Nutrition 72 (2020) 110667

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

Current opinion on dietary advice in order to preserve fat-free mass during a low-calorie diet

Mariangela Rondanelli M.D., Ph.D. [a,b], Milena Anna Faliva Ph.D. [c], Clara Gasparri M.Sc. [c,*], Gabriella Peroni B.Sc. [c], Daniele Spadaccini B.Sc. [c], Roberto Maugeri M.D. [d], Mara Nichetti M.Sc. [c], Vittoria Infantino M.D. [e], Simone Perna Ph.D. [f]

[a] IRCCS Mondino Foundation, Pavia, Italy
[b] Department of Public Health, Experimental and Forensic Medicine, Unit of Human and Clinical Nutrition, University of Pavia, Pavia, Italy
[c] Department of Public Health, Experimental and Forensic Medicine, Section of Human Nutrition, Endocrinology and Nutrition Unit, Azienda di Servizi alla Persona (ASP), University of Pavia, Pavia, Italy
[d] Research and Clinical Investigation Department, Company Medical Dietetics, Savigliano, Italy
[e] Department of Biomedical Science and Human Oncology, University of Bari Aldo Moro, Bari, Italy
[f] Department of Biology, College of Science, University of Bahrain, Sakhir, Kingdom of Bahrain

ARTICLE INFO

Article History:
Received 19 December 2018
Received in revised form 27 November 2019
Accepted 1 December 2019

Keywords:
VLCKD
Leucine
Fat-free mass
Whey protein
Branched chain amino acid
Vitamin D

ABSTRACT

Objectives: The loss of fat-free mass (FFM) that occurs during weight loss secondary to low-calorie diet can lead to numerous and deleterious consequences. We performed a review to evaluate the state of the art on metabolic and nutritional correlates of loss of fat free mass during low calorie diet and treatment for maintaining fat free mass.
Methods: This review included 44 eligible studies. There are various diet strategies to maintain FFM during a low-calorie diet, including adoption of a very low carbohydrate ketogenic diet (VLCKD) and taking an adequate amount of specific nutrients (vitamin D, leucine, whey protein).
Results: Regarding the numerous and various low-calorie diet proposals for achieving weight loss, the comparison of VLCKD with prudent low-calorie diet found that FFM was practically unaffected by VLCKD. There are numerous possible mechanisms for this, involving insulin and the insulin-like growth factor-1–growth hormone axis, which acts by stimulating protein synthesis.
Conclusions: Considering protein and amino acids intake, an adequate daily intake of leucine (4 g/d) and whey protein (20 g/d) is recommended. Regarding vitamin D, if the blood vitamin D has low values (<30 ng/mL), it is mandatory that adequate supplementation is provided, specifically calcifediol, because in the obese patient this form is recommended to avoid seizure in the adipose tissue; 3 to 4 drops/d or 20 to 30 drops/wk of calcifediol are generally adequate to restore normal 25(OH)D plasma levels in obese patients.

Introduction

The decrease in body weight that takes place during a low-calorie diet (protein intake equal to 15% of total energy intake) physiologically involves a loss of both fat and fat-free mass (FFM): the physiology indicates that about 75% of the weight loss consists of a loss of fat mass, whereas the remaining 25% consists of a loss in fat-free mass [1]. The loss of fat-free mass that occurs during a weight loss can lead to numerous and deleterious short- and long-term consequences that can frustrate some of the benefits related to weight loss [2]. In fact, fat-free mass, in addition to its role in locomotion, plays a key role in various metabolic pathways, such as glucose regulation [3] and lipid control [4]. A loss of fat-free mass can then determine significant adverse effects on the body's metabolic health and lead to a significant decrease in basal metabolic rate, contributing to the recovery of body weight [5]. The muscle is then a real endocrine organ that produces substances, defined as myokines, such as interleukin 6 (IL-6), IL-8, IL-15, brain-derived neurotrophic factor, and leukemia inhibitory factor, which have autocrine, paracrine, and

SP, MR, VI and MAF equally contributed to the conception and design of the research. MR and RM contributed to the design of the research. GP, GC, DS and MN contributed to the acquisition and analysis of the data. SP contributed to the analysis of the data. VI contributed to the acquisition, analysis, and interpretation of the data. All authors drafted the manuscript, critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

*Corresponding author. Tel.: 00390382381739.
E-mail address: clara.gasparri01@universitadipavia.it (C. Gasparri).

https://doi.org/10.1016/j.nut.2019.110667
0899-9007/

endocrine activities [6]. In addition, the muscle in return has receptors for numerous molecules that have significant activities, such as the insulin-like growth factor -1 (IGF-1) and vitamin D [7], which control the function of the muscle itself.

The aim of this study is to evaluate the specific factors that play a pivotal role in allowing the preservation of fat-free mass during weight loss as a result of a low-calorie diet.

Materials and methods

The present narrative review was performed following the steps by Egger et al. [8], which are as follows:

1. Configuration of a working group: three operators skilled in endocrinology and clinical nutrition, of whom one acted as a methodologic operator and two participated as clinical operators
2. Formulation of the revision question on the basis of considerations made in the abstract: "the state of the art on metabolic and nutritional correlates of loss of fat-free mass during low-calorie diet and treatment for maintaining fat-free mass"
3. Identification of relevant studies: a research strategy was planned on PubMed (Public Medline run by the National Center of Biotechnology Information of the National Library of Medicine of Bathesda [USA]), as follows:
   a. Definition of the key words (fat-free mass, low-calorie diet), allowing the definition of the interest field of the documents to be searched, grouped in quotation marks ("..."), and used separately or in combination
   b. Use of the Boolean AND operator, which allows the establishments of logical relations among concepts
   c. Research modalities: advanced search
   d. Limits (eg, time limits: papers published in the last 20 y; humans; languages: English)
   e. Manual search performed by the senior researchers experienced in clinical nutrition through the revision of reviews and individual articles on metabolic and nutritional correlates of loss of fat-free mass during low-calorie diet and treatment for maintaining fat-free mass published in journals qualified in the *Index Medicus*
4. The analysis was carried out in the form of a narrative review of the reports. Figure 1 shows the flowchart of the studies evaluated.

Results and discussion

Very low carbohydrate ketogenic diet

Among low-calorie diets, the role of the very low carbohydrate ketogenic diet (VLCKD) in the management of obesity is now well established [9]. Comparing VLCKD with other diets, such as paleo and vegan diets, commonalities included weight loss, and major differences included time frame of weight loss, blood pressure changes, elimination patterns, musculoskeletal effects, psychosocial responses, and environmental and economic impact [10]. A meta-analysis [9] found that individuals assigned to a VLCKD (i.e. a diet with no more than 50 g carbohydrates/d) achieved better long-term body weight and cardiovascular risk factor management compared with individuals assigned to a conventional low-fat diet (LFD; i.e. a restricted-energy diet with less than 30% of energy from fat).

Very recently numerous double-blind studies have confirmed that a VLCKD was highly effective in terms of body weight reduction without inducing lean body mass loss [11–13].

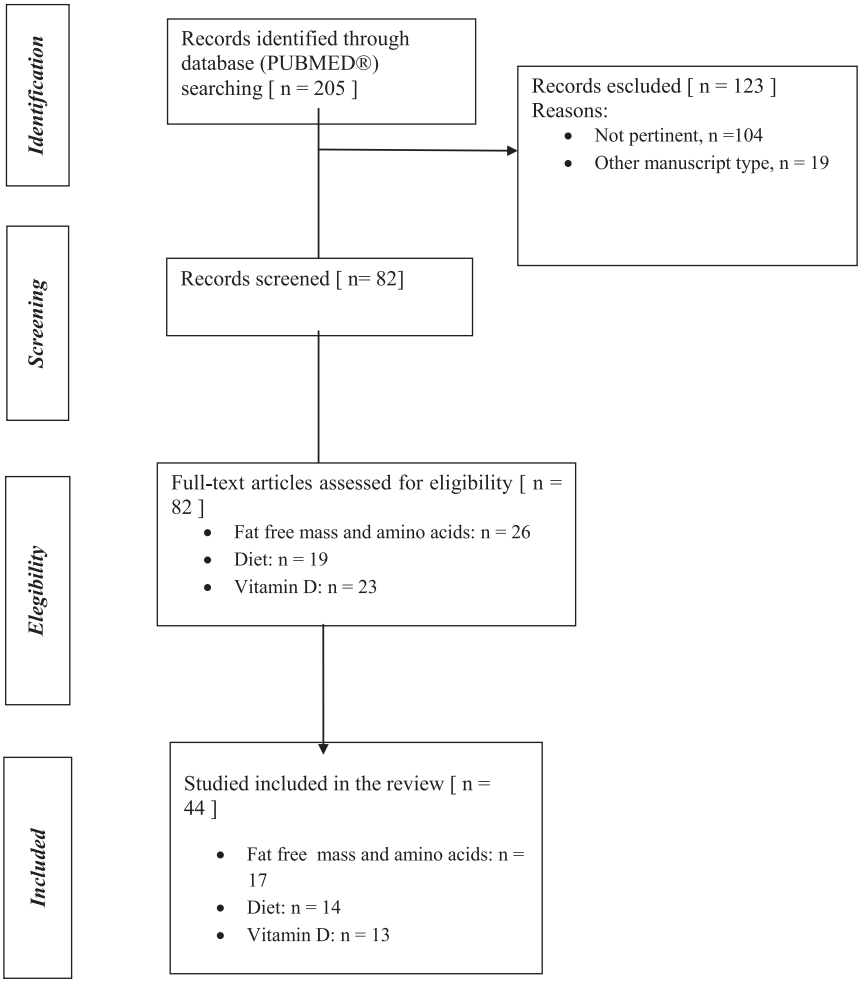

Fig. 1. Flow chart of the studies evaluated.

Further than in obesity, the literature indicates that there are good effects of ketogenic diet on muscle mass in various disease states, such as epilepsy [14,15], Parkinson's disease [16], Alzheimer's disease [17], and multiple sclerosis [18].

In particular, very recently a study reported that a ketogenic diet increased lean mass and decreased inflammation and oxidation, possibly as a consequence of an increase in satiety and decrease in hunger, in patients with multiple sclerosis [18].

VLCKD appears to be protective against muscle catabolism [19,20] for several reasons: the adrenergic stimulation by the protein and by low levels of sugar in the blood inhibits the proteolysis of skeletal muscle; the formation of ketone bodies suppresses the use of protein-derived amino acids by muscle; the β-hydroxybutyrate decreases leucine oxidation and promotes protein synthesis; increased availability of dietary protein causes an increase in IGF-1 in muscle; and the increased protein intake leads to increased protein synthesis, thanks to the presence of amino acids available. It has been suggested that branched chain amino acids (BCAAs), leucine especially, interact with the metabolic pathways that regulate insulin signaling, decreasing hormone levels and simultaneously increasing protein synthesis in skeletal muscle.

Moreover, VLCKD induces a particular metabolic condition that activates fasting pathways during a high or normal energy state, and it can also be argued that the transcription of autophagy-related genes (fundamental for the anabolic/catabolic equilibrium and hence for whole muscle health) can be activated by ketogenic diet, mediated by FoxO3 [21–23].

Molecular effects of ketogenic diet on muscle preservation were investigated in an animal model [24]. In slow-twitch soleus muscle, administration of ketogenic diet for 4 wk can increase skeletal muscle mTOR signaling in old adults rats (28 mo), while decreasing its signaling in young adults muscles (5 mo). Phosphorylation of p70 ribosomal protein S6 kinase (p70S6k) was increased by 400% by ketogenic diet versus standard diet in old rats, and soleus muscles (assessed for muscle size and effects on p70S6k) from old rats receiving ketogenic diet were 6% larger than old rats who received standard diet [24].

Finally, the identified preservation of fat-free mass brought on during a VKLCD is possible at least by four other possible mechanisms [19]. It may be involved in the surge of low levels of blood sugar, which are a stimulus for its secretion, and it could be that the protein mass of skeletal muscle is affected by adrenergic influences. The liver produces ketone bodies during a VKLCD, and they flow from the liver to extrahepatic tissues (e.g., brain, muscle) for use as a fuel. As low blood sugar increases and growth hormone (GH) is secreted, one could speculate that a VKLCD increases GH levels. A VKLCD is almost always relatively high in protein, and there is evidence that high protein intake increases protein synthesis by increasing systemic amino acid availability [25], which is a potent stimulus of muscle protein synthesis [26]. During weight loss, higher protein intake reduces loss of fat-free mass and increases loss of body fat [27], which can interact with the insulin to regulate the control of protein synthesis to support the fat-free mass during periods of reduced caloric intake [28].

Regarding the effects of long-term VLCKDs, the results are in contrast: Although some studies have documented the safety of VLCKD in the long-term period, other studies have reported that intake of KD has been linked to renal stones, gallstones, and elevated liver enzymes, given that dietary intervention included approximately 70% of energy as fat [29]. Moreover, the assessment of the effects of VLCKD on bone health, insulin resistance, and β cell function in the long term is still lacking. Given this background, it is important to consider that VLCKD requires proper medical supervision, along with the routine measurement of urine or blood ketones according to clinical judgment [29]. Considering the limitations of VLCKDs, this included increased low-density lipoprotein levels, arterial stiffening, reduction in REM sleep, interference with endothelial function, and renal stones [10]. As far as mood, it was found that in the first 8 wk participants experienced mood improvement, but after 8 wk, the mood improvement was found to plateau as a result of lower concentrations of serotonin in the brain from limited consumption of carbohydrates over a period of 12 mo [30].

In conclusion, the comparison of VKLCD with a prudent standard low-calorie diet indicated that fat-free mass was practically unaffected. The identified preservation of fat-free mass brought about during a VKLCD is possible as a result of numerous factors, predominantly hormonal mechanisms involving insulin and the IGF-I−GH axis, which acts by stimulating protein synthesis.

Branched chain amino acids and leucine

Unlike other amino acids, the BCAAs are metabolized in skeletal muscle. The BCAAs (leucine, isoleucine, and valine) represent 14% to 18% of the total amino acids present in skeletal muscle [31]. In a resting state, BCAAs, and particularly leucine, have an anabolic effect by increasing protein synthesis and reducing the rate of protein degradation, resulting in a positive net muscle protein balance [32]. Leucine, whose average requirement is 40 mg • kg^{-1} • d^{-1}, is critical to maintaining a healthy muscle tissue; the leucine content in meals is an important regulator of muscle protein synthesis and produces different results on the long-term body composition [33].

Further research has compared the intake of 10 g protein with 18% of leucine with a similar beverage containing 35% of leucine, concluding that the beverage with the highest concentration of leucine (4 g) provided a greater stimulus to muscle protein synthesis, resulting in an inferior muscle catabolism by the action of cortisol [34].

Even if isoleucine and valine have not been found to have the same potential, they play a key role as part of the "construction." In fact, the hypertrophy induced by leucine drops to zero as soon as the presence of the other two BCAAs is poor: No matter how much leucine is made available for the muscles, muscle growth does not occur if the other two BCAAs fall below a certain level [35]. Leucine is capable of interacting with the metabolic insulin pathway with apparent modulation of protein synthesis and consequent maintenance of fat-free mass during a period of caloric restriction, and because the same amino acid also modulates the use of glucose by the skeletal muscle, through stimulation of the glucose-alanine cycle, which allows reuse of glucose, the assumption of adequate amounts of leucine is considered as a potential strategy for the treatment of obese patients, being of assistance in maintaining the lean body mass [28].

In conclusion, an adequate daily intake of the amino acid leucine (4 g/d), along with other amino acids isoleucine and valine (BCAA 2:1:1, leucine/isoleucine/valine), is essential to maintain fat-free mass during weight loss induced by low-calorie diet.

Whey protein

Approximately 300 to 600 g of muscle proteins are degraded and resynthesized daily over 24 h. Food intake stimulates the degree of muscle protein synthesis, resulting in a positive protein balance. After the intake of a meal containing protein, the degree of protein synthesis remains elevated for more than 5 h, with a peak 2 to 3 h after intake. It has been found that in an adult a dose of approximately 15 to 20 g protein (or 7.5 g essential amino acids) is sufficient to stimulate the maximization of the degree of muscle protein synthesis [36].

In comparison, to obtain the same maximization of protein synthesis in an older person, a greater amount of protein is needed, probably 30 g [37].

In the elderly the breakdown of the protein requirement is spread over more meals throughout the day; it is not enough to

determine a peak plasma amino acid capable of inducing a protein-synthetic stimulus in muscle tissue that has significantly reduced its sensitivity to that stimulus.

Not all food proteins possess the same properties in terms of kinetics: The speed of assimilation of dietary amino acids and their effect on the protein metabolism regulation are a function of the molecular characteristics of the protein [38].

This feature has led to the distinction of food proteins in fast and slow. The intake of fast-absorbing proteins may represent an advantage over slowly digesting proteins. Dietary proteins are those in fast absorption of whey protein, which are the β-globulin fraction, characterized by good digestibility, low lactose content, and high biological value.

Hydrolyzed proteins are more easily assimilated than intact proteins, and hydrolyzed proteins obtained from whey (β-globulin fraction) have the highest rate of assimilation [39].

In conclusion, a daily intake of an adequate amount of whey protein (average at least 20 g/d) is beneficial in maintaining fat-free mass.

Vitamin D

Vitamin D, because the muscle has receptors for it [7], plays a key role in muscle activity [40], causing an increase in the accumulation of calcium in the sarcoplasmic reticulum by increasing the number of receptors that bind calcium and by increasing the efficiency of sites to bind calcium and stimulating the transport across cell membranes phosphate.

A study in animal models [41] has found that 1,25(OH)2 D_3 is able to enhance protein synthesis: It enhances the stimulatory effects of insulin and leucine on protein synthesis in myotubes C2C12 cells, increases the stimulation of the insulin receptor in skeletal muscle cells, and stimulates the expression of insulin receptors and the receptor of the same vitamin D (VDR) in skeletal muscle cells, therefore ensuring a greater sensitivity on the part of C2C12 myotubes to vitamin D and insulin. A further in vitro study confirmed that treatment of C2C12 cells with 25-hydroxyvitamin D (25 OHD) and 1,25 dihydroxyvitamin D (1,25 [OH]2 D) alters gene expression with consequent positive effects on the proliferation, differentiation, and size of myotubes [42]. In clinical situations the important relationship between vitamin D and muscle function has been reported in various studies that were extremely significant in terms of number of participants evaluated [43–46], which reported that blood levels of vitamin D are related to the muscle strength, assessed by the hand grip force (using dynamometry). Particularly the Pro.Va study (Veneto project elderly) has found, through a follow-up that lasted 3 y, that the participants who had lower values of vitamin D had a greater loss of fat-free mass and muscle strength [46].

A recent review has reported that low levels of vitamin D are present in many diseases, including obesity [47]. In obese participants there are many reasons for these low serum levels of vitamin D. The vitamin D intake mostly (80%–90%) is due to the skin synthesis of cholecalciferol after exposure to sunlight, and we know that obese participants barely expose themselves to the sun. Furthermore, although the amount of vitamin D contained in the food is equal to 10% to 20%, it is completely insufficient, alone, to cover the needs, and in any case the maximum content of vitamin D is present in foods that obese participants often consume in small quantities because of food habits, tradition, and costs [48,49]. Vitamin D is found in good quantities in fish, especially herring (19 μg/100 g), fresh tuna (16.3 μg/100 g), swordfish, grouper, and anchovies (11 μg/100 g).

A recent review [50] found that daily supplementation with at least 400 IU of vitamin D increases skeletal muscle force an average of 17%. If there is excess fat mass, part of it may be sequestered as vitamin D in this tissue [51].

For this reason, oral supplementation with vitamin D should be recommended in the activated form, calcifediol: It has an elective indication in obesity [52–54]. Calcifediol is available in drops (0.15 mg/mL, where 1 drop contains 5 g); 3 to 4 drops/d or 20 to 30 drops/wk of calcifediol are generally adequate to restore normal 25(OH)D plasma levels in obese participants [55,56].

An assessment of blood concentrations of vitamin D is required in obese patients. In the case of low values of blood vitamin D, less than 30 ng/mL [57], an adequate oral supplementation with calcifediol (3–4 drops/d or 20–30 drops/wk) is mandatory to maintain fat-free mass.

Conclusions

It should be considered that assessment of obese patients must necessarily pass through the analysis of body composition [53], which takes into account adipose mass (with quantifying the amount of visceral fat), fat-free mass, mineral compartment, and fluids.

The results of this review indicate that, to maintain fat-free mass during a low-calorie diet, there are various diet strategies. The comparison of VLCKD with standard low-calorie diet found that fat-free mass was practically unaffected; this is possible for numerous factors, predominantly hormonal mechanisms, involving the insulin and the IGF-I–GH axis, which acts by stimulating protein synthesis.

An adequate daily intake of the amino acid leucine (4 g/d), along with other amino acids isoleucine and valine (BCAA 2:1:1, leucine/isoleucine/valine), and daily intake of adequate amount of whey protein (average 20 g/d) are beneficial in maintaining fat-free mass during weight loss induced by low-calorie diet.

An assessment of blood concentrations of this vitamin is required in the obese patient. In the case of low values of blood vitamin D, less than 30 ng/mL [52], adequate supplementation is mandatory, specifically calcifediol, because in the obese patient this form is recommended to avoid seizure in the adipose tissue.

Table 1 shows the diet strategies useful to maintain the fat-free mass during low-calorie diet together with the various mechanisms behind these strategies.

Table 1
Strategies useful to maintain the fat-free mass during low-calorie diet together with the various mechanisms behind these strategies

Pivotal strategies	Mechanisms
Adopt a very low carbohydrate ketogenic diet (VLCKD)	- Adrenergic stimulation by the protein and by low levels of sugar in the blood inhibits the proteolysis of skeletal muscle. - Formation of ketone bodies suppresses the use of protein-derived amino acids by muscle. - The β-hydroxybutyrate decreases leucine oxidation and promotes protein synthesis. - Increased availability of dietary protein causes an increase in insulin-like growth factor-1 in muscle.
Vitamin D	- Causes an increase in the accumulation of calcium in the sarcoplasmic reticulum by increasing number of receptors that bind calcium and by increasing the efficiency of sites to bind calcium and stimulating the transport across cell membranes phosphate. This activity leads to muscle cell proliferation and differentiation.
Leucine	- Has an anabolic effect by increasing protein synthesis and/or reducing the rate of protein degradation, resulting in a positive net muscle protein balance.
Whey proteins	- Characterized by good digestibility, low lactose content, and high biological value. - Have the highest rate of assimilation.

References

[1] Weinheimer EM, Sands LP, Campbell WW. A systematic review of the separate and combined effects of energy restriction and exercise on fat-free mass in middle-aged and older adults: implications for sarcopenic obesity. Nutr Rev 2010;68:375–88.
[2] Wolfe RR. The underappreciated role of muscle in health and disease. Am J Clin Nutr 2006;84:475–82.
[3] Samuel VT, Petersen KF, Shulman GI. Lipid-induced insulin resistance: unravelling the mechanism. Lancet (London, England) 2010;375:2267–77.
[4] Lewis GF, Carpentier A, Adeli K, Giacca A. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. Endocr Rev Endocr Soc 2002;23:201–29.
[5] Stiegler P, Cunliffe A. The role of diet and exercise for the maintenance of fat-free mass and resting metabolic rate during weight loss. Sports Med 2006;36:239–62.
[6] Pratesi A, Tarantini F, Di Bari M. Skeletal muscle: an endocrine organ. Clin Cases Miner Bone Metab 2013;10:11–4.
[7] Bouillon R, Okamura WH, Norman AW, Bouillon R. Structure-function relationships in the vitamin D endocrine system. Endocr Rev 1995;16:200–57.
[8] Egger M, Smith GD, Altman DG. Systematic reviews in health care: meta-analysis in context. Hoboken, NJ: BMJ Books; 2001.
[9] Bueno NB, de Melo ISV, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. Br J Nutr 2013;110:1178–87.
[10] Bahr M, Chrisostom K, Chrisostom S, Peters N, Thomas P, Catts P. A comparative analysis of the ketogenic, paleolithic, and vegan diets. Nurs Undergrad Work 2019;5:1–57.
[11] Merra G, Costa De Miranda R, Fa T, Chang M, De Lorenzo A. Very-low-calorie ketogenic diet with aminoacid supplement versus very low restricted-calorie diet for preserving muscle mass during weight loss: a pilot double-blind study. Eur Rev Med Pharmacol Stud 2016;20:2613–21.
[12] Moreno B, Bellido D, Sajoux I, Goday A, Saavedra D, Crujeiras AB, et al. Comparison of a very low-calorie-ketogenic diet with a standard low-calorie diet in the treatment of obesity. Endocrine 2014;47:793–805.
[13] Moreno B, Crujeiras AB, Bellido D, Sajoux I, Casanueva FF. Obesity treatment by very low-calorie-ketogenic diet at two years: reduction in visceral fat and on the burden of disease. Endocrine 2016;54:681–90.
[14] Stafstrom CE, Rho JM. The ketogenic diet as a treatment paradigm for diverse neurological disorders. Front Pharmacol 2012;3:59.
[15] Deng-Bryant Y, Prins ML, Hovda DA, Harris NG. Ketogenic diet prevents alterations in brain metabolism in young but not adult rats after traumatic brain injury. J Neurotrauma 2011;28:1813–25.
[16] Cheng B, Yang X, An L, Gao B, Liu X, Liu S. Ketogenic diet protects dopaminergic neurons against 6-OHDA neurotoxicity via up-regulating glutathione in a rat model of Parkinson's disease. Brain Res 2009;1286:25–31.
[17] de la Rubia Ortí JE, García-Pardo MP, Drehmer E, Sancho Cantus D, Julián Rochina M, Aguilar MA, et al. Improvement of main cognitive functions in patients with Alzheimer's disease after treatment with coconut oil enriched Mediterranean diet: a pilot study. J Alzheimers Dis 2018;65:577–87.
[18] Benlloch M, López-Rodríguez MM, Cuerda-Ballester M, Drehmer E, Carrera S, Ceron JJ, et al. Satiating effect of a ketogenic diet and its impact on muscle improvement and oxidation state in multiple sclerosis patients. Nutrients 2019;11:1–14.
[19] Manninen AH. Very-low-carbohydrate diets and preservation of muscle mass. Nutr Metab (Lond) 2006;3:9.
[20] Paoli A, Canato M, Toniolo L, Bargossi AM, Neri M, Mediati M, et al. [The ketogenic diet: an underappreciated therapeutic option?][The ketogenic diet: an underappreciated therapeutic option?] [In Italian.]. Clin Ter 2011;65:e145–53.
[21] Mammucari C, Schiaffino S, Sandri M. Downstream of Akt: FoxO3 and mTOR in the regulation of autophagy in skeletal muscle. Autophagy 2008;4:524–6.
[22] Sandri M. Signaling in muscle atrophy and hypertrophy. Physiology 2008;23:160–70.
[23] Sandri M, Barberi L, Bijlsma AY, Blaauw B, Dyar KA, Milan G, et al. Signalling pathways regulating muscle mass in ageing skeletal muscle: the role of the IGF1-Akt-mTOR-FoxO pathway. Biogerontology 2013;14:303–23.
[24] Bennett SL, Smith AH, Ramirez L, Thomson DM. Effects of ketogenic diet on p70s6k phosphorylation in young adult and old soleus muscle. FASEB J 2019;33.
[25] Motil KJ, Matthews DE, Bier DM. Whole-body leucine and lysine metabolism: response to dietary protein intake in young men. Am J Physiol Endocrinol Metab 1981;240:E712–21.
[26] Paddon-Jones D, Sheffield-Moore M, Zhang X-J, Volpi E, Wolf SE, Aarsland A, et al. Amino acid ingestion improves muscle protein synthesis in the young and elderly. Am J Physiol Endocrinol Metab 2004;286:E321–8.
[27] Layman DK, Evans E, Baum JI, Seyler J, Erickson DJ, Boileau RA. Dietary protein and exercise have additive effects on body composition during weight loss in adult women. J Nutr 2005;135:1903–10.
[28] Layman DK, Walker DA. Potential importance of leucine in treatment of obesity and the metabolic syndrome. J Nutr 2006;136:319S–23S.
[29] Caprio M, Infante M, Moriconi E, Armani A, Fabbri A, Mantovani G, et al. Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology(SIE). J Endocrinol Invest 2019:1365–86.
[30] Brinkworth GD, Buckley JD, Noakes M, Clifton PM, Wilson CJ. Long-term effects of a very low-carbohydrate diet and a low-fat diet on mood and cognitive function. Arch Intern Med 2009;169:1873–80.
[31] Riazi R, Wykes LJ, Ball RO, Pencharz PB. The total branched-chain amino acid requirement in young healthy adult men determined by indicator amino acid oxidation by use of L-[1-13C]phenylalanine. J Nutr 2003;133:1383–9.
[32] Kimball SR, Jefferson LS. Signaling pathways and molecular mechanisms through which branched-chain amino acids mediate translational control of protein synthesis. J Nutr 2006;136:227S–31S.
[33] Northon LE. Leucine is a critical factor determining protein quantity and quality of a complete meal to initiate muscle protein synthesis. University of Illinois; 2010.
[34] Glynn EL, Fry CS, Drummond MJ, Timmerman KL, Dhanani S, Volpi E, et al. Excess leucine intake enhances muscle anabolic signaling but not net protein anabolism in young men and women. J Nutr 2010;140:1970–6.
[35] Layman DK. The role of leucine in weight loss diets and glucose homeostasis. J Nutr 2003;133:261S–7S.
[36] Phillips SM, Tang JE, Moore DR. The role of milk- and soy-based protein in support of muscle protein synthesis and muscle protein accretion in young and elderly persons. J Am Coll Nutr 2009;28:343–54.
[37] Pennings B, Groen B, de Lange A, Gijsen AP, Zorenc AH, Senden JMG, et al. Amino acid absorption and subsequent muscle protein accretion following graded intakes of whey protein in elderly men. Am J Physiol Endocrinol Metab 2012;302:E992–9.
[38] Tang JE, Phillips SM. Maximizing muscle protein anabolism: the role of protein quality. Curr Opin Clin Nutr Metab Care 2009;12:66–71.
[39] Etzel MR. Manufacture and use of dairy protein fractions. J Nutr 2004;134:996S–1002S.
[40] Ceglia L, Harris SS. Vitamin D and its role in skeletal muscle. Calcif Tissue 2013;92:151–62.
[41] Salles J, Chanet A, Giraudet C, Patrac V, Pierre P, Jourdan M, et al. 1,25(OH)2-vitamin D3 enhances the stimulating effect of leucine and insulin on protein synthesis rate through Akt/PKB and mTOR mediated pathways in murine C2C12 skeletal myotubes. Mol Nutr Food Res 2013;57:2137–46.
[42] Girgis CM, Clifton-Bligh RJ, Mokbel N, Cheng K, Gunton JE. Vitamin D signaling regulates proliferation, differentiation, and myotube size in C2C12 skeletal muscle cells. Endocrinology 2014;155:347–57.
[43] Houston DK, Tooze JA, Davis CC, Chaves PHM, Hirsch CH, Robbins JA, et al. Serum 25-hydroxyvitamin D and physical function in older adults: the Cardiovascular Health Study All Stars. J Am Geriatr Soc 2011;59:1793–801.
[44] Houston DK, Cesari M, Ferrucci L, Cherubini A, Maggio D, Bartali B, et al. Association between vitamin D status and physical performance: the inCHIANTI study. J Gerontol Ser A Biol Sci Med Sci 2007;62:440–6.
[45] Hirani V, Naganathan V, Cumming RG, Blyth F, Le Couteur DG, Handelsman DJ, et al. Associations between frailty and serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations in older Australian men: the Concord Health and Ageing in Men Project. J Gerontol A Biol Sci Med Sci 2013;68:1112–21.
[46] Toffanello ED, Perissinotto E, Sergi G, Zambon S, Musacchio E, Maggi S, et al. Vitamin D and physical performance in elderly participants: the Pro.V.A study. PLoS One 2012;7:e34950.
[47] Matysiak-Luśnia K. Vitamin D in critically ill patients. Anaesthesiol Intensive Ther 2016;48:201–7.
[48] Gil JM, Takourabt S. Socio-economics, food habits and the prevalence of childhood obesity in Spain. Child Care Health Dev 2017;43:250–8.
[49] Andreeva VA, Allès B, Feron G, Gonzalez R, Sulmont-Rossé C, Galan P, et al. Sex-specific sociodemographic correlates of dietary patterns in a large sample of french elderly individuals. Nutrients 2016;8.
[50] Beaudart C, Buckinx F, Rabenda V, Gillain S, Cavalier E, Slomian J, et al. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. J Clin Endocrinol Metab 2014;99:4336–45.
[51] Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. Am J Clin Nutr 2008;88:491S–9S.
[52] Vieth R, Bischoff-Ferrari H, Boucher BJ, Dawson-Hughes B, Garland CF, Heaney RP, et al. The urgent need to recommend an intake of vitamin D that is effective. Am J Clin Nutr 2007;85:649–50.
[53] Di Nisio A, De Toni L, Sabovic I, Rocca MS, De Filippis V, Opocher G, et al. Impaired release of vitamin D in dysfunctional adipose tissue: new cues on vitamin D supplementation in obesity. J Clin Endocrinol Metab 2017;102:2564–74.
[54] Cesareo R, Attanasio R, Caputo M, Castello R, Chiodini I, Falchetti A, et al. Italian Association of Clinical Endocrinologists (AME) and Italian Chapter of the American Association of Clinical Endocrinologists (AACE)Position Statement: clinical management of vitamin D deficiency in adults. Nutrients 2018;10:546.
[55] Cashman KD, Seamans KM, Lucey AJ, Stöcklin E, Weber P, Kiely M, et al. Relative effectiveness of oral 25-hydroxyvitamin D3 and vitamin D3 in raising wintertime serum 25-hydroxyvitamin D in older adults. Am J Clin Nutr 2012;95:1350–6.
[56] Shieh A, Ma C, Chun RF, Witzel S, Rafison B, Contreras HTM, et al. Effects of cholecalciferol vs calcifediol on total and free 25-hydroxyvitamin D and parathyroid hormone. J Clin Endocrinol Metab 2017;102:1133–40.
[57] Tanamas SK, Lean MEJ, Combet E, Vlassopoulos A, Zimmet PZ, Peeters A. Changing guards: time to move beyond body mass index for population monitoring of excess adiposity. QJM 2016;109:443–6.