

## 131 - STRENGTH TRAINING AND HOMOCYSTEINE AND ITS RELATIONSHIP WITH CARDIOVASCULAR DISEASES

JOSÉ MORAIS SOUTO FILHO  
ESSA - Escola Superior de Saúde de Arcoverde, Pernambuco.

doi:10.16887/90.a1.131

#### Introduction

Arterial hypertension has been identified as the main risk factor for morbidity and mortality due to the development of cardiovascular diseases. Among these are, the atherosclerotic process, heart failure, stroke and renal diseases. The indices of individuals affected by AH have been increasing due to environmental factors (eg, stress caused by modern lifestyle, neglect of diet and physical inactivity) increasingly present in the daily routine, triggering pathophysiological factors such as endothelial dysfunction, Reduction of nitric oxide (NO-) bioavailability, increased oxidative stress and elevated serum homocysteine levels (Hcy).

It is known that Hcy is an amino acid produced in the liver after the metabolism of methionine. Hcy is basically formed by the transsulfuration (catabolism) and demethylation (from the diet) of methionine. The mechanisms by which Hcy levels increase are still not entirely clear, but notably it is an important marker of cardiovascular diseases.

Genetic and nutritional factors may cause an increase in plasma Hcy levels, which in turn can lead to platelet aggregation and atheromatous plaque formation, implying vascular risk. Hyperhomocysteinemia (HHcy) leads to increased thiolation and homocysteinylolation of proteins in plasma and tissue affecting the function and activity of different enzymes such as superoxide dismutase, catalase or glutathione peroxidase.

Oxidative stress has also been reported as a factor contributing to the elevation of Hcy levels, as well as conditions capable of increasing oxidative stress. Elevated Hcy levels have been identified as a potent independent risk factor for coronary artery disease and stroke.

Physical exercise has been the source of study as a method to reduce circulating Hcy levels. Research has shown the efficacy of aerobic exercise in the reduction of plasma Hcy levels. Aerobic exercise can promote an acute increase of oxidative stress and a subsequent adaptation process that elevates the antioxidant capacity of the individual, generating a possible mechanism capable of explaining the decrease of Hcy levels against aerobic training.

However, the studies involving strength training and their respective intensities on Hcy levels are still scarce and inconclusive.

Thus, this systematic review aimed to identify in the existing literature studies that evaluated the effect of strength training on Hcy serum levels and its contributions in the fight against cardiovascular diseases.

#### Methodology

For the accomplishment of this study a search in PubMed, Lilacs, and Scielo databases was performed, using as descriptors the terms "homocysteine" associated with "strength training" and "resistance exercise".

The terms were typed in English in the databases. Dissertations, meta-analyses, and review articles were disregarded.

The following inclusion criteria were adopted: 1) original articles published in English, 2) studies conducted only in humans, 3) year of publication between 2003 and 2017, 4) clinical or experimental trial with intervention only a strength training program.

#### Results

In the initial stage of search, we found 7 articles. A previous analysis was carried out, using the inclusion and exclusion criteria. Two of these articles were excluded. One due to the use of mixed intervention program (aerobic and force); the other because it was performed in an animal model. Thus, five articles were selected, in which they were obtained and analyzed in their entirety for inclusion in the study. Table 1 shows the number of articles included and excluded in each database.

Table 1. Articles found in the databases

Number of articles: total articles found in each database using the descriptors. Excluded: Items that were not included in the sample based on the exclusion criteria. Included: article inserted in the sample for data analysis.

Table 2 shows the references of the articles included in the sample and their respective authors, years of publication, article title and published journals.

Table 2. References to articles in the sample

In three selected studies, the subjects were classified as healthy sedentary elderly individuals, both in the control group and in the groups, that underwent force training intervention. Two other studies were composed of healthy middle-aged individuals. Two studies had a mixed sample (men and women), two studies obtained only men as a sample, and one study was conducted only with women. The period of intervention was different among some studies. One study had a single acute intervention, the other two studies were performed with 24 weeks of intervention, one with 12 weeks of training and another with intervention of 12 months.

In relation to strength training intensity, two studies were performed with 75 to 80% of 1 maximal repetition (1RM), surveys performed with 60% of 1RM, a study used 50 to 80% of 1 RM and only one research was performed with 35% of 1 RM.

In all the studies, biochemical analyzes were performed to determine the plasma concentration of Hcy. In the study the chemiluminescence immunoassay method using Siemens reagents for homocysteine (Siemens Healthcare Diagnostics Inc., USA) was used. One study carried out the analysis of ethylenediaminetetraacetic acid (EDTA) for homocysteine measurements. The study of used a kit and Elisa method (Axis® Homocysteine EIA) to evaluate the serum levels of Hcy. In the two studies of total plasma homocysteine was evaluated using high performance liquid chromatography with electrochemical colorimetric detection.

It was observed that three studies showed a reduction in Hcy levels after the intervention period with strength training. One study showed no change in plasma levels of Hcy post-intervention. And one study showed an increase in post-intervention Hcy levels with strength training. Table 3 presents the characteristics of strength training interventions and their effects on plasma Hcy concentration.

Table 3. Strength Training Program

Hcy: - (reduction of plasma concentration of Hcy post-intervention); = (Plasma Hcy level did not change post intervention); + (Increased plasma levels of Hcy post-intervention); 1RM (test of maximum repetition).

#### Discussion

The result of this systematic review pointed out that strength training with moderate to high intensity seems to reduce Hcy plasma levels significantly.

Thus, the practice of strength training could contribute to a reduction in Hcy levels, aiding in the attenuation of the risk and incidence of cardiovascular diseases, since high plasma Hcy levels are related to the development of cardiovascular diseases. Research has shown the relationship of HHcy to endothelial dysfunction and vascular smooth muscle proliferation. In addition, HHcy increases oxidative stress and is closely related to the accumulation of asymmetric dimethylarginine (ADMA). ADMA is an endogenous inhibitor of nitric oxide synthase and has been implicated in the pathogenesis of endothelial dysfunction and vascular disease. Another study indicates that an elevation of 5 µmol of plasma Hcy is associated with an increase of 60% to 80% in the incidence of coronary artery disease.

However, it seems that the results obtained in this systematic review are in agreement with the literature, which indicates reduction of Hcy serum levels after strength training, since only one article reported an increase in plasma Hcy levels Intervention. It is possible that the intensity in said (i.e. 35% of 1RM) was weak, in addition to the protocol being performed in only one session, which may not have been sufficient to promote reduction. The increase of Hcy in the study mentioned before, could also have been obtained by deficiency of vitamins B6 and B12 in the respective volunteers. Inadequate intakes of vitamin B6 and B12 have been associated with elevation of Hcy, as their reduction may be observed in subjects who supplemented with vitamin B12.

As already mentioned among the beneficial effects of physical exercise practice, especially aerobic exercise, there is a reduction in Hcy levels associated with improved cardiovascular health. However, it is well described in the literature that aerobic exercises, when performed at inadequate intensity and volume, can trigger the production of reactive oxygen species, leading to greater oxidative stress. This is associated with the development of endothelial dysfunction.

In addition, there was a significant decrease in heart rate and systolic blood pressure ( $P = .045$ ,  $P = .023$ , respectively) in addition to the study of. Of the estimated mean  $\text{Vo}_2$  was significantly altered after 12 weeks ( $F = 28.086$ ,  $P = 0.001$ ). In the studies indicated that high intensity training may inhibit serum lipoprotein levels. These findings resemble the effects of aerobic training.

However, the studies selected in this systematic review focusing on the prescription of moderate to high strength exercise as intervention did not report increased oxidative stress, demonstrating an additional advantage of strength training in Hcy reduction and consequently in the fight against cardiovascular diseases, Especially for middle-aged and elderly.

#### Conclusion

This systematic review has shown that strength training may play an important role in reducing plasma Hcy levels in middle-aged and elderly individuals undergoing a regular exercise program of moderate to high intensity despite the mechanisms by which this occurs Reduction is not clear. Finally, it is cautioned not to generalize this finding, due to the limitations presented by this systematic review, such as the small number of studies used in this research. In this way, we suggest new studies to better elucidate the subject even with other population groups.

#### Referências

- Alomari, Mahmoud A et al.,. Effect of physical activity on levels of homocysteine, folate, and vitamin B12 in the elderly. *The Physician and sportsmedicine*, v. 44, n. 1, p. 68-73, 2016. ISSN 0091-3847.
- Antunes, Hanna Karen M et al.,. Aerobic physical exercise improved the cognitive function of elderly males but did not modify their blood homocysteine levels. *Dementia and geriatric cognitive disorders extra*, v. 5, n. 1, p. 13-24, 2015. ISSN 1664-5464.

- Benser, Jasmín et al., Impact of physical activity and cardiovascular fitness on total homocysteine concentrations in European adolescents: the HELENA study. *Journal of nutritional science and vitaminology*, v. 61, n. 1, p. 45-54, 2015. ISSN 0301-4800.
- Bizheh, Nahid and Jaafari, Mohsen. The effect of a single bout circuit resistance exercise on homocysteine, hs-CRP and fibrinogen in sedentary middle aged men. *Iranian journal of basic medical sciences*, v. 14, n. 6, p. 568-573, 2011. ISSN 2008-3866.
- Böger, Rainer H et al., Asymmetric dimethylarginine (ADMA): a novel risk factor for endothelial dysfunction. *Circulation*, v. 98, n. 18, p. 1842-1847, 1998. ISSN 0009-7322.
- Boushey, Carol J et al., A quantitative assessment of plasma homocysteine as a risk factor for vascular disease: probable benefits of increasing folic acid intakes. *Jama*, v. 274, n. 13, p. 1049-1057, 1995. ISSN 0098-7484.
- Brustolin, S, Giugliani, R and Félix, TM. Genetics of homocysteine metabolism and associated disorders. *Brazilian Journal of Medical and Biological Research*, v. 43, n. 1, p. 1-7, 2010. ISSN 0100-879X.
- Cai, Hua and Harrison, David G. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. *Circulation research*, v. 87, n. 10, p. 840-844, 2000. ISSN 0009-7330.
- Cavalca, Viviana et al., Oxidative stress and homocysteine in coronary artery disease. *Clinical chemistry*, v. 47, n. 5, p. 887-892, 2001. ISSN 0009-9147.
- Choi, Jeong Kyu et al., Regular exercise training increases the number of endothelial progenitor cells and decreases homocysteine levels in healthy peripheral blood. *The Korean Journal of Physiology & Pharmacology*, v. 18, n. 2, p. 163-168, 2014. ISSN 1226-4512.
- Collaboration, Homocysteine Studies. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *Jama*, v. 288, n. 16, p. 2015-2022, 2002. ISSN 0098-7484.
- e Silva, Alexandre de Souza and da Mota, Maria Paula Gonçalves. Effects of physical activity and training programs on plasma homocysteine levels: a systematic review. *Amino acids*, v. 46, n. 8, p. 1795-1804, 2014. ISSN 0939-4451.
- Eberhardt, Robert T et al., Endothelial dysfunction in a murine model of mild hyperhomocyst (e) inemia. *The Journal of clinical investigation*, v. 106, n. 4, p. 483-491, 2000. ISSN 0021-9738.
- Esfarjani, Fahimeh and Laursen, Paul B. Manipulating high-intensity interval training: effects on V' O<sub>2</sub>max, the lactate threshold and 3000 m running performance in moderately trained males. *Journal of science and medicine in sport*, v. 10, n. 1, p. 27-35, 2007. ISSN 1440-2440.
- Finaud, Julien, Lac, Gerard and Filaire, Edith. Oxidative stress. *Sports medicine*, v. 36, n. 4, p. 327-358, 2006. ISSN 0112-1642.
- Gelecek, Nihal et al., The effects of resistance training on cardiovascular disease risk factors in postmenopausal women: a randomized-controlled trial. *Health care for women international*, v. 33, n. 12, p. 1072-1085, 2012. ISSN 0739-9332.
- Hosseinzadeh, Somayeh, Dabidi Roshan, Valiollah and Pourasghar, Mehdi. Effects of intermittent aerobic training on passive avoidance test (shuttle box) and stress markers in the dorsal hippocampus of wistar rats exposed to administration of homocysteine. *Iranian journal of psychiatry and behavioral sciences*, v. 7, n. 1, p. 37-44, 2013.
- Majors, Alana, Ehrhart, L Allen and Pezacka, Ewa H. Homocysteine as a risk factor for vascular disease. *Arteriosclerosis, Thrombosis, and Vascular Biology*, v. 17, n. 10, p. 2074-2081, 1997. ISSN 1079-5642.
- Neves, Lindalva Batista, Macedo, Danielle Mazziere and Lopes, Antonio Carlos. Homocysteine. *Jornal Brasileiro de Patologia e Medicina Laboratorial*, v. 40, n. 5, p. 311-320, 2004. ISSN 1676-2444.
- Refsum, MD, H et al., Homocysteine and cardiovascular disease. *Annual review of medicine*, v. 49, n. 1, p. 31-62, 1998. ISSN 0066-4219.
- Ristow, Michael et al., Antioxidants prevent health-promoting effects of physical exercise in humans. *Proceedings of the National Academy of Sciences*, v. 106, n. 21, p. 8665-8670, 2009. ISSN 0027-8424.
- Safar, Michel E, Levy, Bernard I and Struijker-Boudier, Harry. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular diseases. *Circulation*, v. 107, n. 22, p. 2864-2869, 2003. ISSN 0009-7322.
- Simões, Marcus Vinicius and Schmidt, André. Hipertensão arterial como fator de risco para doenças cardiovasculares. *Medicina (Ribeirao Preto. Online)*, v. 29, n. 2/3, p. 214-219, 1996. ISSN 2176-7262.
- Škovierová, Henrieta et al., The Molecular and Cellular Effect of Homocysteine Metabolism Imbalance on Human Health. *International Journal of Molecular Sciences*, v. 17, n. 10, p. 1733, 2016.
- Sydow, Karsten et al., ADMA and oxidative stress are responsible for endothelial dysfunction in hyperhomocyst (e) inemia: effects of L-arginine and B vitamins. *Cardiovascular research*, v. 57, n. 1, p. 244-252, 2003. ISSN 0008-6363.
- Tawakol, Ahmed et al., Hyperhomocyst (e) inemia is associated with impaired endothelium-dependent vasodilation in humans. *Circulation*, v. 95, n. 5, p. 1119-1121, 1997. ISSN 0009-7322.
- Topal, Gökce et al., Homocysteine induces oxidative stress by uncoupling of NO synthase activity through reduction of tetrahydrobiopterin. *Free Radical Biology and Medicine*, v. 36, n. 12, p. 1532-1541, 2004. ISSN 0891-5849.
- Tsai, Chia-Liang et al., The effects of long-term resistance exercise on the relationship between neurocognitive performance and GH, IGF-1, and homocysteine levels in the elderly. *Frontiers in behavioral neuroscience*, v. 9, p. 23, 2015. ISSN 1662-5153.
- Tsai, Jer-Chia et al., Induction of cyclin A gene expression by homocysteine in vascular smooth muscle cells. *Journal of Clinical Investigation*, v. 97, n. 1, p. 146, 1996.
- Urso, C and Caimi, G. Oxidative stress and endothelial dysfunction. *Minerva medica*, v. 102, n. 1, p. 59-77, 2011. ISSN 0026-4806.
- Vincent, Heather K, Bourguignon, Cheryl and Vincent, Kevin R. Resistance training lowers exercise-induced oxidative stress and homocysteine levels in overweight and obese older adults. *Obesity*, v. 14, n. 11, p. 1921-1930, 2006. ISSN 1930-739X.
- Vincent, Kevin R et al., Homocysteine and lipoprotein levels following resistance training in older adults. *Preventive cardiology*, v. 6, n. 4, p. 197-203, 2003. ISSN 1751-7141.
- Vollaard, Niels BJ, Shearman, Jerry P and Cooper, Chris E. Exercise-induced oxidative stress. *Sports medicine*, v. 35, n. 12, p. 1045-1062, 2005. ISSN 0112-1642.
- Wald, David S, Law, Malcolm and Morris, Joan K. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *Bmj*, v. 325, n. 7374, p. 1202, 2002. ISSN 0959-8138.
- Wald, David S, Morris, Joan K and Wald, Nicholas J. Reconciling the evidence on serum homocysteine and ischaemic heart disease: a meta-analysis. *PLoS One*, v. 6, n. 2, p. e16473, 2011. ISSN 1932-6203.

### TREINAMENTO DE FORÇA E HOMOCISTEÍNA E SUA RELAÇÃO COM AS DOENÇAS CARDIOVASCULARES RESUMO

A hipertensão (HA) arterial vem sendo apontado como principal fator de risco para desenvolvimento de doenças cardiovasculares. Os índices de indivíduos acometidos pela HA vêm crescendo devido a fatores ambientais, como também por fatores fisiopatológicos como a elevação dos níveis séricos de homocisteína (Hci). Porém, as pesquisas envolvendo o treinamento de força suas respectivas intensidades e os níveis de Hci são escassos e não conclusivos. Esta revisão sistemática teve como objetivo identificar na literatura estudos que avaliaram o efeito do treinamento de força nos níveis séricos de Hci e suas contribuições no combate às doenças cardiovasculares. O exercício físico vem sendo fonte de estudo como método para a redução dos níveis de Hci circulantes. Foi realizada uma busca nos bancos de dados PubMed, Lilacs, e Scielo, utilizando como descritores os termos homocisteína associado com treinamento de força. Os artigos selecionados foram obtidos na íntegra e incluídos na amostra. Em relação à intensidade do treinamento de força dois estudos foram realizados com 75 a 80% de 1 RM, umas pesquisas realizaram com 60% de 1RM, um estudo utilizou 50 a 80% de 1 RM e apenas uma pesquisa foi realizado com 35% de 1 RM. Esta revisão sistemática evidenciou que o treinamento de força pode exercer importante papel na redução dos níveis plasmáticos de Hci em indivíduos de meia idade e idosos submetidos a um programa regular de exercício de força com intensidade moderada a alta, apesar dos mecanismos pelos quais ocorra esta redução não está claro.

Palavras-chave: Doenças cardiovasculares, Exercício Físico, Homocisteína.

### STRENGTH AND HOMOCYSTEINE TRAINING AND THEIR RELATIONSHIP WITH CARDIOVASCULAR DISEASES ABSTRACT

Arterial hypertension (AH) has been pointed as the main risk factor for the development of cardiovascular diseases. The rates of individuals with hypertension have been increasing due to environmental factors, as well as pathophysiological factors such as increased serum homocysteine (Hci) levels. However, research involving strength training, its respective intensities and Hci levels is scarce and inconclusive. This systematic review aimed to identify in the literature studies that evaluated the effect of strength training on serum Hci levels and their contributions in the fight against cardiovascular disease. Exercise has been a source of study as a method for reducing circulating Hci levels. A search was performed in the PubMed, Lilacs, and Scielo databases using as descriptors the terms homocysteine associated with strength training. The selected articles were obtained in full and included in the sample. Regarding the intensity of strength training, two studies were performed with 75 to 80% of 1 RM, one research performed with 60% of 1 RM, one study used 50 to 80% of 1 RM and only one research was performed with 35% of 1 RM. This systematic review has shown that strength training can play an important role in reducing Hci plasma levels in middle-aged and elderly individuals undergoing a regular program of moderate to high intensity strength exercise, despite the mechanisms by which this reduction occurs. It is unclear.

Keywords: Cardiovascular diseases, Physical exercise, Homocysteine.

### FORTALEZA Y ENTRENAMIENTO EN HOMOCISTINA Y SU RELACIÓN CON LAS ENFERMEDADES CARDIOVASCULARES RÉSUMÉ

L'hipertension artérielle (AH) a été désignée comme le principal facteur de risque de développement de maladies cardiovasculaires. Les taux d'individus souffrant d'hypertension ont augmenté en raison de facteurs environnementaux, ainsi que de facteurs physiopathologiques tels que l'augmentation des taux d'homocystéine sérique (Hci). Cependant, la recherche impliquant l'entraînement en force, ses intensités respectives et ses niveaux de Hci est rare et peu concluante. Cette revue systématique visait à identifier dans la littérature des études évaluant l'effet de l'entraînement en force sur les taux sériques d'Hci et leurs contributions dans la lutte contre les maladies cardiovasculaires. L'exercice a été une source d'étude comme méthode pour réduire les niveaux de Hci en circulation. Une recherche a été effectuée dans les bases de données PubMed, Lilacs et Scielo en utilisant comme descripteurs les termes homocystéine associés à l'entraînement en force. Les articles sélectionnés ont été obtenus dans leur intégralité et inclus dans l'échantillon. En ce qui concerne l'intensité de l'entraînement en force, deux études ont été réalisées avec 75 à 80% de 1 RM, une recherche effectuée avec 60% de 1 RM, une étude a utilisé 50 à 80% de 1 RM et une seule recherche a été réalisée avec 35% de 1 RM. Cette revue systématique a montré que l'entraînement en force peut jouer un rôle important dans la réduction des niveaux de plasma Hci chez les personnes d'âge moyen et âgées subissant un programme régulier d'exercices de force d'intensité modérée à élevée, malgré les mécanismes par lesquels cette réduction se produit. Ce n'est pas clair.

Maladies cardiovasculaires, exercice physique, homocystéine.

### FORCE ET FORMATION À L'HOMOCYSTEINE ET LEUR RELATION AVEC LES MALADIES CARDIOVASCULAIRES RESUMEN

La hipertensión arterial (AH) se ha señalado como el principal factor de riesgo para el desarrollo de enfermedades cardiovasculares. Las tasas de personas con hipertensión han aumentado debido a factores ambientales, así como a factores fisiopatológicos como el aumento de los niveles de homocisteína sérica (Hci). Sin embargo, la investigación que involucra entrenamiento de fuerza, sus respectivas intensidades y niveles de Hci es escasa e inconclusa. Esta revisión sistemática tuvo como objetivo identificar en la literatura estudios que evaluaran el efecto del entrenamiento de fuerza sobre los niveles séricos de Hci y sus contribuciones en la lucha contra la enfermedad cardiovascular. El ejercicio ha sido una fuente de estudio como método para reducir los niveles circulantes de Hci. Se realizó una búsqueda en las bases de datos PubMed, Lilacs y Scielo utilizando como descriptores los términos homocisteína asociados con el entrenamiento de fuerza. Los artículos seleccionados se obtuvieron en su totalidad y se incluyeron en la muestra. Con respecto a la intensidad del entrenamiento de fuerza, se realizaron dos estudios con 75 a 80% de 1 RM, una investigación realizada con 60% de 1 RM, un estudio utilizó 50 a 80% de 1 RM y solo una investigación se realizó con 35% de 1 RM. Esta revisión sistemática ha demostrado que el entrenamiento de fuerza puede desempeñar un papel importante en la reducción de los niveles plasmáticos de Hci en individuos de mediana edad y ancianos que se someten a un programa regular de ejercicio de fuerza de intensidad moderada a alta, a pesar de los mecanismos por los cuales ocurre esta reducción. No está claro.

PALAVRAS CLAVES: Enfermedades cardiovasculares, ejercicio físico, homocisteína.