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NUTRITIONAL VARIABLES AND SARCOPENIA; A REVIEW ANALYSIS

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ABSTRACT

Sarcopenia is defined as the loss of muscle strength and mass due to the age. Increasing the global and national elderly population, the necessity of investigating the significant factors on such Non Communicable Disease (NCDs) is more considerable. The current study has been conducted to assess the impact of nutritional factors on sarcopenia. We reviewed the studies published in several database on nutritional factors assumed to be in relation with sarcopenia directly or indirectly. The databases include Cochrane Collaboration library, Scopus, and PubMed. According to the studies done so far, the better part of the investigations are about the effect of vitamin D, Carbohydrate, protein and energy balance, and amino acid supplementation. Moreover, there are several topics; few studies have been done about. The effect of particular food groups such as fruits and vegetables, PUFA and fish oil consumption, particular dietary patterns such as Mediterranean dietary pattern; and antioxidant food components such as coffee may be considered in this category. The outcomes of the mentioned studies have been controversial, and there are not absolute results from various studies of same subject. However, some of the main outcomes are resigned in this abstract. The protein intake of 30 gr/meal or 1-1.2 g/kg BW for middle aged and elderly warrants muscle mass and body fat control. The intake of branched chain amino acids may have positive effects on body composition and attenuating muscle wasting. Fish oil and omega-3 fatty acids have been shown anabolic effects on protein metabolism and sarcopenia. The effect of fruits and vegetables represented positive association with lower risk of sarcopenia. Resisting exercises, Protein or essential amino acid supplementation, omega-3 fatty acids, and antioxidant foods may have positive effects on aged related sarcopenia. The studies are controversial, and further investigations are required to find the effect of dietary factors on prevention of sarcopenia as one of the prominent NCDs during elderly.

Keywords: *Sarcopenia, Nutrition, Fat Free Mass and Protein*

INTRODUCTION

Sarcopenia is defined as the loss of muscle function, strength and mass due to aging. However, there is a debate whether to distinct sarcopenia from dynapenia, i.e., loss of muscle power (Haehling *et al.*, 2010). As muscle mass declines below 2 standard deviation of mean muscle mass in the young population and the decrease of gait speed less than 0.8 m/s the clinical situation is clarified as sarcopenia (Haehling *et al.*, 2010). After approaching the age 50, muscle mass degenerates 1-2% annually, and muscle strength declines up to 1.5% during 50-60 and 3% afterward (Haehling *et al.*, 2010).

The main factors are denervation of motor units and modification of fast type muscles into slow type fibers.

According to the large population studies, 20% of 60 to 70 year-olds are sarcopenic, which approaches 50% in over 75 year old (Berger *et al.*, 2010). Sarcopenia is the primary risk factor for falling and disability in the agedness (Houston *et al.*, 2009), and in the United States the expenses of sarcopenia and the related disabilities were more than 18.5 billion dollars (Roth *et al.*, 2006). It is predicted that the elderly population will be almost tripled by the year 2050 (Leonke *et al.*, 2011). Increasing the global and national elderly population, the necessity to study the significant factors on Non Communicable

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Disease (NCDs) seems more considerable. The current study has been aimed to review the recent studies assessed the impact of nutritional factors on sarcopenia.

MATERIALS AND METHODS

We reviewed the studies published in several databases on nutritional factors assumed to be in relation with sarcopenia directly or indirectly. We surfed through Scopus, PubMed, and Cochrane library. The searched key words were “Sarcopeni”, “Sarcopenia AND Nutrition”, “Sarcopenia AND diet”. Scopus yielded 173 review articles with the key words “Sarcopenia and nutrition”, 10 articles of which were related to the association of dietary factors with sarcopenia. In PubMed we searched for the key word “sarcopenia”, among which, 38 articles were found eligible for inclusion. Some of the articles were found in more than one database. In Cochrane database, 12 articles were in the area of our topic. Among all of the found articles those entitled sarcopenia related to other factors such as cancer, cirrhosis, or pulmonary dysfunctions were excluded, and only the geriatric sarcopenia was the matter of review.

RESULTS AND DISCUSSION

Main Findings

According to the studies done so far, the better part of the investigations are about the effect of vitamin D, protein and amino acid supplementation. Moreover, there are several topics, few studies have been done about; The effect of particular food groups such as fruits and vegetables, PUFA and fish oil consumption, particular dietary patterns such as Mediterranean dietary pattern; and antioxidant food components such as coffee may be considered in this category. The main age related nutritional deficiencies ascribed to decrease in muscle function are vitamin D, protein intake, antioxidants, and long chain polyunsaturated fatty acids (PUFAs) (Siparsky *et al.*, 2013).

Protein and Aminoacid Supplementation

Along with aging, the anabolic resistance deteriorates the effect of leucine on muscle, and the insufficient dietary protein among the elderly people aggravates the situation (Darren *et al.*, 2012). Amino acid supplementation and particularly leucine may have benign effects on muscular mass and muscle protein balance. According to Dillon and coworkers (2009), 3 months supplementation of essential 15 gr/day of amino acids increased lean body mass in elderly women. Same results yielded about muscle function with 10 days supplementation of 15 g/day Essential amino acid supplementation during bed rest in older adults, and (Ferrando *et al.*, 2010).

The protein intake of 30 gr/meal or 1-1.2 g/kg body weight (BW) for middle aged and elderly, warrants muscle mass and body fat control (Mithal *et al.*, 2013). Compounding 12 g leucine distributed in three daily meals for 2 weeks increased muscle anabolism in older adults (Casperson *et al.*, 2012). Likewise, 8 g essential amino acid consumed orally by 66-84 year old subjects significantly increased whole body lean mass after 6 months, and the consistency of the results increased after 18 months (Solerte *et al.*, 2008).

Since Leucin or essential amino acid (EAA) supplementation overcomes the anabolic resistance, it may combat muscle mass related to aging (Katsanos *et al.*, 2008; Dreyer *et al.*, 2008). However, the mentioned results confirmed the positive effect on muscle kinetics and not lean body mass (Casperson *et al.*, 2012). Investigating the effect of amino acid supplementation, combination with exercise should be taken into consideration. According to Kim and coworkers (2012), amino acid supplementation increased leg muscle mass and knee extension accompanied by exercise. Knee extension did not improve by only exercise, whereas, leg muscle mass improved in the case of either exercise or the combination of exercise with amino acid supplementation.

The dietary source of protein has different effects on protein synthesis and increase in lean body mass. According to Philips (2012), vegetable proteins such as soy consumption has lower anabolic effects on lean body mass comparing beef as an animal protein. It is worth noting that meat is a more nutrient dense food containing Iron, zinc, vitamin B₁₂. Moreover, meat containing diet induced higher increase in lean body mass versus Lacto-Ovo-Vegetarian diet (Campbell *et al.*, 1999; Haub *et al.*, 2002).

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Fruits, Vegetables, Antioxidants

Fruits and vegetables may prevent acidosis related sarcopenia via blood potassium increase (Millward 2012). According to various studies, oxidative stress is a prominent factor in sarcopenia, and oxidative damage to DNA of muscle cells increases in the elderly (Walston *et al.*, 2006; Cesari *et al.*, 2004). As a result, higher intake of antioxidants such as carotenoids which quench free radicals and decrease pro-inflammatory cytokines such as Interlukin-6 may prevent muscle degeneration (Morley *et al.*, 2001; Zhao *et al.*, 2006; Semba *et al.*, 2003). Some epidemiological studies represented that in the elderly subjects, lower plasma carotenoids is related to increased walking disability and lower skeletal muscle (Semba *et al.*, 2007). Higher plasma concentrations of carotenoids and alpha-tocopherol were associated with higher muscle strength. Regarding the hypothesis of beneficent effects of antioxidant on sarcopenia there has been an *In vivo* study on mice to assess the probable effects of coffee on muscles. The results represented that coffee attenuated the descending trend of muscle mass and increased cell proliferation in damaged muscles (Guo *et al.*, 2014).

Fatty Acids

Omega-3 fatty acids and conjugated linoleic acid have represented some effects on hypertrophy of muscles and prevention of sarcopenia, and other omega-6 fatty acids have opposite impacts (Simopoulos, 2002; Gray and Da Boit, 2013). Linoleic acid (omega 3) fatty acid is the precursor of arachidonic acid, and arachidonic acid is the fatty acid initiating the production of eicosanoids as inflammatory compounds. Although after a resistant exercise the activation of inflammatory factors leads to synthesis of new proteins and degradation of catabolized proteins, chronic low grade inflammation related to aging leads to decline in muscle mass and fiber number (Roubenoff, 2003; Roberts *et al.*, 2007). A review of recent results and investigations by Girolamo and coworkers concluded that omega-3 supplementation combats anabolic resistance and prevents sarcopenia, particularly in the initiating stages of sarcopenia (2014).

Vitamin D

Considering 1 billion Vitamin D deficient people worldwide, the deficiency of vitamin D is a global health challenge (Darren *et al.*, 2012; Holick 2007). The elderly is highly prone to vitamin D deficiency which is the result of various factors such as lower exposure to sunrise (Mithal *et al.*, 2009), decreased absorption, lower activation in kidneys, and descending expression of vitamin D receptors (VDR) (Dawson-Hughes, 2008; Boonen *et al.*, 2006; Pfeifer *et al.*, 2002; Simpson *et al.*, 1985). Muscle atrophy had been related to vitamin D deficiency in several studies (Ceglia, 2008; Irani, 1976; Russell, 1994); which is probably because of anti-inflammatory effects of vitamin D and the existence of VDR (Bischoff-Ferrari *et al.*, 2004) and its function in skeletal muscle (Schleithoff *et al.*, 2006; Van den Berghe *et al.*, 2003). According to the recent studies vitamin D supplementation and higher serum levels of 25 (OH) D was positively related to muscle strength and mass (Bischoff-Ferrari *et al.*, 2004; Muir and Montero-Odasso, 2011). Controversially, Dupuy and colleagues found no association comparing the subjects with low intake and higher intake of vitamin D to be sarcopenic (2013).

Dietary Patterns

The existing studies on nutritional factors and sarcopenia, only one study on dietary patterns of African American and whites 30 to 64 years old has been done. According to the mentioned study, 10 food components were evaluated for the sufficiency of micronutrients including sandwich, sweet drinks, pizza, poultry, frozen meal, dessert, alcoholic drink, bread, starchy vegetables, and pasta/rice. The lowest sufficiency for sweet drinks and highest sufficiency for pasta/ rice was attained. The highest ratio of sarcopenic subjects were reported in alcoholic drink (1.5%), and the lowest ratio were embedded in poultry group (Kuczmarski *et al.*, 2013).

The Inter-correlation of Exercise and Diet

Since sarcopenia prognosis and prevention is in a tight joint with exercise, dismissing the prominent effect of exercise during nutrition therapy may lead to false outputs, and many studies investigate the simultaneous effect of exercise and food on sarcopenia.

The combination of a 10% weight loss diet with 45 minute aerobic per day during 5 week days, had significant effect on appendicular lumbar mass in obese postmenopausal women, whereas weight loss

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without exercise had declining effect on lumbar mass (Mason *et al.*, 2013). Additional calorie intake of 360 cal/day combined with resistance exercise training for 10 weeks represented strength increase in muscle of nursing home subjects and cachectic patients (Haehling *et al.*, 2010).

Conclusion

The main outcomes of the investigatory studies on nutritional factors affecting sarcopenia, represented that moderate physical activity, protein and essential amino acid supplementation, higher fruits and vegetables intake, sufficient fish oil consumption and lower consumption of energy dense foods are some of the benign factors help prevention of sarcopenia. The studies are controversial, and further investigations are required to find the effect of dietary factors on prevention of sarcopenia as one of the prominent NCDs during elderly.

Perspectives; Research Opportunities

There are some factors the effect of which on sarcopenia is recently the matter of few studies; Factors such as β -hydroxy β -methylbutyrate, citrulline malate, ornithine, Acid-base balance isoflavones etc. (Mithal *et al.*, 2013; Barillaro *et al.*, 2013). The effect of micro nutrients such as vitamin B group particularly folic acid and vitamin B₁₂, is related to homocysteine function (Mithal *et al.*, 2013). Additionally, there have been rare studies regarding dietary pattern in relation with sarcopenia. Additionally, the upcoming research plans may be allocated to aforementioned area.

REFERENCES

- Berger MJ and Doherty TJ (2010).** Sarcopenia: Prevalence, Mechanisms, And Functional Consequences. *Interdisciplinary Topics in Gerontology* **37** 94-114, doi: 10.1159/000319997, Epub.
- Stephan Von Haehling, John E Morley and Stefan D Anker (2010).** An overview of sarcopenia: facts and numbers on prevalence and clinical impact. *Journal of Cachexia Sarcopenia Muscle* **1** 129–133.
- Patrick N Siparsky, Donald T Kirkendall and William E Garrett Jr (2014).** Muscle Changes in Aging: Understanding Sarcopenia. *Sports Health: A Multidisciplinary Approach* **6** 36 originally published online 30 August 2013.
- Mason C, Xiao L, Imayama I, Duggan CR, Foster-Schubert KE, Kong A, Campbell KL, Wang CY, Villasenor A, Neuhouser ML, Alfano CM, Blackburn GL and McTiernan A (2013).** *Influence of Diet, Exercise, and Serum Vitamin D on Sarcopenia in Postmenopausal Women* (Lippincott Williams and Wilkins) **45**(4) 607-14.
- Darren G Candow, Scott C Forbes, Jonathan P Little, Stephen M Cornish, Craig Pinkoski and Philip D Chilibeck (2012).** Effect of nutritional interventions and resistance exercise on aging muscle mass and strength. *Biogerontology* **13** 345–358.
- Dillon EL, Sheffield-Moore M, Paddon-Jones D, Gilkison C, Sanford AP, Casperson SL, Jiang J, Chinkes DL and Urban RJ (2009).** Amino acid supplementation increases lean body mass, basal muscle protein synthesis, and insulin-like growth factor-I expression in older women. *Journal of Clinical Endocrinology and Metabolism* **94** 1630–1637.
- Bischoff-Ferrari HA, Borchers M, Gudat F, Du`rmu`ller U, Sta`helin HB and Dick W (2004).** Vitamin D receptor expression in human muscle tissue decreases with age. *Journal of Bone and Mineral Research* **19** 265–269.
- Muir SW and Montero-Odasso M (2011).** Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. *Journal of American Geriatric Society* **59** 2291–2300.
- Schleithoff SS, Zittermann A, Tenderich G, Berthold HK, Stehle P and Koerfer R (2006).** Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, Placebo-controlled trial. *American Journal of Clinical Nutrition* **83** 754–759.
- Van den Berghe G, Van Roosbroeck D, Vanhove P, Wouters PJ, De Pourcq L and Bouillon R (2003).** Bone turnover in prolonged critical illness: effect of vitamin D. *Journal of Clinical Endocrinology and Metabolism* **88** 4623–4632.
- Russell JA (1994).** Osteomalacic myopathy. *Muscle Nerve* **17** 578–580.

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- Irani PF (1976).** Electromyography in nutritional osteomalacic myopathy. *Journal of Neurology, Neurosurgery & Psychiatry* **39** 686–693.
- Ceglia L (2008).** Vitamin D and skeletal muscle tissue and function. *Molecular Aspects of Medicine* **29** 407–414.
- Boonen S, Bischoff-Ferrari HA, Cooper C, Lips P, Ljunggren O, Meunier PJ and Reginster JY (2006).** Addressing the musculoskeletal components of fracture risk with calcium and vitamin D: a review of the evidence. *Calcified Tissue International* **78** 257–270.
- Dawson-Hughes B (2008).** Serum 25-hydroxyvitamin D and functional outcomes in the elderly. *American Journal of Clinical Nutrition* **88** 537S–540S.
- Pfeifer M, Begerow B and Minne HW (2002).** Vitamin D and muscle function. *Osteoporosis International* **13** 187–194.
- Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B and Eisman JA et al., (2009).** Global vitamin D status and determinants of hypovitaminosis D. *Osteoporosis International* **20** 1807–1820.
- Holick MF (2007)** Vitamin D deficiency. *New England Journal of Medicine* **357** 266–281.
- Roberts MD, Iosia M, Kerksick CM, Taylor LW, Campbell B, Wilborn CD, Harvey T, Cooke M, Rasmussen C, Greenwood M, Wilson R, Jitomir J, Willoughby D and Kreider RB (2007).** Effects of arachidonic acid supplementation on training adaptations in resistance-trained males. *Journal of the International Society of Sports Nutrition* **4** 21, Doi 10.1186/1550-2783-4-21.
- Roubenoff R (2003).** Catabolism of aging: is it an inflammatory process? *Current Opinion in Clinical Nutrition and Metabolic Care* **6** 295–299.
- Simpson RU, Thomas GA and Arnold AJ (1985).** Identification of 1,25-dihydroxyvitamin D₃ receptors and activities in muscle. *Journal of Biological Chemistry* **260** 8882–8891.
- Barillaro C, Liperoti R, Martone AM, Onder G and Landi F (2013).** The new metabolic treatments for sarcopenia. *Aging Clinical and Experimental Research* **25**(2) 119-27.
- Mithal A, Bonjour JP, Boonen S, Burckhardt P, Degens H, El Hajj Fuleihan G, Josse R, Lips P, Morales Torres J, Rizzoli R, Yoshimura N, Wahl DA, Cooper C and Dawson-Hughes B (2013).** Impact of nutrition on muscle mass, strength, and performance in older adults. *Osteoporosis International* **24**(5) 1555-1566.
- Gray S, Da Boit M and Marine N (2013).** *Polyunsaturated Fatty Acids: A Potential Role in the Treatment of Sarcopenia* **8**(2) 187-194.
- Kim HK, Suzuki T, Saito K, Yoshida H, Kobayashi H, Kato H and Katayama M (2012).** Effects of exercise and amino acid supplementation on body composition and physical function in community-dwelling elderly Japanese sarcopenic women: a randomized controlled trial. *Journal of the American Geriatrics Society* **60**(1) 16-23.
- Solerte SB, Gazzaruso C, Bonacasa R, Rondanelli M, Zamboni M, Basso C, Locatelli E, Schifino N, Giustina A and Fioravanti M (2008).** Nutritional supplements with oral amino acid mixtures increases whole-body lean mass and insulin sensitivity in elderly subjects with sarcopenia. *American Journal of Cardiology* **101**(11A) 69E-77E.
- Stuart M Phillips (2012).** Nutrient-rich meat proteins in offsetting age-related muscle loss. *Journal of Meat Science* **92** 174-178.
- Campbell WW, Barton ML Jr, Cyr-Campbell D, Davey SL, Beard JL and Parise G et al., (1999).** Effects of an omnivorous diet compared with lactoovovegetarian diet on resistance-training-induced changes in body composition and skeletal muscle in older men. *The American Journal of Clinical Nutrition* **70** 1032–1039.
- Haub MD, Wells AM, Tarnopolsky MA and Campbell WW (2002).** Effect of protein source on resistive-training-induced changes in body composition and muscle size in older men. *The American Journal of Clinical Nutrition* **76** 511–517.
- Millward DJ (2012).** Nutrition and sarcopenia: evidence for an interaction. *Proceeding of the Nutrition Society* **71**(4) 566-75.

Research Article

- Morley JE, Baumgartner RN, Roubenoff R, Mayer J and Nair KS (2001).** Presented at the Seventy-third Meeting of the Central Society for Clinical Research. *Journal of Laboratory and Clinical Medicine* **137** 231–243.
- Weindruch R (1995).** Interventions based on the possibility that oxidative stress contributes to sarcopenia. *Journals of Gerontology Series A: Biological Sciences and Medical Sciences* **50** 157–161 [PubMed: 7493211].
- Mecocci P, Fanó G, Fulle S, MacGarvey U, Shinobu L, Polidori MC, Cherubini A, Vecchiet J, Senin U and Beal MF (1999).** Age-dependent increases in oxidative damage to DNA, lipids, and proteins in human skeletal muscle. *Free Radical Biology & Medicine* **26** 303–308 [PubMed: 9895220]
- Pansarasa O, Bertorelli L, Vecchiet J, Felzani G and Marzatico F (1999).** Age-dependent changes in oxidative damage to DNA, lipids and protein in human skeletal muscle. *Free Radical Biology & Medicine* **27** 617–622 [PubMed: 10490283].
- Lim PS, Cheng YM and Wei YH (2002).** Increase in oxidative damage to lipids and proteins in skeletal muscle of uremic patients. *Free Radical Research* **36** 295–301 [PubMed: 12071348]
- Gianni P, Jan KJ, Douglas MJ, Stuart PM and Tarnopolsky MA (2004).** Blog This! Oxidative stress and the mitochondrial theory of aging in human skeletal muscle. *Experimental Gerontology* **39** 1391–1400 [PubMed: 15489062].
- Hamilton ML, van Remmen H, Drake JA, Yang H, Guo ZM, Kewitt K, Walter CA and Richardson A (2001).** Does oxidative damage to DNA increase with age?. *Proceedings of the National Academy of Sciences USA* **98** 10469–10474 [PubMed: 11517304].
- Çakatay U, Telci A, Kayali R, Tekeli F, Akçay T and Sivas A (2003).** *Clinical Biochemistry* **36** 51–55 [PubMed:12554060].
- Walston J, Xue Q, Semba RD, Ferrucci L, Cappola A, Ricks M, Guralnik J and Fried LP (2006).** Serum Antioxidants, Inflammation, and Total Mortality in Older Women. *American Journal of Epidemiology* **163** 18–26 [PubMed: 16306311].
- Semba RD, Blaum C, Guralnik JM, Totin D, Ricks MO and Fried LP (2003).** Carotenoid and vitamin E status are associated with indicators of sarcopenia among older women living in the community. *Aging Clinical and Experimental Research* **15** 482–487 [PubMed: 14959951].
- Cesari M, Pahor M, Bartali B, Cherubini A, Penninx BW, Williams GR, Atkinson H, Martin A, Guralnik JM and Ferrucci L (2004).** Antioxidants and physical performance in elderly persons: the Invecchiare in Chianti (InCHIANTI) study. *American Journal of Clinical Nutrition* **79** 289–294 [PubMed: 14749236].
- Fanelli Kuczmarski M, Mason MA, Beydoun MA, Allegro D, Zonderman AB and Evans MK(2013).** Dietary patterns and sarcopenia in an urban African American and White population in the United States. *Journal of Nutrition in Gerontology and Geriatrics* **32**(4) 291-316.
- Loenneke JP and Pujol TJ (2011).** Sarcopenia: An emphasis on occlusion training and dietary protein. *Hippokratia* **15** 132–137.
- Houston DK, Nicklas BJ and Zizza CA (2009).** Weighty concerns: the growing prevalence of obesity among older adults. *Journal of the American Dietetic Association*.
- Roth SM, Metter EJ, Ling S and Ferrucci L (2006).** Inflammatory factors in age-related muscle wasting. *Current Opinion in Rheumatology* **18** 625–630.
- Dupuy C, Lauwers-Cances V, Van Kan GA, Gillette S, Schott AM, Beauchet O, Annweiler C, Vellas B and Rolland Y (2013).** Dietary Vitamin D Intake and Muscle Mass in Older Women. *Results from a Cross-Sectional Analysis of the EPIDOS Study* **17**(2) 119-24.
- Semba RD, Blaum C, Guralnik JM, Moncrief DT, Ricks MO and Fried LP (2003).** Carotenoid and vitamin E status are associated with indicators of sarcopenia among older women living in the community. *Aging Clinical and Experimental Research* **15**(6) 482-7.
- Guo Y, Niu K, Okazaki T, Wu H, Yoshikawa T, Ohru T, Furukawa K, Ichinose M, Yanai K, Arai H, Huang G and Nagatomi R (2014).** Coffee treatment prevents the progression of sarcopenia in aged mice in vivo and in vitro. *Journal of Experimental Gerontology* **50** 1-8.

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Di Girolamo FG, Situlin R, Mazzucco S, Valentini R, Toigo G and Biolo G (2014). Omega-3 fatty acids and protein metabolism: enhancement of anabolic interventions for sarcopenia. *Current Opinion in Clinical Nutrition and Metabolic Care* **17**(2) 145-50.