



Remiern 1 Effects of combining a ketogenic diet with resistance training 2 on body composition, strength, and mechanical power in 3 trained individuals: a narrative review 4 Pedro L. Valenzuela ¹, Adrián Castillo-García ², Alejandro Lucia^{3,4} and Fernando Naclerio^{5,*} 5 ¹ Faculty of Sport Sciences, Universidad Europea de Madrid, Madrid, Spain; pedroluis.valenzuela@univer-6 7 sidadeuropea.es Fissac - Physiology, Health and Physical Activity, Barcelona, Spain. 2; adriancastillogarcia@icloud.com 8 Faculty of Sport Sciences, Universidad Europea de Madrid, Madrid, Spain; alejandro.lucia@universidadeu-9 ropea.es 10 Physical Activity and Health Research Group ('PaHerg'), Research Institute of the Hospital 12 de Octubre 11 ('imas12'), Madrid, Spain. 12 Institute for Lifecourse Development. School of Human Sciences. Centre for Exercise Activity and Rehabili-13 tation. University of Greenwich, UK; F.J.Naclerio@greenwich.ac.uk 14 Correspondence: nf10@gre.ac.uk 15 Abstract: Ketogenic diets (KD) have gained popularity in recent years among strength-trained in-16 dividuals. The present review summarizes current evidence - with a particular focus on random-17 ized controlled trials - on the effects of KD on body composition and muscle performance (strength 18 and power output) in strength-trained individuals. Although long-term studies (>12 weeks) are 19 lacking, growing evidence supports the effectiveness of an *ad libitum* and energy-balanced KD for 20 reducing total body and fat mass, at least in the short term. However, no - or negligible - benefits 21

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on body composition have been observed when comparing hypocaloric KD with conventional diets 22 resulting in the same energy deficit. Moreover, some studies suggest that KD might impair re-23 sistance training-induced muscle hypertrophy, sometimes with concomitant decrements in muscle 24 performance, at least when expressed in absolute units and not relative to total body mass (e.g., one-25 repetition maximum). KD might be therefore a beneficial strategy for promoting fat loss, although 26 it might not be a recommendable option to gain muscle mass and strength/power. More research is 27 needed on the adoption of strategies for avoiding the potentially detrimental effect of KD on muscle 28 mass and strength/power (e.g., increasing protein intake, reintroduction of carbohydrates before 29 competition). In summary, evidence is yet scarce to support a major beneficial effect of KD on body 30 composition or performance in strength-trained individuals. Furthermore, the long-term effective-31 ness and safety of this type of diet remains to be determined. 32

Keywords: low-carbohydrate; power output; resistance training; muscle; keto

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1. Introduction

Ketogenic diets (KD) aim at inducing physiological ketosis (*i.e.*, an increase in the 36 concentration of ketone bodies in blood, usually above >0.5 mmol/L) through a marked 37 reduction in carbohydrate intake (commonly <50 g/d or <10% of total energy intake) [1]. 38 KD have gained popularity in recent years among athletes [2]. By virtue of the restriction 39 they induce in carbohydrate availability, KD promote the use of ketone bodies (i.e., aceto-40 acetate, acetone and β -hydroxybutyrate [BHB]) as an alternative energy substrate for dif-41 ferent body tissues. Ketone bodies are produced from free fatty acids mainly in the mito-42 chondria of liver cells. Once in the bloodstream, acetoacetate and BHB (the two ketone 43 bodies used for energy) can reach extrahepatic tissues (notably, skeletal muscles, heart, 44 brain). BHB is converted to acetoacetate by a reaction catalyzed by BHB dehydrogenase, 45 and acetoacetate is converted back to acetyl-CoA by the action of beta-ketoacyl-CoA trans-46 ferase. The resulting acetyl CoA enters the Krebs cycle to produce ATP through the elec-47 tron transport chain. Due to the initial, non-energy demanding activation of ketone bodies 48 into an oxidable form (in a reaction catalyzed by succinyl-CoA:3-oxoacid CoA transferase) 49 ketone bodies represent a more efficient fuel than glucose and fatty acids [3], thereby en-50 abling the muscle tissue to produce more work for a given energy cost [4]. Owing to the 51 low carbohydrate availability induced by this type of diets, KD induce a metabolic switch 52 towards a greater reliance on fatty acids, which are required for the production of ketone 53 bodies. Indeed, strong evidence supports the effectiveness of KD for increasing fat oxida-54 tion rates during exercise [5–7]. 55

Low-carbohydrate diets and particularly KD have been proposed as beneficial nutri-56 tional strategies - at least in the short term - for inducing weight loss and improving car-57 diometabolic health in both healthy and clinical populations [8–10]. The popularity of KD 58 has also grown considerably among endurance athletes. The reduced reliance on glycogen 59 stores along with increased fat oxidation rates when exercising at submaximal intensities 60 could indeed benefit performance in long-duration events [11,12], although the evidence 61 is mixed [13]. Due to their purported benefits on body composition [2], KD are also grow-62 ing in popularity among strength-trained individuals, and indeed these diets have been 63 proposed as an option for some athletes. These include individuals participating in 64 weight-category sports (e.g., combat athletes) or in events where a high ratio of muscle 65 strength relative to body mass is required for success (e.g., jumpers), as well as bodybuild-66 ers aiming at minimizing body fat without losing muscle mass during the so-called 'cut-67 ting phase' [2]. However, controversy exists as to the actual effects of KD on body com-68 position and performance in strength-trained individuals [14,15]. 69

The present narrative review aimed to summarize current evidence on the effects of 70 KD on resistance training-induced changes in body composition and performance, as well 71 as to discuss potential research gaps on this topic. For this purpose, two authors (PLV and 72 ACG) independently conducted a systematic search in PubMed and Web of Science until 73 2nd August 2021 using the term 'ketogenic diet' along with others including 'athlete', 74 'strength', 'power', 'force', 'training', 'trained', or 'exercise'. Studies were first screened by 75 title and abstract and the full text of those studies that seemed to meet the inclusion criteria 76 were assessed. We focused mainly on randomized controlled trials conducted with 77 healthy individuals performing strength training and assessing the effects of a KD (> 2 78 weeks, with <10% of total energy intake coming from carbohydrate intake or daily total 79 carbohydrate intake <50 g) compared with a non-KD. The primary outcome variables 80 were muscle strength or power-related measures and body composition (total body, fat, 81 and muscle mass, respectively). A flow chart of the systematic search is available as Sup-82 plementary Figure 1, and the randomized controlled trials that met the inclusion criteria 83 are summarized in Table 1. 84

2. Effects of combining ketogenic diets with resistance training on body composition in trained individuals

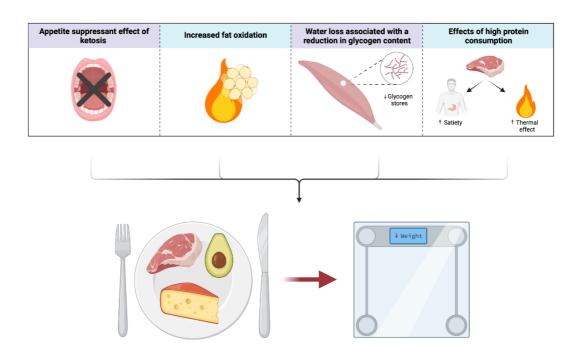
Growing evidence supports the effectiveness of KD for promoting weight loss in the 87 general population [8]. Although the biological mechanisms explaining this effect remain 88 debatable [16], one potential factor is the higher satiating and thermic effect of proteins 89 [17–19], which consumption is sometimes increased in KD. Other proposed mechanisms 90 are the appetite suppressant effect of ketosis [20,21] or the greater rate of fat oxidation – 91 coupled with an increased resting energy expenditure as reported in some studies [22,23]. 92 Of note, because glycogen is stored in human cells along with three to four parts of water, 93 the glycogen-depleting effect of KD could be associated with a further reduction in total 94 body mass [24] (for a graphical summary of these mechanisms, see Figure 1). 95

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Potential mechanisms underlying the beneficial effects of ketogenic diets on weight loss

Figure 1. Summary of some potential mechanisms underlying the beneficial effects of ketogenic diets on weight loss.

Evidence on the effects of KD on total body and fat mass loss in strength-trained99individuals is promising. A recent systematic review and meta-analysis including 13 trials100concluded that KD (5-50 g/d of carbohydrate for 3 to 12 weeks) are effective for reducing101total body (-3.7 kg on average) and fat mass (-2.2 kg) compared with non-KD [15]. None-102theless, KD might also contribute to loss of muscle mass or at least impair resistance train-103ing-induced hypertrophy. Indeed, the abovementioned meta-analysis concluded that KD104reduce fat-free mass (-1.3 kg) compared with non-KD [15].105

A summary of relevant randomized controlled trials assessing the effects of KD on 106 body composition in strength-trained individuals is shown in Table 1. Different studies 107 support the effect of KD vs. non-KD to reduce both total body and fat mass [25–30]. How-108 ever, some detrimental effects have been reported on muscle mass when KD are combined 109 with resistance exercise interventions [25-28,31]. A randomized controlled trial conducted 110 with Olympic-class weightlifters reported that a 3-month ad libitum KD resulted in a total 111 loss of body mass above 3 kg compared with a group maintaining their usual diet ($\sim 45\%$ 112 carbohydrate) [26]. However, ~77% (2.3 kg) of the weight lost by the KD group was at-113 tributed to the muscle component [26]. Another randomized controlled trial conducted 114 with bodybuilders who followed an 8-week energy-balanced KD found a significant re-115 duction in total body and fat mass, respectively, with these changes not reported for a 116 group ingesting an isocaloric westernized diet (~55% carbohydrate) [25]. Of note, only 117 bodybuilders in the westernized diet showed an increase in muscle mass [25]. Two recent 118 studies by the same group of researchers analyzed the effects of an 8-week KD in strength-119 trained men and women [27,28]. The diets were designed to induce no energy deficit and 120 even to produce a moderate energy surplus through a total energy intake of 39 kcal/kg 121 body mass in men [27] and 40-45 kcal/kg fat-free mass in women [28]. Overall, the KD 122 resulted not only in a lower energy intake (~1710 vs. 1979 kcal and 40.1 vs. 45.5 kcal/kg 123 fat-free mass per day for the KD and the non-KD diet, respectively, in the study conducted 124 in women) compared with the control non-KD group (>55% kcal from carbohydrate), but 125 also in a reduced fat mass (by ~0.8 and 1.1 kg for men and women, respectively). However, 126 whereas the control groups showed a trend to increase fat-free mass (~by 1.3 and 0.7 kg 127

for men and women, respectively), participants on the KD showed no changes [27,28]. 128 Recently, Kysel et al. [31] found a comparable reduction in body mass in healthy young 129 resistance-trained men who combined resistance and aerobic training with (i) a hy-130 pocaloric cyclical KD (i.e., 500-kcal energy deficit alternating a phase of KD for 5 days 131 followed by 2 days of carbohydrate reintroduction) or (ii) a hypocaloric non-KD diet, for 132 8 weeks. Although no significant between-group differences were found at post-interven-133 tion (KD -4.6 kg vs. non-KD, 4.5 kg) only participants assigned to the KD treatment 134 showed a significant reduction of muscle mass (KD -1.8 kg vs. non-KD -0.4 kg). On the 135 other hand, Rhyu et al. [32] reported similar losses in body mass (including both fat and 136 muscle components) in high school taekwondo athletes following a 3-week period of hy-137 pocaloric KD or non-KD diet intervention. Additionally, Skemp et al. [30] observed larger 138 reductions of body mass and fat mass in resistance trained women who followed a 4-week 139 hypocaloric, KD or non-KD. Both treatments induced similar detrimental effects on mus-140 cle mass. More recently, Vidic et al. [33] reported that both a hypocaloric KD and a hy-141 pocaloric low-carbohydrate but non-KD (with carbohydrates accounting for 5 and 15% of 142 total energy intake, respectively, both inducing a total energy deficit of ~600 kcal/d) in-143 duced similar losses in total body (-6.1 and -5.3 kg, respectively) and fat mass (-4.3 and -144 3.5 kg) in strength-trained individuals, although a decrease in muscle mass (-1.8 and -1.5 145 kg) was also reported with both diets. 146

Some non-randomized interventional studies have also assessed the effects of KD on 148 body composition. In previously untrained overweight women who started a 10-week 149 resistance training program, Jabekk et al. reported higher total body (-5.6 kg) and fat mass 150 (-5.6 kg) loss in participants following a KD compared to those maintaining their usual 151 eating pattern [34]. However, only those participants who maintained their habitual diet 152 showed significant increases in muscle mass (1.6 kg) [34]. A non-randomized controlled 153 trial conducted in CrossFit athletes who followed a 3-month KD intervention found a ~3 154 kg and -2.5 kg reduction in total body mass and fat mass, respectively, with no significant 155 changes reported in those who chose to maintain their usual diet. Of note, the body mass 156 loss of the KD groups was also accompanied by a non-significant reduction (-0.4 kg) in 157 lower-limb muscle mass [35]. A non-randomized cross-over study in 8 elite artist gym-158 nasts found that, contrary to a usual western diet, 30 days of KD led to a reduction in total 159 body (-1.6 kg) and fat mass (-1.9 kg), while muscle mass remained constant (non-signifi-160 cant reduction of 1.1 kg) [36]. A recent study tested the hypothesis that providing an ex-161 ogenous ketone supplement (ketone salts) combined with a hypocaloric (75% of estimated 162 energy needs) KD might help to preserve muscle mass. Although a trend towards a lower 163 nitrogen excretion was found - which could have potential implications for muscle mass 164 preservation in the long term – no actual benefits on muscle mass or overall body compo-165 sition were observed [37]. 166

The bulk of the evidence that is currently available therefore suggests that combining 167 8 to 12 weeks of KD with resistance training can a favor fat mass reduction in healthy and 168 trained individuals, although muscle mass accretion might be also compromised, at least 169 partly. 170

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Study	Participants	Duration of interven-	KD	CD	Main Findings		
Siduy	i anticipants	tion		CD	Body composition	Performance	
Kysel et al. [31]	25 strength-trained men	8 weeks	Controlled energy intake (500 kcal of energy deficit) Fat: NS CHO: NS (<30 g) Protein: 1.6 g/kg Including 2 days of CHO re-introduc- tion (CHO 70%) each 5 days.	Controlled energy intake (500 kcal of en- ergy deficit) Fat: 30% CHO: 55% Protein: 15%	↓ Muscle mass and water content only with KD. Similar↓ in body mass and fat mass with both diets.	 ↑ maximal muscle strength (lateral pull down and leg press) only with CD. ↑ cardiorespiratory fitness (peak oxygen uptake and peak workload) only with CD. 	
Paoli et al. [25]	19 competitive male bodybuilders	8 weeks	Controlled energy intake (isocaloric) Fat: 68% CHO: 5% (44 g) Protein: 25% (216 g, 2.5 g/kg)	Controlled energy intake (isocaloric) Fat: 20% CHO: 55% Protein: 25% (223 g, 2.5 g/kg)	↓ Body mass only with KD. ↓ Fat mass only with KD. ↑ Muscle mass only with CD.	↑ strength (1RM in squat and bench press) similarly in both groups.	
Rhyu et al. [32]	20 young (15-18 years) Taekwondo athletes		Controlled energy intake (hypocaloric, 75% of estimated energy intake) Fat: 55% CHO: 4.3% (22 g) Protein: 40.7%	Controlled energy intake (hypocaloric, 75% of estimated energy intake) Fat: 30% CHO: 40% Protein: 30%	Similar↓ in total body mass, fat mass and muscle mass for both groups	 ↑ in 2,000-m running trial performance and Wingate test performance (fatigue index) with KD. Similar ↓ in peak and mean power on the Wingate test with both diets. Similar ↑ in back muscle strength and in the number of sit-ups with both diets. No changes in performance in the re- maining outcomes. 	
Skemp et al. [30]	20 strength-trained women	4 weeks	Ad libitum Fat: 70% CHO: 10% Protein: 20%	Ad libitum (normal standard diet) Fat: NS CHO: NS Protein: NS	↓ Body and fat mass with KD vs. CD. Similar ↓ of muscle mass with both di- ets.	N/A	
Greene et al. [26]	14 elite competi- tive lifting athletes (5 female)	12 weeks	Ad libitum Fat: 70% CHO: 8% (39 g) Protein: 23% (120 g, 1.6 g/kg)	Ad libitum Fat: 33% CHO: 45% (223 g) Protein: 22% (120 g, 1.5 g/kg)	↓ of both body mass and muscle mass after KD vs. CD	No differences in performance	
Wilson et al. [29]	25 strength-trained men	11 weeks (10 weeks of KD + 1 week of CHO re- introduction)	Controlled energy intake (isocaloric)	Controlled energy intake (isocaloric) Fat: 25% CHO: 55% (318 g) Protein: 20% (132 g, 1.7 g/kg)	↓ Fat mass with KD vs. CD Similar ↑ in muscle mass and thick- ness, but greater ↑ with KD after CHO reintroduction.	Similar performance in 1RM with CD and KD, although only the former in- creased peak power in the Wingate test	

Table 1. Summary of randomized controlled trials that have assessed the effects of ketogenic diets (KD) on body composition or performance in healthy strength-trained individuals.

2 of 17

		Followed by a week of CHO reintro- duction (increasing from 1 to 3 g/kg of CHO during the last week)			
Vargas et al. 24 strength-trained [27] men	8 weeks	Controlled energy intake (moderate energy surplus, 39 kcal/kg) Fat: 70% CHO: <10% (42 g) Protein: 20% (2.0 g/kg)	Controlled energy intake (moderate en- ergy surplus, 39 kcal/kg) Fat: 25% CHO: 55% Protein: 20% (2.0 g/kg)	↓ Fat mass with KD (no significant in- teraction effect) ↑ Muscle mass and body mass only with CD.	N/A
Vargas et al. 21 strength-trained [28] women	8 weeks	Controlled energy intake (moderate energy surplus, 40-45 kcal/kg FFM) Fat: 64% CHO: 9% (30-40 g) Protein: 27% (115 g, >1.7 g/kg)	Controlled energy intake (moderate en- ergy surplus, 40-45 kcal/kg FFM). Signifi- cantly higher energy intake than KD. Fat: 23% CHO: 57% (282 g) Protein: 20% (>1.7 g/kg)	↓ Body mass and fat mass with KD vs. KD. ↑ Muscle mass with CD vs. KD.	↑ Bench press and squat performance (1RM) with CD vs. KD. Similar improvements in CMJ perfor- mance.
Vidic et al. 20 strength-trained [33] men	8 weeks	Controlled energy intake (hy- pocaloric) Fat: 75% CHO: 5% (27 g) Protein: 20% (108 g, 1.2 g/kg)	Controlled energy intake (hypocaloric, non-ketogenic) Fat: 65% CHO: 15% (82 g) Protein: 20% (110 g, 1.2 g/kg)	Similar↓in body mass, fat mass and muscle mass with KD and CD.	No changes in performance (1RM) with any of the diets.

Abbreviations: 1RM, one-repetition maximum; CD, control diet; CHO, carbohydrate; CMJ, countermovement jump; FFM, fat-free mass; KD, ketogenic diet; NS, not specified.

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2.1. Mechanisms underlying the detrimental effects of ketogenic diets on muscle mass

Several mechanisms have been proposed to explain the potential detrimental effects 177 of KD on muscle mass [38,39] (Figure 2). Due to the hydrophilic properties of the surface 178 of glycogen granules [40], KD-induced glycogen reductions may explain the loss of mus-179 cle mass [24]. Indeed, to the best of our knowledge only one randomized controlled trial 180 to date has reported superior hypertrophic effects in resistance-trained participants fol-181 lowing a KD compared with a non-KD [29]. Wilson et al. found similar gains in muscle 182 mass with an energy-balanced KD or an isocaloric traditional (~55% kcal from carbohy-183 drates) western diet (increase in muscle mass of 2.4 vs 4.4%, respectively) after a 10-week 184 intervention period in which participants in both groups consumed ~1.7 g/kg of protein 185 [29]. However, when reintroducing carbohydrates for one week (in weeks 10-11 of the 186 study), participants on the KD increased their muscle mass to a greater extent than those 187 on the western diet [29]. These findings might support the importance of avoiding a pro-188 longed glycogen depletion status and the potential benefits of reintroducing carbohy-189 drates in order to preserve or even increase muscle mass in athletes following a KD. They 190 might also support the occurrence of the so-called 'sarcoplasmic hypertrophy', that is, an 191 increase in muscle volume caused by sarcoplasmic expansion, which in turn is due to a 192 greater water content ('retention') because of the hydrophilic nature of the surface of gly-193 cogen granules, rather than by 'sarcomeric hypertrophy' (i.e., an actual increase in myofi-194 bril protein content) [41]. 195

It must be noted that besides the potentially 'confounding' effects of low glycogen 196 stores on 'real' (i.e., protein content) muscle mass, low carbohydrate availability might 197 also attenuate resistance training-induced adaptations through a suppression of anabolic 198 pathways. By virtue of the reduced carbohydrate intake, KD can indeed lead to reduction 199 in insulin levels [25,33], with this hormone having been in turn reported to stimulate mus-200 cle protein synthesis - at least when combined with concomitant increases in amino acid 201 availability - and to reduce muscle protein breakdown [42-44]. Preclinical evidence sug-202 gests that compared to isocaloric control diets, KD might promote AMP-activated protein 203 kinase (AMPK) phosphorylation [45] – which can inhibit anabolic pathways such as ki-204 nase B protein (Akt)/ mechanistic target of rapamycin (mTOR) [46]. Additionally, preclin-205 ical evidence in isolated mouse muscle suggests that ketosis (e.g., presence of BHB) can 206 diminish Akt phosphorylation [47], thereby impairing anabolic responses. Conversely, 207 other studies in non-athletic populations have reported that ketosis might induce anticat-208 abolic effects [48] by increasing circulating levels of ketone bodies (induced through oral 209 or intravenous administration of ketone bodies) that in turn help to preserve muscle mass 210 and maintain nitrogen balance during conditions of energy deficit [49,50]. In the same line, 211 ketone bodies have shown to exert anti-inflammatory [51] and antioxidant effects [52], 212 which could have potentially beneficial effects against muscle wasting [53]. In fact, lower 213 levels of inflammatory and oxidative stress markers have been reported in athletes under-214 going a KD compared with those following a conventional western diet [32,54]. Further 215 research is therefore needed to confirm the role of ketosis on muscle anabolism, particu-216 larly on healthy and trained individuals. 217

The appetite suppressant effects of ketosis [20,21] might also play a role on the muscle 218 mass loss observed with KD. Thus, ad libitum KD might result in a reduced caloric intake 219 compared with conventional western diets, which can have in turn detrimental conse-220 quences on muscle protein synthesis and muscle mass accretion [55,56]. Moreover, 221 chronic low energy availability [57] and acute severe energy restriction – which is com-222 monly experienced by athletes who seek to rapidly lose body mass before competition – 223 have been reported to exert detrimental effects on the hormonal environment, notably 224 reduced levels not only of circulating total testosterone but also of thyroid-stimulating 225 hormones [58], with the thyroid hormone signaling playing an important role in muscle 226 homeostasis and repair [59]. In addition, although caloric restriction might have no effects 227 on anabolic hormones such as growth hormone (GH) or insulin-like growth factor 1 (IGF-228

1) [60,61], it can lead to a reduction in sex hormones such as testosterone [62]. However, 229 controversy exists as to whether energy-balanced KD can also affect testosterone levels 230 [63]. Indeed, because lipids and derivatives (particularly cholesterol) are the substrate for 231 the biosynthesis of androgens, high-fat diets (e.g., KD) might be potentially beneficial for 232 promoting testosterone synthesis – at least when sufficient energy is provided [63]. None-233 theless, the evidence is mixed. In healthy moderately-active individuals, Volek et al. re-234 ported no changes in testosterone concentration after 8 weeks of a high-fat diet, although 235 this study did not include a control group and participants performed no strength training 236 [64]. Regarding strength-trained individuals, four recent studies [25,29,33,65] have re-237 ported mixing results. Paoli et al. found a decrease in the concentration of anabolic hor-238 mones (testosterone and IGF-1) after 2 months of an energy-balanced KD (45 kcal/kg mus-239 cle mass) in bodybuilders [25]. Wilson et al. reported no differences in free testosterone 240 along with a significantly higher total testosterone concentration in resistance-trained col-241 lege athletes after a 10-week KD compared with a western isocaloric diet. However, these 242 differences between diets were found after one week of carbohydrate reintroduction [29]. 243 Vidic et al. observed similar increases in testosterone in strength-trained individuals ex-244 posed to a hypocaloric KD and a hypocaloric non-KD [33]. Moreover, Michalczyk et al. 245 [65] reported an increase in the levels of GH and testosterone in male basketball players 246 after 4 weeks of a low-carbohydrate diet (10% of total energy intake) compared with a 247 previous period in which they consumed the same energy intake through their conven-248 tional diet. Of note, after a week of carbohydrate reintroduction, testosterone levels re-249 mained above baseline levels, but those of GH declined to those observed with the con-250 ventional diet [65]. Thus, current evidence shows no consistent effects on KD on the hor-251 monal anabolic environment, although there are mixed and scarce results as well as some 252 confounding factors (e.g., differences between studies in total caloric or protein intake, or 253 in carbohydrate reintroduction), all of which might hinder drawing conclusions. 254

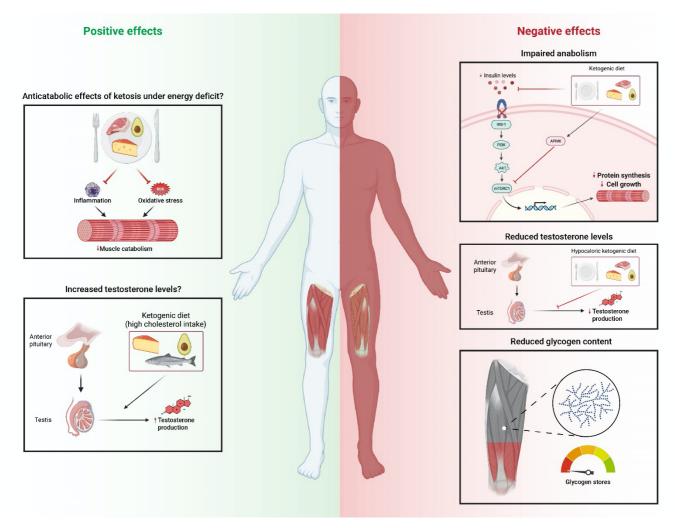


Figure 2. Summary of some potential mechanisms underlying the positive and negative effects of ketogenic diets on muscle mass.

3. Effects of combining ketogenic diets with resistance training on strength and power performance in trained individuals

Given the promising results of KD on body composition, further performance bene-260 fits of KD could be hypothesized at least in those sports in which body mass is a key de-261 terminant (e.g., weight-category sports or those involving actions performed with the own 262 body mass such as jumps) [2]. In turn, the detrimental effects of KD on muscle mass could 263 result in an impaired muscular function, especially when muscle performance is ex-264 pressed in absolute values (e.g., total kg lifted, or total wattage produced) instead of rela-265 tive to body mass (e.g., total kg lifted/kg or watts/kg). For this reason, it is important to 266 explore whether muscle strength is improved or at least maintained during KD. 267

Conflicting results exist regarding the effects of KD on muscle strength or other re-268 lated performance measures (e.g., power output). Reflecting this controversy, a recent sys-269 tematic review assessed seven studies that had analyzed the effects of KD on strength or 270 power measures on 16 performance outcomes studied (mainly muscle strength [one-rep-271 etition maximum, 1RM] in different exercises, jump performance and sprint power out-272 put) [14]. Only two reported a significantly beneficial effect of KD, whereas 11 found no 273 effects and three observed an impaired performance after a KD [14]. Nonetheless, it must 274 be noted that the two performance measures in which benefits were observed corre-275sponded to two cycling tests (6-second sprint and 3-minute critical power test) that were 276 implemented in the same study after a 100-km trial [66]. As such, the performance meas-277 ure in question might have been more indicative of muscle endurance than of muscle 278 power capacity. 279

Table 1 summarizes randomized controlled trials that have assessed the effects of KD 280 on muscle strength- or power-related outcomes in strength-trained individuals. Overall, 281 no effects of KD on strength or power-related performance have been reported. Indeed, 282 except for the study by Rhyu et al., which reported greater benefits with a KD compared 283 with a non-KD on a 2,000-m running trial and on the 'anaerobic' fatigue index assessed 284 by the Wingate test [32], the remainder of randomized controlled trials reported no bene-285 ficial effects of KD on performance or even detrimental effects. It must be noted, however, 286 that some studies have found no changes in performance outcomes despite reporting 287 losses in total body (and even muscle) mass, which could be considered beneficial in some 288 specific situations [26,35]. For instance, Vidic et al. reported no changes in squat and bench 289 press 1RM after an 8-week hypocaloric KD that induced an average body mass loss of 6.1 290 kg [33]. Greene et al. found no variations in 1RM strength on different exercises despite a 291 total body mass loss of 3.2 kg compared with a control (participants' usual) diet [26]. 292 Kephart et al. observed that participants who self-selected to follow a KD during three 293 months maintained their 1RM on the squat and power clean exercises despite a total body 294 mass loss of 3 kg [35]. Similarly, Paoli et al. reported that 30 days of KD did not have a 295 significant impact on performance (jump height, grip chins and push-ups) despite a body 296 mass loss of 1.6 kg [36]. Nonetheless, other studies have found a detrimental effect of KD 297 on performance - or at least lower benefits - compared to a traditional western diet. Var-298 gas et al. reported greater improvements in performance (jump height and 1RM bench 299 press) after a non-KD compared with an 8-week KD [28]. In the study by Wilson et al., 300 those participants who followed a non-KD during 10 weeks increased their peak power 301 output on a Wingate test, whereas those who followed a KD did not - albeit with no sig-302 nificant differences in the pre-post change between conditions [29]. Kysel et al. reported 303 larger benefits on maximal strength (1RM on the bench press and lateral pull-down exer-304 cises) and on some markers of cardiorespiratory fitness (peak oxygen uptake and peak 305 workload during an incremental test) in individuals who followed a hypocaloric non-KD 306 compared with those who followed a hypocaloric cyclical KD [31]. In a non-controlled 307 study by Urbain et al., participants who followed a KD for 6 weeks showed an impairment 308 of peak power during an incremental cycling test (-4.1%), although handgrip strength in-309 creased slightly (+2.5%) [67]. Similarly, Fleming et al. observed that a 6-week high-fat diet 310 (61% fat, 8% carbohydrate) resulted in a reduced peak and mean power during a Wingate 311 test compared with a control diet [68]. More recently, a study conducted in CrossFit ath-312 letes revealed that a 4-week KD induced no beneficial effects on CrossFit-specific perfor-313 mance (assessed through a workout including jumps, push presses and rowing, among 314 other exercises) and even resulted in an impaired cardiorespiratory fitness (lower peak 315 oxygen uptake) in women [69]. 316

In summary, although some studies support the effectiveness of KD for reducing total body – and particularly fat – mass in strength-trained individuals without harming sports performance, there is also evidence for some performance decrements compared to non-KD western diets. 320

4. Perspectives

Evidence on the effects of KD on strength-trained individuals is rapidly growing. 322 Many studies have methodological limitations (e.g., not following a randomized con-323 trolled trial design, not monitoring dietary intakes, small sample sizes, short duration of 324 the intervention, or variation in the amount and type of carbohydrates [high or low gly-325 cemic index] during the intervention) impeding to draw evidence-based inferences. In 326 addition, as shown in Table 1, the number of randomized controlled trials conducted in 327 healthy strength-trained individuals is still scarce, and no study has assessed the long-328 term effects (>12 weeks) of KD in this population. 329

There is only one study to date reporting muscle mass gains after a KD, with this 330 effect found after reintroducing carbohydrates for one week [29]. Similarly, Michalczyk et 331 al. recently reported that although following a low-carbohydrate diet (10% of total energy 332 intake) for 4 weeks resulted in an impaired performance during the Wingate test (-11% 333

total work capacity) compared to a conventional diet, after reintroducing carbohydrates 334 for one week (75% of total energy intake) performance recovered to levels similar to those 335 observed with the conventional diet [65]. These findings suggest that carbohydrate rein-336 troduction might be an optimal pre-competition strategy to avoid the potential detri-337 mental consequences of KD on muscle mass and performance in those athletes not con-338 cerned about potential increases in body mass. However, another trial that applied a hy-339 pocaloric cyclical KD (i.e., by alternating 5 days of KD with 2 days of high carbohydrate 340 intake [70% of total energy intake]) reported lower performance gains and a greater loss 341 of muscle mass compared with a regular non-KD designed to induce the same energy 342 deficit (-500 kcal in both cases) [31]. Further research is therefore warranted to confirm 343 whether including a carbohydrate reintroduction phase might mitigate some of the detri-344 mental consequences of KD. 345

The neutral effects of KD on absolute strength/power (e.g., 1RM, maximal power output) might support their potential benefits on muscle strength/power relative to total body 347 mass (e.g., watts/kg), on performance in weight-bearing exercises such as jumps, pushups, pull-ups, and also for athletes competing in weight-category sports (e.g., combat 349 sports) although the evidence is still controversial and overall not promising [28,36,69]. 350 Further research including randomized controlled trials is needed to confirm the actual 351 effects of KD on performance outcomes in which body mass plays an important role. 352

Although more research is also needed to confirm the exact mechanisms underlying 353 the impairment effect of KD vs. non-KD on resistance training-induced hypertrophy, it 354 might be recommendable to closely monitor the protein intake of KD. As summarized in 355 Table 1, several studies – including those that found a reduced muscle mass with the KD 356 - have provided daily protein intakes ranging between 1.2 and 2.5 g/kg/day, with similar 357 protein intakes in those individuals who followed a KD or a non-KD. In this regard, pro-358 tein intakes of 1.6-2.0 g/kg/day have been recommended to maximize resistance training-359 induced gains in muscle mass and strength [70–72]. However, under conditions of energy 360 restriction, higher protein intakes (1.7 to 3.1 g/kg) might be needed to maintain muscle 361 mass [71,73]. Moreover, it has been reported that, compared with an energy-matched 362 high-carbohydrate diet, higher protein intakes might be needed for those people on a low-363 carbohydrate diet in order to meet protein requirements during post-exercise recovery 364 [74]. Bodybuilders who followed an 8-week KD with a protein intake of 2.5 g/kg/day were 365 able to maintain their muscle mass, although those who followed a non-KD westernized 366 diet increased their muscle mass to a greater extent [25]. Further evidence is therefore 367 needed to confirm whether increasing protein intake through diet or protein (>1.6 g/kg)/ 368 amino acid (e.g., leucine) supplementation can negate the potentially detrimental effects 369 of KD on muscle anabolism. Conversely, given the rapid adaptation of the human body 370 to maximize liver gluconeogenesis under situations of increasing aminoacidemia and low 371 carbohydrate availability, following a KD with high protein intake could stimulate hepatic 372 gluconeogenesis from proteins [75,76], with subsequent reduction in ketosis. However, 373 the role of dietary protein on gluconeogenesis remains controversial [77]. Indeed, high 374 circulating ketone levels (>1 mmol/L) have been reported even with very low carbohy-375 drate diets coupled with high protein intakes (0 and 30% of the total energy intake, re-376 spectively) despite the occurrence of gluconeogenesis [78]. The role of protein intake on 377 the effects of KD should therefore be further addressed. 378

Future studies should also determine a range of effective nutritional ketosis. Wilson 379 et al. [29] reported circulating ketone levels consistently surpassing >0.5 mmol/L and 380 reaching $\geq 1 \text{ mmol/L}$ after 3 weeks of isocaloric KD. Similarly, Vidic et al. [33] observed 381 that those individuals following a hypocaloric KD presented steady blood ketone levels 382 of 1-2 mmol/L, whereas those following a hypocaloric LCD but non-KD had ketone con-383 centrations of 0.1-0.2 mmol/L. Other studies have confirmed the presence of urinary ke-384 tones using reagent strips, with some of them removing from the study those individuals 385 who did not show positive ketosis [27,28] and others just confirming participants were 386 under nutritional ketosis most of the days (range 69-100%) [67]. In turn, Greene et al. [26] 387 and Fleming et al. [68] observed an average ketone concentration <0.5 mmol/L (0.4 and 0.3 388

mmol/L, respectively) after a KD despite keeping carbohydrate intake <10% of total energy intake (or <50 g/d), which might reflect that some individuals did not adhere to the dietary recommendations or did not attain ketosis. Future studies should confirm whether higher levels of circulating ketones (e.g., >1.0 instead of 0.5 mmol/L) can maximize KD 392 benefits. Preliminary evidence combining a KD intervention with an exogenous ketone 393 supplement vs. a KD alone failed to find any additional benefit in spite of reaching higher 394 levels of ketosis, particularly during the first weeks [37].

Another potentially confounding factor might be the energy intake associated with 396 KD. Evidence overall suggests that KD are more effective than western diets for promot-397 ing loss of total body and fat mass. Thus, studies have reported that ad libitum KD result 398 in a greater loss of total body or fat mass than an *ad libitum* western diet [26,30]. In the 399 same line, studies comparing energy-balanced KD with isocaloric western diets also show 400 superior benefits of the former on total body and fat mass reduction [25,27,29]. However, 401 studies comparing hypocaloric KD with western diets or non-KD low-carbohydrate diets 402 resulting in the same energy deficit have found a similar effect on total body/fat mass [31-403 33]. More controversy exists, however, on how energy intake might affect the effects of 404 KD on muscle mass. Thus, a study analyzing the effect of an energy-balanced KD reported 405 that it was as effective as a non-KD western diet for increasing muscle mass [29]. In turn, 406 other authors have found that an energy-balanced KD is less effective than an isocaloric 407 Western diet for improving muscle mass [25], and others have reported losses in muscle 408 mass with ad libitum and hypocaloric KD - being this loss of muscle mass greater than that 409 observed with an *ad libitum* Western diet - [26,33]. Further research analyzing the effects 410 of KD with different energetic conditions (energy-balanced vs. hypocaloric vs. hyperca-411 loric) is needed to draw definite conclusions on the influence of energy balance on the 412 effects of KD, as well as to compare the actual effectiveness for promoting fat loss of hy-413 pocaloric KD and conventional diets resulting in the same energy intake. 414

Finally, a major concern with KD is their eventual long-term safety [79]. KD have 415 been overall reported to be safe and to improve different cardiovascular disease risk fac-416 tors such as obesity and glucose metabolism, although the long-term sustainability of KD-417 induced benefits remains unclear [80,81]. Moreover, a great proportion of individuals 418 starting KD reports several symptoms (known as 'keto flu') during the first weeks includ-419 ing headache, fatigue, nausea, dizziness and gastrointestinal discomfort [82]. There is also 420 evidence of increased levels of low-density lipoprotein cholesterol and apo-B-containing 421 lipoprotein with this type of diet [83]. It should be taken in mind that, as with any diet 422 (including low-fat diets) the quality of the nutrients ingested (e.g., ultra-processed vs un-423 processed or minimally processed foods, refined vs unrefined carbohydrates, saturated vs 424 unsaturated fats) should be a primary focus [80]. In this regard, given that KD are typically 425 characterized by a high intake of saturated fats or animal-based foods and also by a low 426 fiber intake, which could be detrimental for cardiovascular health, inclusion of polyun-427 saturated fats (as found in avocado, nuts, coconut or olive oil) and plant-based foods that 428 are also rich in proteins (e.g., tofu, pea, tempeh, seitan) might be recommendable [84,85]. 429

5. Conclusions

Evidence overall supports the effectiveness – at least in the short term, as no study 432 has yet assessed the long-term effects of these diets - of KD for reducing total body and 433 fat mass in strength-trained individuals compared with non-KD. Nonetheless, further re-434 search is needed to confirm the superiority of hypocaloric KD over non-KD with the same 435 energy intake. Conversely, KD might impair resistance training-induced gains on muscle 436 mass and performance - particularly when expressed in absolute values (e.g., total kg 437 lifted, watts). Further evidence is needed regarding the long-term safety of these diets. 438 Caution should be therefore taken when maintaining a KD in the long term or when in-439 creases in muscle mass and performance are sought. 440

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Refe	rences	448
1.	Aragon, A.A.; Schoenfeld, B.J.; Wildman, R.; Kleiner, S.; VanDusseldorp, T.; Taylor, L.; Earnest, C.P.; Arciero, P.J.; Wilborn,	449
	C.; Kalman, D.S.; et al. International society of sports nutrition position stand: Diets and body composition. J. Int. Soc. Sports	450
	Nutr. 2017 , 14, 1–19.	451
2.	Paoli, A.; Bianco, A.; Grimaldi, K.A. The Ketogenic Diet and Sport: A Possible Marriage? Exerc. Sport Sci. Rev. 2015, 43, 153-	452
	162.	453
3.	Puchalska, P.; Crawford, P.A. Multi-dimensional Roles of Ketone Bodies in Fuel Metabolism, Signaling, and Therapeutics.	454
	<i>Cell Metab.</i> 2017 , <i>25</i> , 262–284.	455
4.	Egan, B.; D'Agostino, D.P. Fueling Performance: Ketones Enter the Mix. Cell Metab. 2016, 24, 373-375.	456
5.	Burke, L.M.; Ross, M.L.; Garvican-Lewis, L.A.; Welvaert, M.; Heikura, I.A.; Forbes, S.G.; Mirtschin, J.G.; Cato, L.E.; Strobel,	457
	N.; Sharma, A.P.; et al. Low carbohydrate, high fat diet impairs exercise economy and negates the performance benefit from	458
	intensified training in elite race walkers. J. Physiol. 2017, 595, 2785–2807.	459
6.	Burke, L.M.; Whitfield, J.; Heikura, I.A.; Ross, M.L.R.; Tee, N.; Forbes, S.F.; Hall, R.; McKay, A.K.A.; Wallett, A.M.; Sharma,	460
	A.P. Adaptation to a low carbohydrate high fat diet is rapid but impairs endurance exercise metabolism and performance	461
	despite enhanced glycogen availability. J. Physiol. 2020, In press.	462
7.	Burke, L.M.; Sharma, A.P.; Heikura, I.A.; Forbes, S.F.; Holloway, M.; McKay, A.K.A.; Bone, J.; Leckey, J.J.; Welvaert, M.; Ross,	463
	M.L.R. Crisis of confidence averted: Impairment of exercise economy and performance in elite race walkers by ketogenic	464
	Low Carbohydrate, High Fat (LCHF) diet is reproducibleitle. PLoS One 2020, 1–31.	465
8.	Bueno, N.B.; De Melo, I.S.V.; De Oliveira, S.L.; Da Rocha Ataide, T. Very-low-carbohydrate ketogenic diet v. low-fat diet for	466
	long-term weight loss: A meta-analysis of Randomised controlled trials. Br. J. Nutr. 2013, 110, 1178–1187.	467
9.	Santos, F.L.; Esteves, S.S.; da Costa Pereira, A.; Yancy, W.S.; Nunes, J.P.L. Systematic review and meta-analysis of clinical	468
	trials of the effects of low carbohydrate diets on cardiovascular risk factors. Obes. Rev. 2012, 13, 1048–1066.	469
10.	Ge, L.; Sadeghirad, B.; Ball, G.D.C.; Da Costa, B.R.; Hitchcock, C.L.; Svendrovski, A.; Kiflen, R.; Quadri, K.; Kwon, H.Y.;	470
	Karamouzian, M.; et al. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight	471
	and cardiovascular risk factor reduction in adults: Systematic review and network meta-analysis of randomised trials. BMJ	472
	2020 , <i>369</i> .	473
11.	Volek, J.S.; Noakes, T.; Phinney, S.D. Rethinking fat as a fuel for endurance exercise. Eur. J. Sport Sci. 2015, 15, 13–20.	474
12.	Noakes, T.; Volek, J.S.; Phinney, S.D. Low-carbohydrate diets for athletes: What evidence? <i>Br. J. Sports Med.</i> 2014, 48, 1077–1078.	475 476
13.	Burke, L.M. Ketogenic low-CHO, high-fat diet: the future of elite endurance sport? J. Physiol. 2020, In press.	477
14.	Murphy, N.E.; Carrigan, C.T.; Margolis, L.M. High-Fat Ketogenic Diets and Physical Performance: A Systematic Review. Adv.	478
	Nutr. 2020 , 1–11.	479
15.	Ashtary-Larky, D.; Bagheri, R.; Asbaghi, O.; Tinsley, G.; Kooti, W. Effects of resistance training combined with a ketogenic	480
	diet on body composition: a systematic review and meta-analysis. Crit. Rev. Food Sci. Nutr. 2021, In press.	481
16.	Paoli, A. Ketogenic diet for obesity: Friend or foe? Int. J. Environ. Res. Public Health 2014, 11, 2092–2107.	482
17.	Dominik, P.; Varman, S. A high-protein diet for reducing body fat: mechanisms and possible caveats. Nutr. Metab. 2014, 11,	483
	1–8.	484

- Veldhorst, M.; Smeets, A.; Soenen, S.; Hochstenbach-Waelen, A.; Hursel, R.; Diepvens, K.; Lejeune, M.; Luscombe-Marsh, N.;
 Westerterp-Plantenga, M. Protein-induced satiety: Effects and mechanisms of different proteins. *Physiol. Behav.* 2008, 94, 300–
 307.
- Whitehead, J.; McNeill, G.; Smith, J. The effect of protein intake on 24-h energy expenditure during energy restriction. *Int. J.* 488 Obes. Relat. Metab. Disord. 1996, 20, 727–732.
- Gibson, A.A.; Seimon, R. V.; Lee, C.M.Y.; Ayre, J.; Franklin, J.; Markovic, T.P.; Caterson, I.D.; Sainsbury, A. Do ketogenic diets 490 really suppress appetite? A systematic review and meta-analysis. *Obes. Rev.* 2015, *16*, 64–76.
- Laeger, T.; Metges, C.C.; Kuhla, B. Role of β-hydroxybutyric acid in the central regulation of energy balance. *Appetite* 2010, 492 54, 450–455.
- Hall, K.; Chen, K.; Guo, J.; Lam, Y.; Leibel, R.; Mayer, L.; Reirman, M.; Rosenbaum, M.; Smith, S.; Walsh, B.; et al. Energy 494 expenditure and body composition changes after an isocaloric ketogenic diet in overweight and obese men. *Am. J. Clin. Nutr.* 495 2016, 104, 324–333.
- Tagliabue, A.; Bertoli, S.; Trentani, C.; Borrelli, P.; Veggiotti, P. Effects of the ketogenic diet on nutritional status, resting
 energy expenditure, and substrate oxidation in patients with medically refractory epilepsy: A 6-month prospective
 observational study. *Clin. Nutr.* 2012, *31*, 246–249.
- Kreitzman, S.N.; Coxon, A.Y.; Szaz, K.F. Glycogen storage: Illusions of easy weight loss, excessive weight regain, and distortions in estimates of body composition. *Am. J. Clin. Nutr.* **1992**, *56*.
- Paoli, A.; Cenci, L.; Pompei, P.L.; Sahin, N.; Bianco, A.; Neri, M.; Caprio, M.; Moro, T. Effects of two months of very low 502 carbohydrate ketogenic diet on body composition, muscle strength, muscle area, and blood parameters in competitive 503 natural body builders. *Nutrients* 2021, 13, 1–14. 504
- Greene, D.; Varley, B.; Hartwig, T.; Chapman, P.; Rigney, M. A low-carbohydrate ketogenic diet reduces body mass without 505 compromising performance in powerlifting and Olympic weightlifting athletes. *J. strength Cond. Res.* 2018, *32*, 3373–3382. 506
- Vargas, S.; Romance, R.; Petro, J.L.; Bonilla, D.A.; Galancho, I.; Espinar, S.; Kreider, R.B.; Benítez-Porres, J. Efficacy of ketogenic diet on body composition during resistance training in trained men: A randomized controlled trial. *J. Int. Soc. Sports* 508 *Nutr.* 2018, 15, 1–9. 509
- Vargas-Molina, S.; Petro, J.L.; Romance, R.; Kreider, R.B.; Schoenfeld, B.J.; Bonilla, D.A.; Benítez-Porres, J. Effects of a 510 ketogenic diet on body composition and strength in trained women. *J. Int. Soc. Sports Nutr.* 2020, *17*, 1–10. 511
- Wilson, J.M.; Lowery, R.P.; Roberts, M.D.; Sharp, M.H.; Joy, J.M.; Shields, K.A.; Partl, J.M.; Volek, J.S.; D'Agostino, D.P. Effects 512 of Ketogenic Dieting on Body Composition, Strength, Power, and Hormonal Profiles in Resistance Training Men; 2020; Vol. 34; ISBN 0000000000. 514
- 30. Skemp, K.; Stehly, M.; Baumann, D. The Effects of a Ketogenic Diet on Body Composition in resistance training females. *Ann.* 515 Sport. Med. Res. 2021, 8, 1176. 516
- Kysel, P.; Haluzíková, D.; Doležalová, R.P.; Laňková, I.; Lacinová, Z.; Kasperová, B.J.; Trnovská, J.; Hrádková, V.; Mráz, M.;
 Vilikus, Z.; et al. The influence of cyclical ketogenic reduction diet vs. Nutritionally balanced reduction diet on body
 composition, strength, and endurance performance in healthy young males: A randomized controlled trial. *Nutrients* 2020,
 12, 1–12.
- Rhyu, H.; Cho, S.-Y. The effect of weight loss by ketogenic diet on the body composition, performance-related physical fitness
 factors and cytokines of Taekwondo athletes. J. Exerc. Rehabil. 2014, 10, 326–331.
- Vidić, V.; Ilić, V.; Toskić, L.; Janković, N.; Ugarković, D. Effects of calorie restricted low carbohydrate high fat ketogenic vs.
 non-ketogenic diet on strength, body-composition, hormonal and lipid profile in trained middle-aged men. *Clin. Nutr.* 2021, 40, 1495–1502.
- Jabekk, P.; Moe, I.; Meen, H.; Tomten, S.; Hostmark, A. Resistance training in overweight women on a ketogenic diet
 conserved lean body mass while reducing body fat. *Nutr. Metab. (Lond).* 2010, *7*, 17.

35.	Kephart, W.; Pledge, C.; Roberson, P.; Mumford, P.; Romero, M.; Mobley, C.; Martin, J.; Young, K.; Lowery, R.; Wilson, J.; et	528
	al. The Three-Month Effects of a Ketogenic Diet on Body Composition, Blood Parameters, and Performance Metrics in	529
	CrossFit Trainees: A Pilot Study. Sports 2018, 6, 1.	530
36.	Paoli, A.; Grimaldi, K.; D'Agostino, D.; Cenci, L.; Moro, T.; Bianco, A.; Palma, A. Ketogenic diet does not affect strength	531
	performance in elite artistic gymnasts. J. Int. Soc. Sports Nutr. 2012, 9, 1–9.	532
37.	Buga, A.; Kackley, M.L.; Crabtree, C.D.; Sapper, T.N.; Mccabe, L.; Fell, B.; LaFountain, R.A.; Hyde, P.N.; Martini, E.R.;	533
	Bowman, J.; et al. The Effects of a 6-Week Controlled, Hypocaloric Ketogenic Diet, With and Without Exogenous Ketone	534
	Salts, on Body Composition Responses. Front. Nutr. 2021, 8.	535
38.	Paoli, A.; Cancellara, P.; Pompei, P.; Moro, T. Ketogenic diet and skeletal muscle hypertrophy: A Frenemy relationship? J.	536
	Hum. Kinet. 2019 , 68, 233–247.	537
39.	Tinsley, G.M.; Willoughby, D.S. Fat-free mass changes during ketogenic diets and the potential role of resistance training.	538
	Int. J. Sport Nutr. Exerc. Metab. 2016 , 26, 78–92.	539
40.	Prats, C.; Graham, T.E.; Shearer, J. The dynamic life of the glycogen granule. J. Biol. Chem. 2018, 293, 7089–7098.	540
41.	Roberts, M.D.; Haun, C.T.; Vann, C.G.; Osburn, S.C.; Young, K.C. Sarcoplasmic Hypertrophy in Skeletal Muscle: A Scientific	541
	"Unicorn" or Resistance Training Adaptation? Front. Physiol. 2020, 11, 1–16.	542
42.	Abdulla, H.; Smith, K.; Atherton, P.J.; Idris, I. Role of insulin in the regulation of human skeletal muscle protein synthesis	543
	and breakdown: a systematic review and meta-analysis. <i>Diabetologia</i> 2016 , <i>59</i> , 44–55.	544
43.	Fujita, S.; Rasmussen, B.B.; Cadenas, J.G.; Grady, J.J.; Volpi, E. Effect of insulin on human skeletal muscle protein synthesis	545
	is modulated by insulin-induced changes in muscle blood flow and amino acid availability. Am. J. Physiol Endocrinol. Metab.	546
	2006, 291.	547
44.	Biolo, G.; Fleming, R.Y.D.; Wolfe, R.R. Physiologic hyperinsulinemia stimulates protein synthesis and enhances transport of	548
	selected amino acids in human skeletal muscle. J. Clin. Invest. 1995, 95, 811–819.	549
45.	Kennedy, A.R.; Pissios, P.; Otu, H.; Xue, B.; Asakura, K.; Furukawa, N.; Marino, F.E.; Liu, F.F.; Kahn, B.B.; Libermann, T.A.;	550
	et al. A high-fat, ketogenic diet induces a unique metabolic state in mice. Am. J. Physiol Endocrinol. Metab. 2007, 292, 1724-	551
	1739.	552
46.	Lantier, L.; Mounier, R.; Leclerc, J.; Pende, M.; Foretz, M.; Viollet, B. Coordinated maintenance of muscle cell size control by	553
	AMP-activated protein kinase. FASEB J. 2010, 24, 3555–3561.	554
47.	Yamada, T.; Zhang, S.J.; Westerblad, H.; Katz, A. B-Hydroxybutyrate Inhibits Insulin-Mediated Glucose Transport in Mouse	555
	Oxidative Muscle. Am. J. Physiol Endocrinol. Metab. 2010, 299, 364–373.	556
48.	Thomsen, H.H.; Rittig, N.; Johannsen, M.; Møller, A.B.; Jørgensen, J.O.; Jessen, N.; Møller, N. Effects of 3-hydroxybutyrate	557
	and free fatty acids on muscle protein kinetics and signaling during LPS-induced inflammation in humans: Anticatabolic	558
	impact of ketone bodies. Am. J. Clin. Nutr. 2018, 108, 857–867.	559
49.	Pawan, G.L.S.; Semple, S.J.G. Effect of 3-Hydroxybutyrate in Obese Subjects on Very-Low-Energy Diets and During	560
	Therapeutic Starvation. Lancet 1983, 321, 15–17.	561
50.	Sherwin, R.S.; Hendler, R.G.; Felig, P. Effect of ketone infusions on amino acid and nitrogen metabolism in man. J. Clin. Invest.	562
	1975 , <i>55</i> , 1382–1390.	563
51.	Youm, Y.H.; Nguyen, K.Y.; Grant, R.W.; Goldberg, E.L.; Bodogai, M.; Kim, D.; D'Agostino, D.; Planavsky, N.; Lupfer, C.;	564
	Kanneganti, T.D.; et al. The ketone metabolite β -hydroxybutyrate blocks NLRP3 inflammasome-mediated inflammatory	565
	disease. Nat. Med. 2015, 21, 263–269.	566
52.	Rojas-Morales, P.; Pedraza-Chaverri, J.; Tapia, E. Ketone bodies, stress response, and redox homeostasis. Redox Biol. 2020, 29,	567
	101395.	568
53.	Sartori, R.; Romanello, V.; Sandri, M. Mechanisms of muscle atrophy and hypertrophy: implications in health and disease.	569
	Nat. Commun. 2021 , 12, 1–12.	570

54.	Rhyu, H.; Cho, SY.; Roh, HT. The effects of ketogenic diet on oxidative stress and antioxidative capacity markers of	571
	Taekwondo athletes. J. Exerc. Rehabil. 2014, 10, 362–366.	572
55.	Pasiakos, S.M.; Vislocky, L.M.; Carbone, J.W.; Altieri, N.; Konopelski, K.; Freake, H.C.; Anderson, J.M.; Ferrando, A.A.; Wolfe,	573
	R.R.; Rodriguez, N.R. Acute energy deprivation affects skeletal muscle protein synthesis and associated intracellular	574
	signaling proteins in physically active adults. J. Nutr. 2010, 140, 745–751.	575
56.	Areta, J.L.; Burke, L.M.; Camera, D.M.; West, D.W.D.; Crawshay, S.; Moore, D.R.; Stellingwerff, T.; Phillips, S.M.; Hawley,	576
	J.A.; Coffey, V.G. Reduced resting skeletal muscle protein synthesis is rescued by resistance exercise and protein ingestion	577
	following short-term energy deficit. Am. J. Physiol Endocrinol. Metab. 2014, 306, 989–997.	578
57.	McCall, L.M.; Ackerman, K.E. Endocrine and metabolic repercussions of relative energy deficiency in sport. Curr. Opin.	579
	Endocr. Metab. Res. 2019 , 9, 56–65.	580
58.	Cannataro, R.; Cione, E.; Gallelli, L.; Marzullo, N.; Bonilla, D.A. Acute Effects of Supervised MakingWeight on Health	581
	Markers, Hormones and Body Composition in Muay Thai Fighters. Sports 2020, 8, 1–23.	582
59.	Salvatore, D.; Simonides, W.S.; Dentice, M.; Zavacki, A.M.; Larsen, P.R. Thyroid hormones and skeletal muscle - New insights	583
	and potential implications. <i>Nat. Rev. Endocrinol.</i> 2014 , <i>10</i> , 206–214.	584
60.	Redman, L.M.; Veldhuis, J.D.; Rood, J.; Smith, S.R.; Williamson, D.; Ravussin, E. The effect of caloric restriction interventions	585
	on growth hormone secretion in nonobese men and women. Aging Cell 2010, 9, 32–39.	586
61.	Fontana, L.; Weiss, E.; Villareal, D.; Klein, S.; Holloszy, J. Long-term effects of calorie or protein restriction on serum IGF-1	587
	and IGFBP-3 concentration in humans. Aging Cell 2008, 7, 681–687.	588
62.	Cangemi, R.; Friedmann, A.J.; Holloszy, J.O.; Fontana, L. Long-term effects of calorie restriction on serum sex-hormone	589
	concentrations in men. Aging Cell 2010, 9, 236–242.	590
63.	Santos, H.O. Ketogenic diet and testosterone increase: Is the increased cholesterol intake responsible? to what extent and	591
	under what circumstances can there be benefits? <i>Hormones</i> 2017 , <i>16</i> , 266–270.	592
64.	Volek, J.S.; Gómez, A.L.; Love, D.M.; Avery, N.G.; Sharman, M.J.; Kraemer, W.J. Effect of a high-fat diet on postabsorptive	593
	and postprandial testosterone responses to a fat-rich meal. Metabolism. 2001, 50, 1351–1355.	594
65.	Michalczyk, M.M.; Chycki, J.; Zajac, A.; Maszczyk, A.; Zydek, G.; Langfort, J. Anaerobic performance after a low-	595
	carbohydrate diet (LCD) followed by 7 days of carbohydrate loading in male basketball players. Nutrients 2019, 11, 1–13.	596
66.	McSwiney, F.T.; Wardrop, B.; Hyde, P.N.; Lafountain, R.A.; Volek, J.S.; Doyle, L. Keto-adaptation enhances exercise	597
	performance and body composition responses to training in endurance athletes. <i>Metabolism</i> 2018, 81, 25–34.	598
67.	Urbain, P.; Strom, L.; Morawski, L.; Wehrle, A.; Deibert, P.; Bertz, H. Impact of a 6-week non-energy-restricted ketogenic diet	599
	on physical fitness, body composition and biochemical parameters in healthy adults. Nutr. Metab. 2017, 14, 1–11.	600
68.	Fleming, J.; Sharman, M. Endurance capacity and high-intensity exercise performance responses to a high fat diet. Int. J. Sport	601
	Nutr. Exerc. Metab. 2003, 13, 466–478.	602
69.	Durkalec-Michalski, K.; Nowaczyk, P.M.; Główka, N.; Ziobrowska, A.; Podgórski, T. Is a four-week ketogenic diet an	603
	effective nutritional strategy in crossfit-trained female and male athletes? Nutrients 2021, 13, 1–19.	604
70.	Morton, R.W.; Murphy, K.T.; McKellar, S.R.; Schoenfeld, B.J.; Henselmans, M.; Helms, E.; Aragon, A.A.; Devries, M.C.;	605
	Banfield, L.; Krieger, J.W.; et al. A systematic review, meta-analysis and meta-regression of the effect of protein	606
	supplementation on resistance training-induced gains in muscle mass and strength in healthy adults. Br. J. Sports Med. 2018,	607
	52, 376–384.	608
71.	Phillips, S.M.; van Loon, L.J.C. Dietary protein for athletes: From requirements to optimum adaptation. J. Sports Sci. 2011, 29.	609
72.	Jäger, R.; Kerksick, C.M.; Campbell, B.I.; Cribb, P.J.; Wells, S.D.; Skwiat, T.M.; Purpura, M.; Ziegenfuss, T.N.; Ferrando, A.A.;	610
	Arent, S.M.; et al. International Society of Sports Nutrition Position Stand: Protein and exercise. J. Int. Soc. Sports Nutr. 2017,	611
	14, 1–25.	612
73.	Longland, T.M.; Oikawa, S.Y.; Mitchell, C.J.; DeVries, M.C.; Phillips, S.M. Higher compared with lower dietary protein	613

	during an energy deficit combined with intense exercise promotes greater lean mass gain and fat mass loss: A randomized	614
	trial. Am. J. Clin. Nutr. 2016, 103, 738–746.	615
74.	Gillen, J.B.; West, D.W.D.; Williamson, E.P.; Fung, H.J.W.; Moore, D.R. Low-Carbohydrate Training Increases Protein	616
	Requirements of Endurance Athletes. Med. Sci. Sports Exerc. 2019, 51, 2294–2301.	617
75.	Azzout-Marniche, D.; Gaudichon, C.; Blouet, C.; Bos, C.; Mathé, V.; Huneau, J.F.; Tomé, D. Liver glyconeogenesis: A pathway	618
	to cope with postprandial amino acid excess in high-protein fed rats? Am. J. Physiol Regul. Integr. Comp. Physiol. 2007, 292,	619
	1400–1407.	620
76.	Veldhorst, M.A.B.; Westerterp-Plantenga, M.S.; Westerterp, K.R. Gluconeogenesis and energy expenditure after a high-	621
	protein, carbohydrate-free diet. Am. J. Clin. Nutr. 2009, 90, 519–526.	622
77.	Fromentin, C.; Tomé, D.; Nau, F.; Flet, L.; Luengo, C.; Azzout-Marniche, D.; Sanders, P.; Fromentin, G.; Gaudichon, C. Dietary	623
	proteins contribute little to glucose production, even under optimal gluconeogenic conditions in healthy humans. Diabetes	624
	2013 , <i>62</i> , 1435–1442.	625
78.	Veldhorst, M.A.B.; Westerterp, K.R.; Westerterp-Plantenga, M.S. Gluconeogenesis and protein-induced satiety. Br. J. Nutr.	626
	2012 , <i>107</i> , 595–600.	627
79.	Joshi, S.; Ostfeld, R.; McMacken, M. The Ketogenic Diet for Obesity and Diabetes- Enthusiasm Outpaces Evidence. JAMA	628
	Intern. Med. 2019 , 179, 1163–1164.	629
80.	Ludwig, D.S. The Ketogenic Diet: Evidence for Optimism but High-Quality Research Needed. J. Nutr. 2020, 150, 1354–1359.	630
81.	Kosinski, C.; Jornayvaz, F.R. Effects of ketogenic diets on cardiovascular risk factors: Evidence from animal and human	631
	studies. <i>Nutrients</i> 2017 , <i>9</i> , 1–16.	632
82.	Bostock, E.C.S.; Kirkby, K.C.; Taylor, B. V.; Hawrelak, J.A. Consumer Reports of "Keto Flu" Associated With the Ketogenic	633
	Diet. Front. Nutr. 2020, 7, 1–6.	634
83.	Retterstøl, K.; Svendsen, M.; Narverud, I.; Holven, K.B. Effect of low carbohydrate high fat diet on LDL cholesterol and gene	635
	expression in normal-weight, young adults: A randomized controlled study. Atherosclerosis 2018, 279, 52-61.	636
84.	Kim, H.; Caulfield, L.E.; Garcia-Larsen, V.; Steffen, L.M.; Coresh, J.; Rebholz, C.M. Plant-Based Diets Are Associated With a	637
	Lower Risk of Incident Cardiovascular Disease, Cardiovascular Disease Mortality, and All-Cause Mortality in a General	638
	Population of Middle-Aged Adults. J. Am. Heart Assoc. 2019, 8.	639
85.	Hooper, L.; Martin, N.; Jimoh, O.F.; Kirk, C.; Foster, E.; Abdelhamid, A.S. Reduction in saturated fat intake for cardiovascular	640
	disease. Cochrane Database Syst. Rev. 2020, 2020.	641
		642