A UTILIZAÇÃO DO WHEY PROTEIN NA SUPLEMENTAÇÃO DE IDOSOS

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Review

Whey protein ingestion in elderly diet and the association with physical, performance and clinical outcomes

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ABSTRACT

Nutrition is critical to the health of the elderly, since most of them have a deficiency in key nutrient. The use of whey protein may be a food strategy to increase protein intake. The objective of this work was to evaluate the ingestion of whey protein for the elderly and the association with physical performance and clinical outcomes. A systematic review was conducted in order to find papers that shed some light in the correlation between whey protein and the elderly. Inclusion criteria: population: elderly; intervention: use of whey protein when compared to control group; outcome: related to health, nutrition, or quality of life. Database: PubMed, with papers published in the last 5 years. Search strategy: (elder OR senior OR elderly OR aging OR aged OR old OR older) AND (whey OR “whey protein”). 35 papers were selected of which 22 had a physical performance outcome and 13 had clinical outcomes. Studies indicate that whey protein supplements promote protein synthesis in the elderly, improving muscle performance and aerobic capacity, protecting against sarcopenia and reducing the risk for falls. In the papers studied, the age group considered to be elderly was ≥65 years in 27 papers and ≥60 years in the other 8 papers. Whey protein also appears to contribute to improved health, recovery from disease, prevention of cardiovascular and metabolic risks, and hepatic steatosis complications. Data suggest that whey protein supplements may be promising for the health improvement of the elderly.

1. Introduction

Aging is a process in which there is a decline of the body structure and functions in general, which can lead to chronic diseases (Gonçalves et al., 2013; Malta et al., 2013). The elderly population growth is a global milestone since the number of elderly people has been increasing significantly in recent years in developing countries, such as Brazil (Brasil, 2013). It is estimated that in Brazil there will be about 32 million elderly in 2025, thus the country will occupy the sixth position among the longest-lived countries worldwide (Garcez-Leme and Leme, 2014), and that the number of elderly will equal or exceed the number of children and teenagers between zero and 15 years old in 2050 (Brasil, 2013).

This is due to better quality of life and health care, which contributes to a greater longevity (Oliveira et al., 2015). The World Health Organization considers as elderly people who are 60 years-old or older in developing countries and 65 or older in developed countries.

Because of the large number of elderly, it is important to find ways to supply the nutritional amount of this population. Nutrition science is a great ally, since a balanced diet can bring many benefits to this group either as prevention or as diet therapy for diseases (Abreu et al., 2013; Deon et al., 2015). In addition, physiologically with aging, there are changes in nutrient intake, absorption and digestion (Malta et al., 2013).

Protein is indicated as the key nutrient for the health of the elderly, aiding in a better performance of the organism and in a better quality of life (Wolfe et al., 2008). However, many studies indicate that the elderly population has an insufficient intake of proteins of high biological value (Deon et al., 2015).

The whey protein fraction is obtained from the whey resulting from cheese making process through caseification. Whey proteins have around 15% to 20% of the total milk proteins (Patel, 2015; Camargo et al., 2018). They also have β-lactoglobulin (35% to 65%), and α-lactalbumin (12% to 25%). In smaller amounts, it has immunoglobulins (8%), albumin (5%), and lactoferrin (1%) as their main components. It is rich in branched chain amino acids, such as leucine, isoleucine, and valine; as well as cysteine (Patel, 2015). Whey protein is easily digestible, which rapidly increases the concentration of amino acids in

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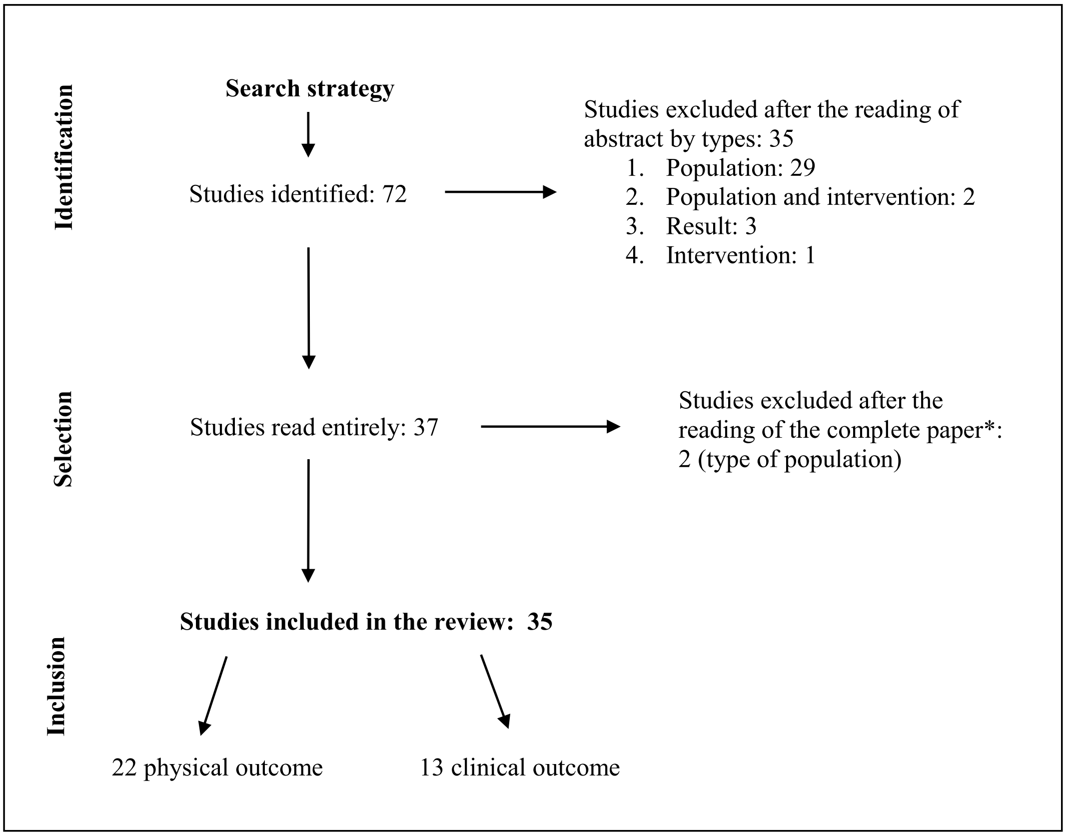

Fig. 1. Diagram of the search strategy used in this review (for further details, see Methods section).
*Did not meet the inclusion criteria.

plasma, promoting protein synthesis in tissues (Pacheco et al., 2005). It can be found for commercialization as: concentrated (containing lipids and lactose along with proteins – 29% to 89%), isolate (90% of protein), or hydrolyzed (partially digested, facilitating metabolism, besides being hypoallergenic) (Patel, 2015; Camargo et al., 2018). There are several functionalities attributed to whey protein in research: increasing of the technological quality of bakery products (Camargo et al., 2018), oxidative stress reduction, appetite reduction, hypoglycemia, attenuation of cardiovascular risks and increasing in muscle mass (Patel, 2015).

The main changes in body composition during the aging process are progressive loss of muscle mass and increase in fat mass (Chung et al., 2013; Verreijen et al., 2015). The loss of muscular mass and functionality (sarcopenia) contributes to the aggravation of many health outcomes, such as metabolic disorders, especially diabetes mellitus 2, as well as greater fragility, related to sarcopenia. Studies have shown that whey protein, along with resistance training, can improve muscle performance by stimulating protein synthesis, a protective factor against sarcopenia (Niitsu et al., 2015; Bell et al., 2017). It can also contribute to significant reductions in the risk of cardiovascular disease, improved metabolic health and cardiorespiratory capacity (Bell et al., 2017).

Considering the characteristics of the elderly population, as well as the nutritional properties of whey protein, this study reviews the literature and analyzes the use of whey protein in the elderly. It also investigates if whey protein supplementation generates some benefit in the process of aging because of its functionality when compared to the control population.

2. Methods

A systematic review was conducted in order to find papers that shed some light in the correlation between whey protein and elderly.

The search for data was carried out by two researchers from April 2016 to September 2018. The identification of the studies was carried out using a list of references of the papers published in the last five years in Portuguese, English, and Spanish, selected for full reading.

Inclusion criteria were type of study: clinical trial, controlled clinical trial, multicenter study, randomized controlled trial; species: human study; population: elderly population that had intervention with whey protein and were compared to control group and that had some outcome related to health, nutrition, and quality of life; period of publication: published in the last five years.

The exclusion criteria were: adult population, middle-aged adults, mixed adults and elderly or not having elderly described in the research; the intervention did not describe whey protein in the research; articles without results and surveys that did not fit into the inclusion criteria.

For electronic search strategy, the PubMed database was consulted. Two sets of terms were crossed for the electronic search: (elder OR senior OR elderly OR aging OR aged OR old OR older) AND (whey OR "whey protein") NOT Elder [Author]. The research resulted in 72 papers (Fig. 1), which data were inserted in a worksheet previously built with the items of interest, which model was followed by two reviewers independently and placed in Table 1 with: a) authors, country, and year; b) objective of the study; c) used methods; d) outcomes. Possible biases will also be presented in relation to the analysis performed.

3. Results

The results of the search strategy are shown in Fig. 1. After reading the papers, considering the inclusion and exclusion criteria, 35 studies were included in the present review. In the papers selected, the age group considered as elderly was ≥65 years old in 27 papers and ≥60 years old in the other 8 papers. The studies were divided by outcome of physical performance (Table 1) and clinical outcome (Table 2).

Table 1
Data summaries from articles containing physical performance outcome.

Authors (year)/country	Objectives	Methods	Main results
			Positive outcomes
Englund et al. (2018)-USA	To test the efficacy of long-term nutritional supplementation + physical activity in the elderly with limited mobility in order to improve muscle composition.	Randomized double-blind. Whey protein or placebo intake.	Both groups improved muscle strength and body composition. Higher intermuscular fat loss ($p = 0.049$) and increased muscle density ($p = 0.018$) in the supplemented group.
Chanet et al. (2017)-France	To investigate the acute effects of supplementing breakfast with vitamin D and whey protein + leucine on postprandial muscle protein synthesis and the long-term effect on lean mass in the elderly.	Randomized double-blind. Whey protein or placebo intake, measured in basal and postprandial state.	Postprandial FSR increase (0–240 min) in the test group ($p = 0.001$). Increase in lean mass in the test group after 6 weeks ($p = 0.035$), especially in lean leg mass ($p = 0.034$).
Bell et al. (2017)-Canada	To evaluate the effectiveness of 2×/day intake of a multi-ingredient protein-based supplement for increasing strength and lean mass, independently and in combination with exercise.	Randomized controlled. Phase 1: Whey protein or placebo intake for 6 weeks. Phase 2: both groups associated with exercise for 12 weeks.	Phase 1: only the supplemented group gained strength ($p < 0.001$) and lean mass ($p < 0.001$). After phase 2, increased upper body strength in the supplemented group ($p = 0.039$).
Agergaard et al. (2017a)-Denmark	To test whether light-weight resistance exercise (LW-RE) affects postprandial amino acid transporter (AAT) expression in skeletal muscle aging.	Randomized controlled. 3 groups: 2 whey protein intake modalities and 1 placebo.	LW-RE increased membrane-associated AAT protein expression and mRNA expression. Altered AAT protein expression was only observed in groups in which whey protein was ingested.
Dideriksen et al. (2016b)-Denmark	To study the influence of NSAID treatment on skeletal muscle during immobilization and rehabilitation resistance training (recycling).	Randomized study. Treatment with ibuprofen or placebo. Whey protein intake during the study. Variables: Plasma inflammatory markers, mass and strength of the quadriceps muscle and muscle gene expression.	Reduction of muscle mass and strength after 2 weeks of immobilization ($p < 0.001$) but returned to baseline levels after 2 weeks of combined whey protein training ($p < 0.001$). Muscle mass and strength exceeded baseline levels after re-training ($p < 0.05$) and the effects of NSAID were not affected. Differences over time were observed for muscle gene expression.
Holst et al. (2016)-Denmark	To assess whether it was possible to influence nutritional intake, loss of muscle function, and quality of life with an evidence-based intervention in hospitalized clinical patients with acute illness.	Randomized control. Whey protein intake soon after training and nutritional counseling. Functional and quality of life (QoL) measurements were made on admission and discharge.	Energy and protein intake increased 729.2 kcal ($p < 0.001$) and 28 g protein ($p < 0.001$), when compared with historical controls. Functional and QoL parameters improved for the total group, most notably in > 70 years old patients, from admittance to discharge.
Niitsu et al. (2015)-Japan	To investigate the effect of resistance training in combination with whey protein intake in the immediate postoperative period.	Randomized, double-blind. Intake of whey protein or placebo. Variables: knee extension strength and common daily activities by the Barthel Index (BI).	The whey protein group showed increased knee extension strength in the operated limb when compared to the control group ($p = 0.02$). Functional abilities presented greater improvements in the whey protein group than in the control group by the BI ($p < 0.05$).
Bauer et al. (2015)–Belgium, Germany, Ireland, Italy, Sweden and UK	To test the hypothesis that a specific nutritional supplement may result in improvements in sarcopenia measurements.	Multicenter, randomized, controlled, double-blind. 2 groups: whey protein or placebo 2×/day for 13 weeks. HGS (Hand-grip strength), SPPB, chair test, gait velocity, balance score, and lean mass	HGS and SPPB improved in both groups without differences. The whey protein group improved further in the chair test when compared to the control. The whey protein group gained more lean mass than the control group. Effect between groups: 0.17 kg ($p = 0.045$).
Karelis et al. (2015)-Canada	To examine the effects of whey protein supplementation with cysteine (Immunocal®) + resistance training (RT) on muscle strength and lean mass in the elderly.	Randomized, double-blind, controlled. The experimental group received whey protein and received casein. Both groups performed RT (3×/week).	The whey protein group showed increase in all 3 variables of muscle strength after the intervention ($p < 0.05$). Increase in muscle strength favored whey protein vs. casein by approximately 10% ($p < 0.05$).
Luiking et al. (2014)-USA	To evaluate whether a supplement specifically designed for the elderly stimulates muscle protein synthesis more acutely than a conventional dairy product.	Randomized, controlled, double-blind, intake of whey protein or control, immediately after exercise. FSR was measured for 4 h using a marker infusion protocol with phenylalanine, and regular blood and muscle sampling.	The FSR was higher in the whey protein vs the control group ($p = 0.049$). Increased postprandial concentrations in the whey protein group are possible mediating factors for the FSR response. There was a correlation with protein intake and postprandial FSR at rest ($p = 0.038$).
			Other findings
Fielding et al. (2017)-USA	To examine the impact of nutritional supplementation + physical activity on walking capacity in the elderly with limited mobility for 400 m.	Randomized for 24 weeks, vitamin D deficiency. Whey protein or placebo intake.	No statistical differences between groups, both improved gait speed ($p = 0.06$). Increased vitamin D in the supplemented group when compared to placebo.

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Table 1 (*continued*)

Authors (year)/country	Objectives	Methods	Main results
Gorissen et al. (2017)-Netherlands	To assess the impact of low protein intake (LowPro) when compared to high protein intake (HighPro) on basal and postprandial muscle protein synthesis rates after whey protein intake.	Randomized parallel group. LowPro or HighPro diet for 14 days. After this period, they ingested whey protein.	Increased plasma concentrations of amino acids after protein intake ($p < 0.01$), with no difference between treatments ($p > 0.05$). Higher rates of muscle protein synthesis in the fasting state than in the postprandial state after LowPro, when compared to HighPro, ($p < 0.01$), with no difference between treatments.
Kataoka et al. (2016)-Japan	To investigate the effects of hypervolemia by protein and glycemic supplementation during aerobic training in blood pressure (BP) and thermal regulation in elderly hypertensive males.	Randomized. Intake of whey protein or control. The plasma volume (PV), baroreflex sensitivity (BRS), carotid arterial compliance (CAC), esophageal temperature (EST), and blood flow of the forearm skin were measured.	Increased vascular conductance response of the forearm skin to EST increase with increased PV in the supplemented group, but this was not found in the control. However, despite the increase in PV, there was a reduction of BP with increase in CAC and increase of BRS in the supplemented group.
Agergaard et al. (2017b)-Denmark	To assess whether light-weight resistance exercise (LW-RE) affects FSR and anabolic intracellular signaling to combat age-related lean mass loss.	Randomized double-blind, placebo-controlled. 3 groups: 2 whey protein intake modalities and 1 placebo. Biopsies of the quadriceps muscle and the exercised leg were performed.	Resistance exercise at only 16% of 1-MR, increased myofibrillar FSR, regardless of nutrient type and feeding pattern, indicating the anabolic effect of LW-RE in the elderly. Increased signaling for translation initiation and translation elongation in response to LW-RE.
Dideriksen et al. (2016a)-Denmark	To determine if baseline FSR and its response to whey protein intake were impaired in the elderly with mild inflammation and whether it could be affected by treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and if the FSR response was related to the level of inflammation.	Randomized, transverse, double-blind, placebo-controlled, NSAID treatment or placebo for 1 week and healthy control. Intake of whey protein and acute heavy resistance exercise.	The baseline myofibrillar FSR and myofibrillar FSR responses in whey protein intake with and without exercise of acute resistance were maintained in the elderly with inflammation when compared with healthy controls ($p > 0.05$). Treatment with NSAIDs did not improve myofibrillar FSR responses or reduced plasma C-reactive protein (CRP) levels in inflamed elderly patients ($p > 0.05$).
Bülow et al. (2016)-Denmark	To determine the effects of daily physical activities on muscle protein synthesis (MPS) in the elderly male.	Randomized. 3 groups: inactivity (IA), daily physical activities (DA) or resistance exercises (RE). The whey protein served to determine the FSR of the myofibrillar protein of 10 h. Variables: physical activity, blood biopsies, and venous muscle.	Physical activity was higher in DA when compared to IA and RE groups. Nutrient intake increased plasma concentrations of insulin, leucine, and phenylalanine in all groups. FSR of myofibrillar protein was similar in groups IA, DA, and RE ($p = 0.44$).
Collins et al. (2016)-USA	To gather knowledge on the feasibility, safety, and efficacy of co-supplementation with creatine and protein supplementation.	Randomized, placebo-controlled exploratory, double-blind. Co-supplementation of whey protein and creatine (whey + CR) or just whey.	There were no differences between groups ($p > 0.05$). Both groups were effective in improving muscle function. All of them showed improvements in at least 2 of the 3 functional tests. Body composition and blood parameters were not altered ($p > 0.05$).
Zhu et al. (2015)-Australia	To evaluate the effects of whey protein supplementation on muscle mass and physical function in female elderly Australians.	Randomized, double-blind, placebo-controlled. Intake of whey protein or placebo. Radiological absorptiometry, lean mass, strength, physical function, TUG, and 24-h urinary nitrogen were measured at baseline, and at 1 and 2 years.	Over the 2 years, in both groups, there was reduction in muscle area and hand-grip strength ($p < 0.05$), but not in muscle mass. There were no significant effects of protein intervention on any of the measures of muscle mass or physical function.
Karelis et al. (2015)–Canada	To examine the effects of whey protein supplementation with cysteine (Immunocal®) + resistance training (RT) on muscle strength and lean mass in the elderly.	Randomized, double-blind, controlled. The experimental group received whey protein and received casein for 135 days. Both groups performed RT (3×/week).	No change between pre- and post-intervention in both groups for total lean mass.
Bukhari et al. (2015)–UK	To determine if the intake of essential amino acids (EAAs) rich in leucine in high doses stimulates muscular anabolism in a manner equivalent to whey protein in the female elderly at rest and after exercise.	Randomized. Ingestion of whey protein or EAA. Muscle protein and albumin synthesis (APS) was quantified at baseline and in response to diet (FED) and diet + exercise (FED-EX), insulin/AA concentrations and muscle anabolic signaling.	Plasma insulinemia and EAA/aemia were markedly increased after the use of whey protein ($p < 0.001$). Anabolic signal increased after FED-EX (2 h, $p < 0.05$). Similar increase in APS in both groups. The female elderly remains subtly responsive to nutrition ± exercise. However, whey protein does not offer a trophic advantage over EAA.
Villanueva et al. (2014)-USA	To examine the effects of resistance training with and without supplementation of creatine and whey protein on changes in body composition, muscle strength, and functional performance.	Randomized. Divided into 3 groups: resistance training + supplement (RTS, n = 7), only RT (n = 7) or control (C, n = 8). RT and RTS trained 3×/week.	There were no significant differences in the main outcome variables measured between TR and TRS after 12 weeks of study.

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Table 1 (*continued*)

Authors (year)/country	Objectives	Methods	Main results
Arnarson et al. (2013)-Iceland	To investigate whey protein supplementation results in a greater increase of lean mass, muscle strength, and physical function in the elderly during 12 weeks of exercise.	Randomized, controlled, double-blind. Supplementation + exercise intervention. Intake of whey protein or placebo after each workout. Exercise program 3×/weeks.	Lean mass, strength, and physical function increased during the study. The type of supplementation did not influence lean mass gains, quadriceps strength, or performance during 6-min walk or up and down test.
Chalé et al. (2013)–USA	Comparing effects of whey protein supplementation with control on changes in lean mass, muscle strength, and ladder climbing performance in elderly with limited mobility in 6 months of resistance training (RT).	Randomized. Intake of whey protein or placebo for 6 months. All participants also completed a progressive intervention of high-intensity RT.	Stair climbing performance improved in both groups. There were no statistical differences in the change in any of the variables studied between the groups.

Legend: EAA = essential amino acids, HGS = hand-grip strength, FSR = fractional synthetic rate, MR = maximum repetition, SPPB = Short Physical Performance Battery, TUG = Timed Up and Go.

3.1. The use of whey protein and physical performance outcomes

We found 22 papers relating the use of whey protein with the following outcomes related to physical performance (Table 1): muscle strength and muscle mass = 9; speed = 8; muscle protein synthesis rate (MPS) = 7; body composition and amino acid concentration = 3; fat loss = 2; and muscle density, expression of the postprandial amino acid transporter (AAT) in muscle and vitamin D = 1.

3.2. The use of whey protein and clinical outcomes

We found 13 papers relating the use of whey protein with the following clinical outcomes (Table 2): body composition = 6; protein and amino acid synthesis = 5; muscle strength and physical components = 3; caloric intake, glomerular filtration rate (GFR) and fat loss = 2; blood volume, thermoregulation, bone mineral density, waist circumference, fat loss, and total cholesterol/HDL ratio = 1.

4. Discussion

According to the countries where the studies were carried out, two distinct age groups were considered to be elderly in the papers surveyed, which corroborates with WHO (2002), which considers the elderly people who are 60 or older in developing countries, and 65 or older in developed countries. However, developed countries such as the Netherlands (Gorissen et al., 2017), Denmark (Dideriksen et al., 2016a; Dideriksen et al., 2016b), Japan (Niitsu et al., 2015), and United States of America (Luiking et al., 2014; Kerstetter et al., 2015; Jonker et al., 2017) used the age of 60 years as cut-off.

The data found in our research indicate that whey protein supplementation was favorable to the elderly. As is also evidenced in the study by Bauer et al. (2013), there may be a greater need for protein in the elderly when considering the recovery from disease and maintenance of functionality than in adults, making whey protein an interesting supplement for such purpose. In this sense, Paddon-Jones et al. (2008) demonstrated that whey protein supplements promoted protein synthesis in the elderly, thus, improving protective factor against sarcopenia, and acting positively on aerobic capacity. This demonstrates the benefits of whey protein for the elderly, according to Bell et al. (2017).

4.1. The use of whey protein and physical performance outcomes

Regarding physical performance outcomes, the studies evaluated the effect of whey protein use in the elderly accordingly to the following variables: muscle strength, density, muscle mass, gait velocity, fractional synthetic rate - FSR, body composition, fat loss, amino acid concentration, expression of the postprandial amino acid transporter (AAT) in muscle, and vitamin D.

4.1.1. Muscle strength, density, muscle mass, and gait speed

Bell et al. (2017), Niitsu et al. (2015), and Karelis et al. (2015) observed, in their interventions, an improvement in strength parameters with whey protein supplementation when compared to the control group. However, Englund et al. (2018), Bauer et al. (2015), Chalé et al. (2013), Villanueva et al. (2014), Zhu et al. (2015), and Arnarson et al. (2013) did not observe statistical difference between the intervention group and the control group.

Several papers on the outcome of density and muscle mass in the elderly were reviewed. Englund et al. (2018) observed that the supplemented group showed a significant increase in muscle density. Similarly, Chanet et al. (2017), Bell et al. (2017), Dideriksen et al. (2016b), Bauer et al. (2015), and Villanueva et al. (2014) found a significant increase in lean mass in the test group when compared to placebo. In contrast, in the studies of Zhu et al. (2015), Karelis et al. (2015), Chalé et al. (2013), and Arnarson et al. (2013), the researchers did not observe differences between the group supplemented with whey protein and the control group.

Several studies have addressed gait speed. Holst et al. (2016) noticed an improvement in the supplemented group, being even more remarkable with statistical difference in patients > 70 years old. Similarly, Collins et al. (2016), Niitsu et al. (2015), and Bauer et al. (2015) observed faster walking speed in the intervention groups when compared to the control group. However, Fielding et al. (2017), Villanueva et al. (2014), Arnarson et al. (2013), and Chalé et al. (2013) did not observe significant statistical differences in such parameter.

4.1.2. Fractional synthetic rate - FSR, body composition and fat loss

Papers that addressed fractional synthetic rate (FSR), Chanet et al. (2017) and Luiking et al. (2014), the authors observed that FSR increased in the supplemented group when compared to the control group. However, Agergaard et al. (2017a, 2017b), Dideriksen et al. (2016a), and Bülow et al. (2016) found no statistical differences between the two groups.

Englund et al. (2018) found no significant statistical difference in body composition in general, but the supplemented group had greater fat loss. Yet, Collins et al. (2016) and Villanueva et al. (2014) did not observe a significant difference in body composition and fat loss between the supplemented groups and the control group.

4.1.3. Amino acid concentration, amino acid transporter, and vitamin D

No significant increase in amino acid concentrations in the intervention group was observed when compared to the control group among the studies of Gorissen et al. (2017), Bülow et al. (2016), and Bukhari et al. (2015).

In Agergaard et al. (2017a, 2017b), a significant increase in the expression of the postprandial amino acid transporter (AAT) in the skeletal muscle was observed in the groups supplemented with whey protein, pointing to an importance of AATs in the anabolic response

Table 2
Data summaries from articles containing clinical outcome.

Author (year)/country	Objectives	Methods	Main results
			Positive outcomes
Kemmler et al. (2018)-Germany	To evaluate the effect of whole body electromyostimulation (EM) on parameters of obesity and cardiometabolic risk in men with Sarcopenic Obesity (SO).	Randomized controlled. 3 groups: whey protein, whey protein + EM, or control. The outcomes were: total fat mass (TFM), trunk fat mass (TF), waist circumference (WC), and total cholesterol/HDL ratio (TC/HDL).	TFM reduced in the whey protein ($p = 0.005$) and EM ($p < 0.001$) groups, but not in the control group. Changes in the EM group ($p < 0.001$) and in the whey protein group ($p = 0.011$) differed from control. TF decreased with EM ($p < 0.001$) and whey protein ($p = 0.117$) and increased in the control ($p = 0.159$). WC reduced in the treatment groups and remained in control. The TC/HDL ratio improved in the EM group and whey protein and remained in control. Differences between EM and whey protein were determined only for WC ($p = 0.015$).
Uchida et al. (2018)–Japan	To find out if the training-induced increase in plasma volume (PV) improves thermoregulation, and if supplementation has greater effects in the elderly.	Randomized. Pre and post-intervention measurement of PV, plasma albumin content (Albcont), fasting glucose concentration, and HbA1c. Supplementation of carbohydrate or carbohydrate + whey protein, during the additional training of 5 months.	Pre: PV and Albcont were correlated with the number of training days in the previous 12 months ($p < 0.001$). Post: Reduced PV and Albcont in the carbohydrate group and increased HbA1c ($p < 0.001$), but these values remained unchanged in the carbohydrate + whey protein group, with differences in the changes between groups.
Niccoli et al. (2017)-Canada	To evaluate the efficacy of whey protein in the rehabilitation results in a fragile and hospitalized elderly population.	Randomized controlled double-blind, supplementation with whey protein or control group during hospitalization. Several functional and serum measures were determined before and after intervention.	Whey protein increased the average daily protein intake and was well tolerated. The whey protein group exhibited improvements in HGS and knee extension strength over the control group, and a positive correlation was found between the change in pre-albumin and the increased percentage of the knee extension strength.
Giezenaar et al. (2017)-Australia	To determine the effects of whey protein on caloric intake, appetite, gastric emptying, and intestinal hormones in the elderly.	Randomized. Whey protein intake of 30 g or 70 g or placebo on 3 occasions. At regular intervals (> 180 min), appetite, gastric emptying glucose, and hormones (insulin, glucagon, ghrelin, CCK, GIP, GLP-1 and PYY) were measured, in addition to caloric intake from a buffet meal.	Higher caloric intake in men ($p < 0.001$). There was no effect of gender on gastric emptying, appetite, gastrointestinal symptoms, glucose, or intestinal hormones. Reduced gastric emptying dependent on protein load. Higher concentrations of insulin, glucagon, CCK, GIP, GLP-1, and PYY. Increase in total caloric intake (whey protein + meal: increase of 12% with 30 g and increase of 32% with 70 g, $p < 0.001$). Caloric intake was inversely related to the volume of the stomach and the area under the curve of hormonal concentrations ($p < 0.05$).
Stojkovic et al. (2017)–USA	To verify whether high glycemic index/glycemic load (GI/GL) diets increase risk of chronic inflammation and age-related changes in body composition and insulin resistance.	Randomized. Supplementation of whey protein in bone density to assess the impact of increase in GI/GL on inflammation, insulin resistance, and body composition. Inflammatory markers, HOMA, body composition, and GI/GL (estimated from 3-day food records) evaluated before and after the intervention (PRO).	Increased GL in control and no change in the whey group ($p < 0.0001$). There were no differences in serum CRP, IL-6, or HOMA at 18 months between groups, nor associations between GC and inflammatory markers. Increase in lean body mass ($p = 0.0375$) and total lean mass ($p = 0.038$) in the PRO group. Associations for GL and change in total fat mass ($p = 0.01$), change in BMI ($p = 0.005$), and change in the lean mass/fat ratio ($p = 0.002$).
Gorissen et al. (2016)-Netherlands	To assess postprandial plasma AA concentrations and muscle protein synthesis rates following ingestion of a bolus of 35 g of hydrolyzed wheat protein when compared to casein and whey protein.	Randomized, male. 5 groups: 35 g wheat protein (n = 12), 35 g wheat protein hydrolyzed (WPH-35; n = 12), 35 g micellar casein (MCas-35; n = 12), 35 g whey protein (Whey- 12) or 60 g wheat protein hydrolyzed (WPH-60; n = 12). Plasma and muscle samples were collected at regular intervals.	Postprandial increase in plasma AA concentrations was greater after Whey-35 intake than after MCas-35 and WPH-35 ($p < 0.01$). Myofibrillar protein synthesis rates were higher after ingestion of MCas-35 ($p < 0.01$) than after WPH-35 ($p = 0.03$). Postprandial increase in plasma leucine concentrations was higher after Whey-35 intake than after WPH-60 ($p < 0.01$), despite the similar content of leucine. However, ingestion of WPH-60 increased myofibrillar protein synthesis rates above baseline ($p = 0.02$).

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Table 2 (*continued*)

Author (year)/country	Objectives	Methods	Main results
Luiking et al. (2016)-Netherlands	To evaluate the impact of nutritional supplements with different protein sources and energy density on serum AA levels and gastrointestinal behavior.	Randomized, controlled, single-blind and crossover. Intake of 4 supplements: whey protein + leucine 150 or 320 kcal (W150/W320) or casein 150 or 320 kcal (C150/C320). Gastrointestinal behavior was studied in vitro, observing gastric coagulation and cumulative digestion of intestinal protein over time.	The peak of leucine serum concentration was 2× higher in W150 vs. C150 ($p < 0.001$), increased in W320 vs. C320 ($p < 0.001$), and higher for hypocaloric vs caloric products ($p < 0.00$). Similar effects were observed for maximum concentrations of EAA and AAT. In vitro gastric coagulation was observed only for casein supplements. Intestinal digestion for 90 min. Resulted in higher levels of free AAT, EAA, and leucine for W150 vs. C150, for W150 Vs. W320, and C150 Vs. C320 ($p < 0.0125$).
Rondanelli et al. (2016)-Italy	To find out whether supplementation + regular physical activity increases fat-free mass, strength, physical function, and quality of life, and reduces risk of malnutrition in sarcopenic elderly.	Randomized, double-blind, placebo-controlled study lasting 12 weeks. Intake of supplementation or placebo. Examined: body composition, muscle strength, and biochemical indexes of nutritional status and health. Evaluated: global nutritional status, physical function, and quality of life before and after intervention.	When compared with physical activity and placebo, supplementation with physical activity increases fat free mass ($p < 0.001$), relative skeletal lean mass ($p = 0.009$), body fat distribution ($p = 0.021$), HGS ($p = 0.001$), physical component scores ($p = 0.030$), daily life activities ($p = 0.001$), mini nutritional assessment ($p = 0.003$), and IGF-1 ($p = 0.002$), and lower CRP ($p = 0.038$).
Ooi et al. (2015)–Australia	To investigate the effect of increasing the nutritional intake of whey protein in relation to carbohydrate in hepatic steatosis.	Randomized, double-blind. Intake of whey protein or control for cardiometabolic and bone health. Hepatic steatosis was quantified through computed tomography ratio of liver to spleen (L/S). Fatty Liver Disease (FLD) was defined as liver-spleen difference < 10 units Hounsfield.	Control and whey protein were similar in BMI, insulin resistance, L/S ratio, and prevalence of DHG at baseline. In 2 years, dietary protein increased by 20 g in whey protein group, not in control. Greater L/S ratio in control, not in whey protein group, in 2 years, with no difference between groups. In a comparison within the group, the change in BMI correlated with changes in the control L/S ratio ($p = 0.0007$), but not with whey protein ($p = 0.73$).
Ramel et al. (2013)–Iceland	To ascertain changes in kidney function after a 12-week resistance exercise program + protein supplementation in the elderly.	Randomized. Exercise 3×/week, designed to increase strength and muscle mass of major muscle groups. Intake of one of the 3 supplements right after the workout: whey protein drink, milk protein, or carbohydrate. Kidney function was estimated by GFR and food intake at the beginning and at end of the intervention.	There was an increase in carbohydrate intake in the carbohydrate group and in protein in the milk group. In the whey protein group, there was no increase in protein intake, but there was in carbohydrate intake. After 12 weeks, lean mass, TUG, and gait speed improved. GFR increased after the intervention ($p < 0.001$) with no difference between gender and age. Changes in GFR at the end of the intervention were not associated with lean mass, supplements, or total protein intake.
			Other findings
Jonker et al. (2017)–USA	To compare the efficacy of EAA supplementation in the stimulation of anabolism of liquid proteins among COPD patients and healthy elderly.	Randomized, double-blind, moderate to very severe COPD. Intake of EAA added by leucine or AAT mixture, like whey protein. The net whole body protein gain and splenic phenylalanine extraction were evaluated.	Excellent positive linear relationship between phenylalanine intake and net protein gain in both groups ($p < 0.001$), net protein gain was 42% higher in control and 49% higher in COPD after ingestion of EAA when compared to AAT ($p < 0.0001$). Higher net gain of protein in the COPD group for both mixtures due to a 40% lower splenic extraction ($p < 0.0001$), but similarly related to dietary phenylalanine (i.e. EAA).
Kramer et al. (2015)-Netherlands	To determine the impact of the macronutrient composition of a supplement on the synthetic response of postprandial muscle protein in the elderly.	Randomized, non-sarcopenic male. Intake of whey protein with leucine + carbohydrates + lipids (Whey-En), whey protein with leucine (Whey), or just carbohydrates + lipids (En). The stable isotopic markers methodology was applied to evaluate the basal and postprandial FSRs in the 3 groups.	Protein intake in the Whey-En and Whey groups had higher FSR when compared to basal rates ($p < 0.05$), carbohydrate and lipid intake did not increase FSR in the En group. Highest postprandial increase in insulin concentration in the Whey-En group. No differences in postprandial FSR were observed between Whey-En and Whey groups. Postprandial FSR rates were higher in the Whey-En vs. In ($p = 0.01$).

(*continued on next page*)

Table 2 (*continued*)

Author (year)/country	Objectives	Methods	Main results
Kerstetter et al. (2015)-USA	To investigate the impact of a moderately high protein diet on bone mineral density (BMD).	Randomized, double-blind. Indication of whey protein or maltodextrin to its usual diet for 18 months. BMD, body composition, and markers of skeletal and mineral metabolism were measured at baseline, at 9 and 18 months.	There were no differences between groups regarding changes in BMD. Lean body mass was highest in the protein group at 18 months ($p = 0.048$). C-terminal Telopeptide ($p = 0.041$), IGF-1 ($p = 0.005$), and urinary urea ($p < 0.001$) were also higher in the protein group at the end of the study period. There was no difference in the estimated GFR at 18 months.

Legend: TAA = total amino acids, COPD = chronic obstructive pulmonary disease, EAA = essential amino acids, HGS = hand-grip strength, FSR = fractional synthetic rate, GIP = gastric inhibitory polypeptide, GLP-1 = glucagon-like peptide-1, HbA1c = glycated hemoglobin, HCY = homocysteine, HOMA = homeostasis model assessment, IGF-1 = insulin grow factor-1, IL-6 = interleucine-6, CRP = C-reactive protein, GFR = glomerular filtration rate, TUG = Timed Up and Go.

after protein intake along with low intensity exercise.

Fielding et al. (2017), who examined the impact of nutritional supplementation and physical activity on mobility in the elderly, found an increase in vitamin D in the supplemented group when compared with placebo, as expected.

4.2. The use of whey protein and clinical outcomes

Regarding clinical outcomes, the studies evaluated the effect of whey protein on the following variables: body composition, fat loss, waist circumference, caloric intake, glycemic load index, total cholesterol/HDL cholesterol ratio, muscle strength, physical components, protein and amino acid synthesis, GFR, plasma volume, thermoregulation, and bone mineral density.

Ramel et al. (2013) investigated kidney function in the elderly after a 12-week exercise program combined with post-exercise protein intake and found that the participants' kidney function was not impaired, including an average increase in GFR. Kerstetter et al. (2015), who investigated the impact of whey protein on bone mineral density in the elderly for 18 months, have also found no impairment in GFR, suggesting that supplementation may preserve lean mass without impairing the skeletal health or kidney function on the healthy elderly. Paddon-Jones et al. (2008) point out that there is little evidence linking high protein intake to increased risk of impaired kidney function in healthy subjects. However, considering that kidney function decreases with age, its evaluation in the elderly is recommended before joining a hyperproteic diet.

4.2.1. Body composition, fat loss, and waist circumference

In this study, several papers addressed the outcome on body composition. Kemmler et al. (2018), Stojkovic et al. (2017), Rondanelli et al. (2016), Kerstetter et al. (2015), and Ramel et al. (2013) found significant differences in the body composition of the supplemented group, when compared to the control group. However, Ooi et al. (2015) did not observe significant difference between the test and control groups.

Kemmler et al. (2018) also observed greater fat loss and greater waist circumference reduction in the supplemented groups.

4.2.2. Caloric intake, glycemic load, and lipid profile

Two papers in our research addressed the caloric intake in the elderly. Giezenaar et al. (2017) observed higher caloric intake in the test groups: the higher the whey protein content, the higher the caloric intake. However, Ramel et al. (2013) did not observe a significant increase in caloric intake between the groups.

Only one paper dealt with GI/GL. Stojkovic et al. (2017) found an increase in glycemic load (GL) in the carbohydrate group (34%), but not in the whey protein group.

Kemmler et al. (2018) observed a significant improvement in the total cholesterol/HDL-cholesterol ratio in the whey protein supplemented groups when compared to the control in obese, sarcopenic elderly individuals.

4.2.3. Muscle strength, physical components, protein and amino acid synthesis

The aspects of muscular strength and physical components were addressed in the clinical outcome as well. Niccoli et al. (2017), Rondanelli et al. (2016), and Ramel et al. (2013) demonstrated that whey protein supplementation significantly improves the parameters of muscle strength and physical function, improving the quality of life of the elderly.

The present study found that some papers addressed the topic of protein and amino acids synthesis specifically, such as Jonker et al. (2017), Gorissen et al. (2016), Luiking et al. (2016), and Kramer et al. (2015), who found a significant increase in protein and amino acid concentrations in the whey protein group when compared to the control group.

4.2.4. Glomerular filtration rate (GFR), plasma volume, thermoregulation, and bone mineral density

The GFR was investigated in two studies in our research. Ramel et al. (2013), observed that GFR increased significantly after the intervention and the changes were similar in both genders and at similar ages. However, Kerstetter et al. (2015) did not observe a significant difference in GFR at the end of their study.

Uchida et al. (2018) observed significant differences in plasma volume (PV) between the group supplemented with whey protein and the control group. In addition, a significant increase in glycated hemoglobin (HbA1c) was observed only in the control group.

Kerstetter et al. (2015) did not observe significant changes in bone mineral density (BMD) between the intervention and control groups. However, lean body mass was significantly higher in the supplemented group after study completion.

5. Conclusion

In general, the data found in this review suggest that whey protein supplementation was promising for the health of the elderly population, since several authors found positive results in groups of elderly people who received supplementation when compared to the control groups.

However, there are still outcomes whose results of supplementation are not well understood, as well as some studies that found no difference between the respective groups supplemented with whey protein and the control groups. This can occur due to the heterogeneity of the research, as well as to the short period of intervention of some studies. It is also observed that most of the research was carried out in developed countries. Further studies should be done to analyze the effects of long-term whey protein intake with different elderly profiles such as very old elderly, and in developing countries.

Declaration of competing interest

The authors declare that they do not have any conflicts of interest.

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