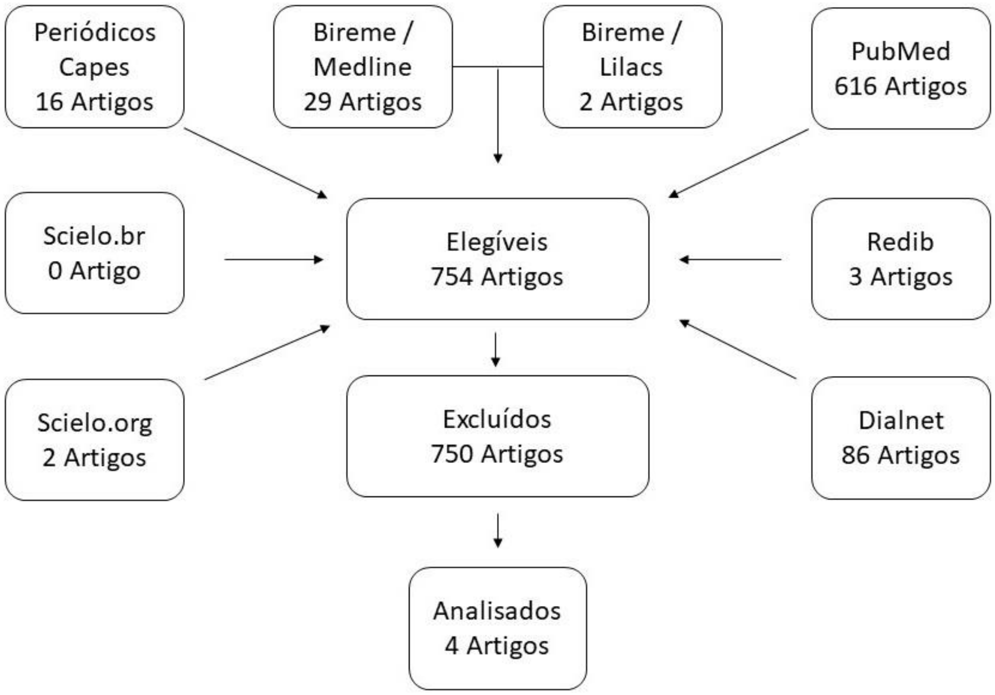
Exclusion Criteria

It was excluded from this systematic review and meta-analysis, texts of theses, dissertations, editorials, journal articles and repeated articles found on different bases, systematic reviews, cell culture studies, human studies, animal studies (except rats and mice), studies that did not evaluate gene expression, and presented an index equal to or less than 7.9 on the Galna scale.

In this way, a synoptic picture was elaborated to evaluate the variables: sample characteristics, exercises, model, gene expression, muscles. Of the 754 articles evaluated, there were 4 that corresponded the stipulated criteria. The flow chart below represents the experimental design of the study.

All the terms and criteria of the procedures for searching for articles, reading and analyzing the variables in the articles, assigning the index to the Galna scale for the articles and the wording of the text presented are agreed between the researchers of this systematic review and meta-analysis

Experimental Design



RESULTS AND DISCUSSION

The following information, in chart 2, in relation to the time period of the publications, these comprise a 5 year interval between 2010 and 2014; In relation to the characteristics the samples, we have studies variating between 32 rats (75% of the studies), and with 96 rats (25% of the studies), and with Wistar rats (50% of the studies) and Fischer (50% of the studies) all males (100% of studies), aged 60 days (25% of studies) and 90 days (25% studies), and 50% of the studies did not report the age of the rat, with initial total body weight 110 grams (25% of the studies), 150 grams (25% of the studies) and 50% of the studies did not report the initial weight of the rats.

Chart 2 - Sample characteristics of selected studies.

Study	Author-date	Characteristics of samples				
		(n)	Lineage	Sex	Age	Weight
(1)	Haraguchi and et al., (2010)	32	Fischer	Male	-	-
(2)	Aparício and et al., (2011)	96	Wistar	Male	-	150 grams
(3)	Nunes et al., (2013)	32	Wistar	Male	90 Days	-
(4)	Haraguchi et al., (2014)	32	Fischer	Male	60 Days	110 grams

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Chart 3 - Exercises / training and models.

Study	Characteristics of the exercises					Model
	Total duration	Weekly frequency	Duration of session	Determination of load	Training protocol	
(1)	8 weeks	5 times a week	-	25% of body mass and increase of 5% per week up to 55%	4 sets of 10 jumps and 1 minute interval between sets	Jumping in liquid medium, cylinder corresponding to 150% of the height of the mouse
(2)	12 weeks	3 - 4 times a week	-	1RM test and flat surface	Constant speed of 40cm / s with 55 - 90% of 1RM	Weathered motorized treadmill training
(3)	8 weeks	4 times a week	-	1 RM test	4 sets of 10 to 12 repetitions and load of 65% to 75% of 1RM with 90 seconds interval between sets	Squatting apparatus with electric stimulation at the base
(4)	8 weeks	5 times a week	-	25% of body mass and increase of 5% per week up to 55%	4 sets of 10 jumps and 1 minute interval between sets	Jumping in liquid medium, cylinder corresponding to 150% of the height of the mouse

In chart 3, about the exercises, 75% of the studies had a duration of 8 weeks, and 25% of the studies had a duration of 12 weeks, with a frequency of 3, 4 and 5 times a week. No studies presented the session duration and in relation to the determination of the training load, 50% of the studies reported a 1RM test, and 50% of the studies reported using 25% of total body weight and increase 5% per week up to 55%. In relation to the protocol adopted to the training, 50% 50% of the studies used 4 sets of 10 repetitions with interval of 60 seconds, and 25% of the studies used 4 sets of 10 to 12 repetitions, with 90 seconds interval, but with a load of 65% to 75% of 1RM, and finally 25% of the studies reported using the load between 55% and 90% of 1RM with a speed of 40 cm/s.

Chart 4 - Type, duration and dose of supplement.

Study	Type	Duration	Dose
(1)	Whey proteins	8 weeks	-
(2)	Whey proteins Isolated	12 weeks	Experimental diet: NP: 11,7% of protein HP: 44,3% of protein
(3)	Whey proteins	8 weeks	1,8g/kg
(4)	Whey proteins	8 weeks	-

100% of the studies used whey proteins as supplementation, probably due its characteristics conforming demonstrated by Macedo (2018), and 75% of the studies were prescribed for 8 weeks and 25% of the studies were prescribed for 12 weeks and in relation to the dosage of the supplement, 25% of the studies dose was 1.8g / kg and the other studies the percentage in the diet, in chart 4.

Chart 5 - Gene and muscle.

Study	Synthesis	Degradation	Muscle	Evaluation of hypertrophy
(1)	-	-	Gastrocnemius	Muscle Mass
(2)	-	-	Quadriceps and Gastrocnemius	Muscle Mass
(3)	-	-	-	-
(4)	MTOR	MURF-1, MAFBX	*Extensor Digitorum Longus* (EDL)	Muscle Mass

Regarding the effects of resistance training and supplementation of whey proteins, Table 4, in 25% of the studies, did not presented the gene expression of MTOR, MURF-1, MAFBX, the Extender Digitorum Longus (EDL) muscle mass, 75% of the studies did not verify the effect on genes of synthesis or degradation, 50% verified the mass of the gastrocnemius muscle.

Next, we will present a description, involving the observed variables for this systematic review and meta-analysis, on the four original articles selected.

Endurance Training in water

In the study by Haraguchi et al., (2010), using 32 male rats Fischer lineage (the authors do not report the age and the initial body mass of rats), and divided into 4 groups: 1) Sedentary Control; (CS) 2) Control Endurance Training (CE); 3) Sedentary Whey Proteins (WS); 4) Whey Proteins Endurance Training (WE). The CS and CE groups used AIN-93M standard ration, taking casein as a protein source, and the WS and WE groups used standard ration enriched with Whey Proteins instead of Casein.

The rats of the EC and WE groups performed resistance training over a period of 8 weeks and a frequency of 5 times a week in a liquid endurance training model, inducing rats to jump in a circular container corresponding to 150% of the length of the animal.

The protocol adopted was 4 series of 10 jumps, with 1 minute of interval between sets and the load attached to the syringe corresponding to 25% of body mass and increase of 5% per week to 55% of body mass in the last two weeks of Endurance training.

At the end, the food intake, body weight and gastrocnemius muscle weight were analyzed. Food intake was lower with statistical significance ($p=0.002$) in the groups that underwent endurance training, and this was not modified by the type of diet as we can understand based on the value of the statistical test ($p= 0.382$).

In relation to body weight and gastrocnemius muscle weight, these presented similar increases when compared to the initial moment in all groups; however, the EC group presented lower values when compared to the other groups, with statistical significance of ($p=0.032$) for body weight when seen the influence of the diet versus training and to the muscle ($p= 0.032$) of dietary influence and ($p=0.046$) when we evaluated the influence of endurance training.

These findings demonstrate the efficiency of the Whey Protein-enriched diet in maintaining a steady increase in body mass and muscle mass, in addition to preventing its decrease.

Endurance Training in treadmill

In study by Aparício et al., (2011), 96 male Wistar rats (the authors did not report the age, initial body weight) were submitted to endurance training 12-weeks duration in treadmill at a constant speed of 40 cm/s and a load in the tail between 55% and 90% of 1RM on a flat and stable surface, at a frequency of 3 to 4 times a week. The rats were randomized into 4 groups: 1) normal protein intake and sedentary; 2) normal protein intake and endurance training; 3) high intake of sedentary protein; 4) high protein intake and endurance training.

For the normal protein intake groups, the amount of 11.7% of daily protein was considered and for the high amount groups the daily value of 44.3% of protein was considered, using Whey Proteins as the sole source of protein.

After the experimental period, body weight in the group that underwent resistance training and low protein intake was lower ($p < 0.01$) when compared to the sedentary and high protein consumption groups.

In addition, the weight of the quadriceps and gastrocnemius muscles were higher ($p < 0.01$) in the groups that had high protein intake, and in the group that underwent training and high protein intake.

Combined training

In the study by Nunes et al., (2013), 32 male Wistar rats, 90 days old (the authors do not report initial body mass) were evaluated and divided into four groups: Training plus Whey Protein Supplementation (TRW); Sedentary plus Whey Protein Supplementation (SEDW); Training (TR); and Sedentary (SED).

These rats were submitted to an 8-week resistance training protocol, with frequency of 4 times weekly, in a squatting apparatus with low intensity electrical stimulation (4-5mA with 0.3 seconds duration and 3 seconds interval between each repetition).

After a period of adaptation and test of one maximal repetition (RM) the rats performed sessions with 4 sets of 10 to 12 repetitions with load of 65% to 75% of 1 RM and 90 seconds of pause between sets.

In addition, the supplemented groups were given a dose of $1.8 g.kg^{-1}$ of Whey Proteins diluted in distilled water by gavage immediately after the endurance training session.

The body mass, did not show differences between groups, presenting ($p > 0.05$), however the values for the 1RM test for the groups that underwent resistance training were higher in comparison to the sedentary groups ($p < 0.05$), but did not differ in the condition of supplementation (the authors do not describe the value of p, only that of significance).

In another study by Haraguchi et al., (2014), 32 male Fischer rats with approximately 60 days of age and 110 grams of body mass were divided into four groups: 1) Sedentary Control (CS); 2) Control Exercise (CE); 3) Sedentary Whey Proteins (WS); 4) Whey Proteins Exercise (WE), with a total of 8 rats per group. The groups CE and WE performed endurance training for the 8-week period and frequency of 5 times a week in the model swimming endurance training.

For this, the protocol adopted was 4 series of 10 jumps in a circular vessel corresponding to 150% of the length of the mouse, 1 minute of interval between series and the load attached to the tail corresponding to 25% of the body mass and increase of 5 % per week to 55% of body mass in the last two weeks of training. The CS and CE groups received standard ration for rodents, and the WS and WE groups received standard ration modified with Whey Proteins instead of the control protein.

After that, body weight gains, gastrocnemius muscle weight and extensor digitorum longus (EDL) were evaluated, as well as the gene expression of muscle proteins MTOR, MURF-1 and MAFBX. Body weight and gastrocnemius muscle and EDL were similar in the CS, WS and WE groups, but larger ($p = 0.021$) than the EC group.

In relation to the gene expression of MTOR, it was higher in the groups that did diet with Whey Proteins, besides the CE group presented a sharp drop ($p < 0.05$) when compared to the others (the authors did not describe the value of p, only that of significance). The expression of MAFBX did not show significant differences between groups ($p = 0.115$) and MURF-1 was significantly reduced in the groups that underwent resistance training ($p < 0.001$) independent of the Whey Proteins diet.

These results indicate that Whey Proteins contributes as a nutritional aid reducing the expression of protein degradation pathways and preventing the reduction of the synthesis pathways, however the authors point out limitations observed in the study, among them, a n of low representativeness for the study aim and the results demonstrated in the rat species used in this study (Fischer) may not reflect results obtained in the skeletal muscle in humans.

Due to the above, we infer that the models of endurance training adopted in the experiments are: jump in liquid medium, motorized treadmill and squatting apparatus for electric stimulation at the base. In this way, a meta-analysis is not possible in relation to the endurance training model, according to the methodological procedure proposed by Berwanger et al., (2007).

In relation to the supplementation of whey proteins, also, it can be inferred that in terms of experimental study in relation to the dose, the prescribed was recommended by manuals (Lancha Junior, Campos-Ferraz and Rogeri, 2009; Institute of Medicine, 2005). In this way, a meta-analysis regarding the dosage is also impossible, according to the methodological procedure proposed by Berwanger et al., (2007).

Although, the gene expression of MTOR, MURF-1, MAFBX, have been verified the same did not occur due to the effect of endurance training and the supplementation of whey proteins and therefore absent.

In this way, a meta-analysis is not feasible according to the methodological procedure proposed by Berwanger et al., (2007), but not the systematic review and therefore performed in this study, in relation to the gene expression of MTOR, MURF-1, MAFBX due to the effect of endurace training and the supplementation of whey proteins.

CONCLUSION

In relation of experimentation, there are not enough studies to compose the proper procedure for a meta-analysis, even after a systematic review, on the effects of resistance training and whey protein supplementation on MTOR gene expression, protein synthesis, and in the gene expression of MURF-1, protein degradation MABX, in wistar rats.

DECLARATION OF CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest of any kind.

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