

Exercise with Energy Restriction as a Means of Losing Body Mass while Preserving Muscle Quality and Ameliorating Co-morbidities: Towards a Therapy for Obesity?

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Abstract

Obesity and related co-morbidities are a major public health threat worldwide and efforts to counteract obesity by means of physiological interventions are currently being explored and applied. Here we present an overview of the literature on the effect of dietary/exercise-based programs on loss of different components of body mass. We also discuss gain or lack of loss of lean mass in view of muscle quality maintenance, which is an important aspect to consider when employing weight-loss strategies to tackle obesity. By comparing results obtained in participants with mild to severe obesity with those obtained in lean participants, we highlight variations in the success of these interventions. Furthermore, we briefly address the observation that although certain interventions may not always affect body composition they can nevertheless ameliorate co-morbidities (insulin resistance, non-alcoholic fatty liver disease). Based on what is currently known, in this narrative review we include data from human and animal studies related to the process of unravelling the mechanisms underlying conservation of functional muscle mass.

Keywords: exercise; nutritional interventions; body composition; metabolic co-morbidities; obesity

Introduction

Overt obesity, irrespective of age, has increased over the past 30 years and so have its related co-morbidities (insulin resistance, cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), etc.)¹. In both men and women around the world, body mass is steadily rising. Over a period of 40 years (1975–2014), global age-standardized mean body mass index (BMI) increased from 21.7 kg/m² to 24.2 kg/m² in 2014 in men and

from 22.1 kg/m² to 24.4 kg/m² (24.2–24.6) in women². Whatever the strategy explored with the aim to reduce body mass, one aspect to consider is that it is crucial to preserve muscle power following body mass loss, especially in the elderly. Loss of muscle power compromises daily activities, which clearly manifests itself as age progresses³⁻⁷. These aspects are worsened when persons are obese⁸⁻¹⁵. Hence it is clear that interventions, which are aimed to improve body composition, reducing body and fat mass and preserving lean mass, while at the same time preserving muscle power, are warranted and are indeed being developed. Recently, interventions involving dietary restriction and/or exercise (resistance and/or endurance exercise) have been increasingly employed in obese subjects. Studies

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regarding muscle strength are currently prevalently performed in recreationally exercised non-obese subjects and findings from these studies are included to underline the effectiveness of specific interventions on muscle quality maintenance, which may offer suggestions for applications in the form of exercise therapy in obesity. Body composition measurements [performed by dual-energy X-ray absorptiometry (DXA) unless otherwise noted] have been performed either or not in combination with assessment on the effects on muscle strength or quality. When performed, android/gynoid fat ratios are included since excess android fat is associated with obesity-related diseases more so than excess gynoid fat¹⁶. This narrative review aims to highlight the state-of-the-art concerning these experimental interventions and addresses insights obtained from studies in rodent models as well as in humans regarding the mechanisms underlying the related conservation of muscle mass.

Energy restriction

One approach to induce body mass loss is energy restriction. Besides body mass loss, this intervention often also induces loss of lean mass and muscle strength. The outcomes do not substantially differ between obese and lean subjects, as is discussed in the following section.

Obese subjects

A 1-year dietary restriction intervention carried out in obese older adults resulted in 3% lean mass loss measured by magnetic resonance imaging (MRI) (Table 1), but loss of muscle strength (by measuring the maximal weight by a single lift) was

not observed¹⁰. In analogy, submission of obese participants to a 4-month daily caloric restriction resulted in loss of body mass and fat mass, as well as lean mass¹⁸ (Table 1). These subjects displayed decreased thigh muscle crosssectional areas¹⁸, while the effect on muscle strength was not reported. A follow-up study applying energy restriction in 30 clinically severe obese women over a period of 1 year showed a constant reduction of fat mass throughout the intervention but a reduced reduction of lean mass in the longer term (6 months and 1 year)¹⁹ (Table 1). Of note, a 6-month energy restriction intervention in obese subjects caused loss of muscle mass and over 10% loss of muscle strength, even while being submitted to treadmill walking of at least 150 min/wk with lower extremity resistance training⁸. In contrast to endurance training, resistance training is known to increase muscle strength in non-obese subjects^{26,30}, as will be discussed in the following sections. In order to avoid loss of lean mass, obese participants have been submitted to alternate day caloric restriction for shorter periods (8 or 12 weeks)^{21,23}. However, these shorter-term interventions did not always exhibit loss of fat mass²¹ (Table 1). The results of these interventions imply that attempts to reduce fat mass through energy restriction alone are often accompanied by loss of lean mass and muscle strength. With regard to muscle quality, body mass loss by energy restriction has been shown to lead to reduced muscle lipid content in obese participants^{8,33-35}. Lipidomic analysis of obese participants undergoing a 3-week daily 1000 kcal diet (20% of calories from fat) revealed altered intramuscular lipid profiles, in particular phosphatidylcholine and triglyceride species, accompanied with amelioration of the homeostasis model assessment-insulin resistance (HOMA-IR) index³⁶.

Table 1 Dietary/exercise interventions in human participants and their impact on body mass, fat mass and lean mass loss and on decreased android fat or android/gynoid fat ratios

Type of intervention	Specific intervention (duration)	Gender	n	Brief description of intervention	Reduction of total body mass	Reduction of total fat mass	Reduction of lean mass	Reduction of android fat or android/gynoid fat ratio	References
Energy restriction	Alternate day fasting (22 days)	MF	16	No caloric intake on the fasting day.	2.5 ± 0.5 ^c	0.8 ± 0.3 ^c	0.6 ± 0.3 ^c (P<0.05)	ND	17
	Daily caloric restriction (4 months)	MF	11	A caloric restriction of 500-1000 kcal/d based on baseline body mass (<30% of calories from fat) was applied. Energy intake was calculated to obtain a weekly loss of 0.5–1 kg of body mass.	9.1% ± 1.0% ^a	16.5% ^a	4.3% ± 1.2% (P<0.05)	ND	18
	(3 months)	F	30	Participants started with an intensive phase for 12 weeks, followed by a transition phase for 6–12 weeks, a maintenance phase for 6–12 weeks and a stabilization phase for 6 months. The energy restriction intervention consisted of a very low energy diet protocol (Optifast®, Nestle, Australia) with an energy intake ranging from 450–680 kcal (1900–2800 kJ) per day during the intensive phase to 1200 kcal (5000 kJ) per day during the stabilization phase.	9.9 ± 1.3 ^a	6.5 ± 1.0 ^a	3.4 ± 0.7 ^a	ND	19
	(6 months)				10.9 ± 2.2 ^a	9.3 ± 2.0 ^a	1.9±0.7 ^a	ND	
	(1 year)				8.9 ± 2.7 ^a	8.1 ± 2.8	1.7±0.8 ^a	ND	

	(1 year)	MF	26	Energy deficit of 500–750 kcal per day from their daily energy requirement containing approximately 1 g of high quality protein per kilogram of body weight per day.	9.7±5.4 ^a	7.1±3.9 ^a	3.2±2.0 ^a	ND	10
	(2 years)	M	44	Immediate and sustained 25% restriction of energy intake from individual baseline measured by a doubly labeled water-based method.	8.33 ± 0.42 ^c	3.24 ± 0.18 ^c	3.24 ± 0.33 ^c	ND	20
		F	99		7.32 ± 0.29 ^c	2.81 ± 0.13 ^c	1.63 ± 0.16 ^c	ND	
	Alternate day caloric restriction (8 weeks)	MF	13	25% of daily recommend energy intake in 3 days alternately (400–500 kcal) consumed between 12 and 2 pm and ad libitum food consumption on the remaining 4 days of the week.	2.4 ± 3.1 ^a (<i>P</i> =0.064, NS)	1.6 ± 2.3 ^a (<i>P</i> =0.036, NS)	0.5 ± 0.9 ^a (<i>P</i> =0.696, NS)	ND	21
	(12 weeks)	MF	32	Participants consumed 25% of their baseline energy needs on the fast day (24 h) and ad libitum on each alternating feed day (24 h). Fast day meals consisted of a 3-day rotating menu, containing 30% kcal from fat, 15% kcal from protein, 55% kcal from carbohydrate.	5.2 ± 1.0 ^e	3.6 ± 0.6 ^c	1.5 ± 0.5 ^e (NS)	ND	22
		MF	16	25% of baseline energy needs on each “fasting” day and ad libitum feeding on each “feed” day.	3.0 ± 1.0 ^a	2.0 ± 1.0 ^a	1.0 ± 1.0 ^a (<i>P</i> =0.527, NS)	ND	23
Exercise	Endurance exercise (12 weeks)	MF	15	Treadmill walking for 30 min, 5 times/wk.	1.0± 0.5 ^a (NS)	0.75 ± 0.45 ^a (NS)	ND	0.4 ± 0.6 ^a (Android fat) (NS)	24
		M	12	Treadmill run three times a week (on non-consecutive days) and a 20 min pre-session with 60% of maximal heart rate to 60 min at 75% of maximal heart rate.	5.44 ± 4.88 ^c (<i>P</i> =0.003)	3.80 ± 1.92 ^c (<i>P</i> =0.003)	0.05 ± 4.62 ^c	ND	25
		MF	16	Cycling with increasing intensity from 60%–75% of maximal heart rate.	1.0 ± 0.0 ^a	1.0 ± 0.0 ^a	1.0± 0.0 ^a (<i>P</i> =0.527, NS)	ND	23
Resistance exercise (8 weeks)	M	8	Three non-consecutive days per week of training, with four sets of alternating upper and lower body workouts using weights eliciting muscle failure after 8–12 repeats.	-3.0 ^c (<i>P</i> =0.38, NS)	-0.8 ^c (<i>P</i> =0.32,NS)	-2.3 ^c (<i>P</i> =0.49, NS)	ND	26	
	MF	28	Resistance exercise was performed three times per week on non-consecutive days for 8 weeks. Initially, participants did two circuits of a prescribed resistance exercise program with 50% of 1RM, up to three circuits with minimum 70% on the seventh week.	No change	0.1 (% body mass) ^a (<i>P</i> =0.12, NS)	ND	0.01 (<i>P</i> =0.21, NS)	27	
	(12 weeks)	MF	12	Training protocol aiming at an expenditure of 500 kcal during the training phase at 40%–80% of 1RM after completing a resistance circuit (including upper and lower muscle groups, 30–40 min, eight exercises, 3 times per week).	4.8± 8.0 ^a (<i>P</i> =0.01)	4.0 ± 6.5 (% ^a) (<i>P</i> <0.01)	-0.1 ± 0.04 ^a (NS)	0.1 ± 0.0 ^a (NS)	28
		MF	16	30 min of resistance exercise (four sets of 8–12 repetitions at 10 RM level as determined during the initial session).	0.1 ± 0.3 ^a (NS)	0.4 ± 0.35 ^a (NS)	ND	0.2 ± 0.6 ^a (Android fat) (NS)	24
		M	12	The training intensity was 60% 1RM during the first 2 weeks of training and increased to 75%–80% and consisted of 10 strength movements for the lower and upper body muscle groups.	-1.00 ± 5.82 ^c (<i>P</i> =0.003)	1.74 ± 1.72 ^c (<i>P</i> =0.03)	-5.33 ± 4.34 ^c	ND	25
	Combined endurance/resistance exercise (8 weeks)	MF	10	The aerobic exercise was by treadmill runs for at least 20 min, with exercise intensity being approximately 60%–85% of age-predicted maximal heart rate. Resistance training used weight training machines, barbells, and dumbbells, with individualized intensity assessed by 10 RM.	1.4 ± 2.1 ^a (<i>P</i> =0.06, NS)	1.2 ± 1.9 ^a (<i>P</i> =0.036)	0.1 ± 0.9 ^a (<i>P</i> =0.69, NS)	ND	21

(12 weeks)	MF	17	See for both separate protocols elsewhere in this table.	1.6 ± 0.7 ^a (<i>P</i> <0.05)	1.6 ± 0.5 ^a (<i>P</i> <0.05)	ND	1.3 ± 0.5 ^a (Android fat) (<i>P</i> <0.05)	24
	M	11	See for both separate protocols elsewhere in this table.	3.02 ± 2.90 ^f (<i>P</i> <0.03)	4.48 ± 4.56 ^c (<i>P</i> <0.03)	-8.59 ± 5.98 ^c	ND	25
(1 year)	MF	26	Aerobic exercises included treadmill walking, stationary cycling and stair climbing. From 65% to 85% of heart rate maximum, resistance training included upper- and lower-extremity exercises increasing from 65% to 80% of each individual's 1RM, and exercises to improve flexibility and balance.	0.5±3.6 ^a	1.8±1.9 ^a	-1.3±1.6 ^a	ND	10
High- intensity interval exercise (12 weeks)	MF	14	Fast walking or running on a treadmill with the deck inclined to reach the desired intensity, with participant-adjusted training energy expenditure, preparatory periods starting with an exercise dose of 6 kcal·kg ⁻¹ ·wk ⁻¹ , progressively increasing by 2 kcal·kg ⁻¹ ·wk ⁻¹ until week 4, remaining at 12 kcal·kg ⁻¹ ·wk ⁻¹ up to week 12.	4.5 ± 7.0 ^a (<i>P</i> <0.05)	3.4 ± 5.0 (%) ^a	-0.32 ± 0.01 ^a (NS)	0.1 ± 0.0 ^a (NS)	28
Combined resistance/high-intensity interval exercise (12 weeks)	MF	14	See elsewhere in this table for description of the separate interventions.	1.7 ± 3.4 ^a (<i>P</i> <0.05)	1.8 ± 3.1 (%) ^a (<i>P</i> <0.05)	-0.14 ± 0.2 ^a (NS)	0.0 ± 0.0 ^a (NS)	28
Energy restriction and exercise								
Caloric restriction and endurance exercise (4 months)	MF	18	For caloric restriction intervention see elsewhere in this table. Exercise was performed 5 days per week for 45 min at a range of 65%–75% of maximal heart rate. Exercise was intensified such that during the last 8 weeks, exercise intensity was 75% of maximal heart rate. Exercise sessions consisted of treadmill or outside brisk walking or cycling.	9.2% ± 1.0% ^a	20.7% ^a	1.1% ± 1.0% ^a (NS)	ND	18
Caloric restriction and endurance/resistance exercise (6 months)	MF	19	Total daily fat (mono- and poly-unsaturated fats rather than saturated fat and cholesterol), limited to approximately 25% of total calories, with 5 servings of fruits or vegetables and 6 servings of grains with multivitamin/mineral and calcium/vitamin D supplementation in order to achieve 7% reduction in body weight with a weekly rate of 1 to 2 pounds per week for 6 months, with a stable body mass after a 6-month follow-up, even if this group was submitted to treadmill walking of at least 150 min/wk with lower extremity resistance training.	4.9 ^a	4.4 ^a	1.5 ^a	ND	8
(3 months)	F	30	For caloric restriction intervention see elsewhere in this table. Exercise training sessions consisted of 20–30 min aerobic (60%–80% heart rate reserve) and 30 min resistance training (1–3 sets of 8–10 repetitions for 8 different upper and lower body exercises). The program consisted of 3 supervised training sessions per week for the first 6 weeks, 2 sessions per week for weeks 7–12, 1 session per week for the next 3 months and 1 session every 2 weeks for the final 6 months.	14.6 ± 1.2 ^a	11.4 ± 1.0 ^a	3.0 ± 0.6 ^a	ND	19
(6 months)				16.1 ± 2.2 ^a	14.5 ± 1.9 ^a	2.2 ± 0.7 ^a	ND	
(1 year)				12.3 ± 2.7 ^a	11.2±2.7 ^a	1.4 ± 0.7 ^a	ND	
(1 year)	MF	26	See elsewhere in this table for description of the separate interventions.	8.6 ± 3.8 ^a	6.3 ± 2.8 ^a	1.8 ± 1.7 ^a	ND	10

Alternate day caloric restriction and endurance/resistance exercise (8 weeks)	MF	12	See elsewhere in this table for description of the separate interventions.	3.3 ± 2.4 ^a (<i>P</i> <0.064, NS)	2.7 ± 2.0 ^a (<i>P</i> <0.036)	0.4 ± 0.5 ^a (<i>P</i> <0.69, NS)	ND	21
Alternate day caloric restriction and endurance exercise (12 weeks)	MF	16	See elsewhere in this table for description of the separate interventions.	6.0 ± 4.0 ^a	5.0 ± 1.0 ^a	0.0 ± 1.0 ^a <i>P</i> =0.527, NS	ND	23
Fasting and endurance exercise (10 days)	M		Ten day nutritional intervention: on days 1 to 3 participants consumed a prescribed diet containing 1800, 1200, and 800 kcal, respectively. Water consumption was ad libitum, with an advised minimum of 2 L per day. On days 4 to 6 participants consumed 189 kcal/d in liquid form and on days 7 to 10 a prescribed diet containing 800, 1200, 1800 and 2200 kcal, each respective day. The exercise sessions included daily 30 min cycling at 75% of maximal heart rate.	3.9 ± 1.9 ^b	3.3 ± 1.3 ^b	0.6 ± 1.5 ^b	0.05 ± 0.1 ^b	29
Caloric restriction and resistance exercise (4 weeks)	M	13	Classic caloric restriction: normal daily feeding schedule with a prescribed 25% caloric deficit. The resistance exercise protocol involved full body sessions performed three times per week during the participants' feeding window. Weights used were based on percentages from the pre-intervention repetition maximum.	1.4 ± 0.1 ^c	1.4 ± 0.4 ^c	No change ^c	ND	30
Time-restricted feeding (TRF) and resistance exercise (4 weeks)	M	13	Time-restricted feeding: all calorie and macronutrient consumption occurring within an 8 h period each day and a prescribed 25% caloric deficit. For the resistance training scheme, see above.	1.2 ± 0.3 ^c	1.5 ± 0.1 ^c	No change ^c	ND	30
(8 weeks)	M	17	TRF participants consumed 100% of their energy needs divided into three meals consumed at 1 pm, 4 pm and 8 pm and fasted for the remaining 16 h per 24 h period. Resistance exercise included a first (bench press, incline dumbbell fly, biceps curl), a second (military press, leg press, leg extension, leg curl) and a third session (wide grip lat pulldown, reverse grip lat pulldown and tricep pressdown). The protocol involved 3 sets of 6–8 repetitions at 85%–90% 1RM, and repetitions were performed to failure.	ND	1.62 ^c (<i>P</i> =0.0005)	-0.64 ^c (NS)	ND	31
	F	10	Participants were required to consume all calories between 12 pm and 8 pm each day, resistance training (RT) consisted of 2 different upper- and lower-body sessions, which were alternated to momentary muscular exhaustion during each set, adjusting the load to ensure compliance with the specified repetition range. Resistance training in the fasted state was avoided. Following each RT session, participants from each group were provided with 25 g whey protein (Elite 100% Whey, Dymatize Enterprises, LLC).	2% ^c (NS)	2% ^c (NS)	No change ^c	ND	32
	M	10	On non-workout days participants were required to consume all calories in any four-hour window between 4 pm and midnight, see for resistance training scheme elsewhere in this table.	1.0 ^c (<i>P</i> =0.38, NS)	0.6 ^c (<i>P</i> =0.32, NS)	0.2 ^c (<i>P</i> =0.49, NS)	ND	26

All values are means ± standard deviation (where indicated). Values of total body mass, fat mass and lean mass are expressed in kg or % (the latter indicated near the data). Negative values are increases. Changes depicted are compared to controls or to intra-person baseline values. ^a Results are obtained from obese individuals, ^b Results obtained include data from obese individuals, ^c Results obtained from non-obese individuals. *P*<0.001 unless otherwise noted. *P* values derive from different statistical analytical approaches and are not directly comparable. ND: not determined; NS: not significant; MF: males and females; M: males; F: females.

Non-obese subjects

A 2-year study on daily caloric restriction in non-obese males and females reported equal, gender-independent decreases in fat mass and lean mass, with no beneficial changes in body composition toward conservation of lean mass²⁰ (Table 1). Similarly, alternate day fasting in non-obese subjects for a shorter period (22 days) resulted in a similar decrease of fat mass and lean mass, indicating no beneficial change in body composition¹⁷ (Table 1). In contrast, alternate day caloric restriction for 12 weeks did not result in loss of fat-free mass²² (Table 1).

From these studies it may be concluded that longer periods of mild energy restriction may favor conservation of lean mass, especially compared to shorter periods of more intense energy restriction, but in general, energy restriction tends to be accompanied by loss of lean mass, both in obese and non-obese subjects.

Resistance versus endurance exercise

In analogy to energy restriction interventions, exercise interventions have been assessed for beneficial body composition changes. Interestingly, the data discussed below reveal differential outcomes between obese and lean subjects.

Obese subjects

Exercise interventions in obese participants produce outcomes that are not always as predicted. Endurance exercise for 12 weeks^{23,24} failed to induce beneficial effects on body composition in obese subjects, albeit that android fat was reduced in one study²⁴ (Table 1). In recent years, there has been an emerging and increasing recognition of the potential benefits of resistance training in the aging population. Indeed, beneficial body composition changes (measured by using a pencil beam densitometer) were obtained by a 12-week resistance exercise protocol²⁸ (Table 1), although similar changes were not reported using a resistance exercise program analogous to the latter for the same period²⁴ (Table 1). It can be concluded that exercise alone, being either endurance or resistance exercise, does not unequivocally lead to efficient beneficial body composition changes in obese subjects.

Non-obese subjects

By contrast to what has been observed in obese participants, in non-obese participants endurance exercise for the same period (12 weeks) favourably altered body composition toward increased fat mass loss over lean mass loss²⁵ (Table 1). Resistance exercise for 8 weeks in non-obese elderly²⁷ as well as young subjects²⁶ did not reveal significant changes in either body mass, fat mass or lean mass.

The results of the above discussed studies show that resistance exercise, as opposed to endurance exercise, may generate better outcomes on body composition in the obese, whereas the contrary is true in the non-obese. This may be due to the fact that metabolic reprogramming by resistance exercise prevalently involves increased glucose metabolism, whereas endurance exercise predominantly increases fat metabolism³⁷. These metabolic changes may have differential outcomes on body composition in obese versus lean subjects, which warrants further studies.

Different combinations of exercise

It is now becoming increasingly clear that combining different forms of exercise may lead to beneficial effects on body composition albeit that not all combinations produce similar results.

Obese subjects

Although resistance exercise does not unequivocally reduce body mass in obese subjects^{24,28}, the combined intervention with endurance exercise has been shown to reduce body and fat mass^{10,24}. Ho et al. also showed that android fat mass was significantly reduced following both endurance exercise and in combination with, but not following resistance exercise alone²⁴ (Table 1). One long-term study (1 year) in elderly obese subjects confirmed the above study, also revealing increased lean mass¹⁰ (Table 1). Given the outcomes of the above studies, combined endurance and resistance exercise may be an effective approach to achieve beneficial body composition changes in obesity (Table 2).

Table 2 Summary box indicating the main results of dietary/exercise interventions in obesity

Intervention	Fat mass	Lean mass	Muscle strength	Optimal period
Caloric restriction	↓	↓	↓	2 years
Endurance exercise	—	—	ND	3 months
Resistance exercise	↓	—	ND	3 months
<i>Endurance / Resistance exercise</i>	↓	—	—	12 weeks – 2 years
High-intensity interval training / Resistance exercise	—	—	—	12 weeks
<i>Caloric restriction / Endurance exercise</i>	↓	—	—	10 days, 3–4 months
<i>Caloric restriction / Resistance exercise</i>	↓	—	—	5 months
Caloric restriction / Endurance (or Resistance) exercise	↓	↓	↓	2–4 months – 1 year

Arrows pointing downward depict decrease, and horizontal lines depict no change. Interventions depicted in italics are concluded to be the most appropriate for application in a therapeutic context in the obese. ND: not determined.

Combining different types of exercise does not always add up to increasing beneficial effects on body composition. A recent study by Ramírez-Vélez et al. compared high-intensity interval training, resistance training and their combination on local fat/lean mass indexes in adults with excess of adiposity using pencil beam densitometry²⁸. They found that lean mass was not reduced by either one of the interventions. Interestingly, high-intensity interval training and resistance training individually had a relatively higher impact on reductions of total body mass and fat mass than the combined intervention. Android/gynoid fat mass ratios were not significantly altered by the individual or combined interventions (Table 1).

Non-obese subjects

One study found that the increase of lean body mass in middle aged male participants with a 12-week resistance exercise intervention further increased with combined endurance/resistance training²⁵. Although resistance exercise increased total body mass, the combination reduced this parameter²⁵ (Table 1).

From the above it can be concluded that in obese as well as in non-obese subjects, combining endurance training with resistance training, in the short term as well as longer term, improves body composition.

Combined energy restriction and exercise

The following section discusses how combining energy restriction (fasting, caloric restriction, alternate day caloric restriction or time restricted feeding) with exercise increases body mass loss while at the same time resulting in beneficial effects on body composition, with conserved muscle strength, both in obese and non-obese participants.

Obese subjects

Bhutani et al. studied the effect of a 12-week alternate fasting intervention plus endurance exercise in obese males and females and observed loss of total body mass predominantly due to loss of fat mass in the group that underwent the combined intervention²³ (Table 1). Conserving muscle mass and strength during interventions that counteract obesity during aging is crucial and thus has been explored in several studies. One 4-month study in obese older subjects compared the effect of combined energy restriction and endurance exercise to energy restriction alone. Submission to combined energy restriction and endurance exercise led to similar decreases of whole body mass and fat mass compared to energy restriction alone, whereas lean mass was only decreased in the energy restricted only participants¹⁸ (Table 1). Regarding muscle volume, the combination

of exercise with energy restriction tended to rescue the energy restriction-induced decrease in thigh muscle cross-sectional area; however significance was not reached. Only the participants subjected to energy restriction alone had reduced type I and type II muscle fiber areas¹⁸. From these data it can be concluded that the combination of endurance exercise and energy restriction results in a beneficial shift in loss of body mass toward loss of fat mass, while sparing lean mass and can be envisaged as an optimal way of reaching beneficial effects on body composition in obese individuals (Table 2). Similarly, a 5-month resistance exercise intervention induced thigh muscle mass increase has been reported to be abolished but not worsened with respect to baseline values, when combined with caloric restriction in elderly people with obesity¹². The combination of both endurance and resistance exercise with caloric restriction has also been studied. In a follow-up study with 30 clinically severe obese women over a period of 1 year, combined endurance/resistance exercise with energy restriction led to a greater loss of fat mass, but not to a lesser lean mass loss with respect to the energy restriction intervention alone. In the longer term (6 months and 1 year) reduction of lean mass improved¹⁹ (Table 1). Instead, Oh et al. found a predominant loss of fat mass with no significant loss of lean mass after 8 weeks of combined endurance/resistance exercise and alternate day caloric restriction²¹ (Table 1). A 1-year caloric restriction and combined resistance/endurance exercise intervention in elderly obese adults did not result in loss of muscle strength¹⁰ and showed a relatively greater beneficial change in body composition, with a lower reduction of lean mass compared to energy restriction alone (see Table 1 for data and details relative to the separate and combined interventions). It has to be noted that in contrast to what has been reported in the above mentioned study, endurance/resistance exercise in moderately obese elderly for 4 months with concomitant caloric restriction did induce a 12.4% reduction in muscle strength⁸ (Table 1). Interestingly, loss of muscle strength was almost abolished when the same combined exercise intervention was accompanied by a “healthy lifestyle” program (participants followed workshops with topics including cholesterol, smoking, social contact, blood pressure, bone and muscle health, diabetes, cancer screening, depression, immunizations and physical activity for a total of 12 sessions)⁸. Reports on the effects on muscle mass of daily brisk walking versus energy restriction in the obese elderly are not univocal. Some studies favor exercise^{38,39}, whereas others report no difference^{18,35}. In conclusion, studies in the obese have revealed that combining caloric restriction with both endurance and resistance exercise has beneficial effects on body composition (Table 2). Of note though, combined endurance and resistance exercise can reduce muscle strength while caloric restriction is undertaken, which has to be taken into account.

Non-obese subjects

Tinsley et al. studied the effect of an 8 week intervention of time restricted feeding plus resistance training compared to resistance training alone and did not find beneficial effects on body composition, either in males²⁶ or females³² (Table 1). Despite this, the nutritional intervention was found not to compromise improvements in muscular strength produced by resistance training²⁶, although 2.3 kg of lean soft tissue on average tended to be gained with resistance training and 0.2 kg tended to be lost with the combination (Table 1). This indicates that hypertrophic adaptations to resistance training may have been compromised by time restricted feeding. The use of the leucine metabolite β -hydroxy- β -methylbutyrate as a supplement has been shown to improve muscle mass and strength in healthy young and older adults^{40,41}. The effect of the latter compound on muscle strength has also been tested during the fasting periods of a time restricted feeding program in young women in combination with resistance training³² (Table 1). The compound improved body composition as it caused a significant increase in lean mass and decrease in fat mass, but did not improve muscle performance (measured by counter-movement vertical jump performance, with muscular strength and endurance assessment). In apparent contrast to the studies of Tinsley et al.^{26,32}, in a similar study on time restricted feeding combined with resistance exercise, the effects on body composition were beneficial, showing increased fat mass loss over lean mass loss, in absence of supplements³¹ (Table 1). In accordance, a study carried out in the shorter term found similar beneficial effects on body composition. Stratton et al. compared the effect of 4 weeks of time restricted feeding to classic caloric restriction on body composition induced by resistance exercise in non-obese, recreationally active, healthy men and found no differences between the two nutritional interventions; both had the same beneficial effect on reductions of total body mass and total fat mass, whereas lean mass was not reduced³⁰ (Table 1). Although in analogy to the results of Tinsley and co-workers²⁶, muscle strength increased, in apparent contrast endurance was not found to be increased by either intervention³⁰, which the authors attribute to the style of training rather than the nutritional intervention.

Because of possible energy restriction induced limitations on the ability to gain lean tissue during an energy restriction training program, matched protein intake to allow muscular hypertrophy to proceed normally has been suggested. However, no consensus has been reached in the literature on whether protein intake counteracts energy restriction induced loss of lean mass^{9,10,42-51}. Although it has been shown that amino acids and dietary protein stimulate muscle protein synthesis^{52,53}, increased protein intake and functional muscle mass do not always go hand in hand^{9,11,13,43,50}. Supplement addition to diets has been

shown to influence muscle mass such as fish oil derived n-3 fatty acid, improving muscle mass, strength and physical function in weight-stable older adults^{54,55}.

Since short-term interventions with relatively mild exercise bouts are easier to complete, they are likely to result in a relatively lower number of dropouts. A ten-day protocol termed Sportfasting, including mild endurance exercise and a three-day fasting period, is currently applied in the Netherlands in healthy volunteers with a wide range of body mass and BMI values that often well exceed 30 kg/m². Over 10,000 individuals have successfully completed the intervention. The first scientific evaluation of the Sportfasting protocol consisted of a baseline/follow-up study in 107 recreationally active male participants²⁹, which brought to light that all participants substantially lost body mass, predominantly involving fat mass, with a favourable decrease in android/gynoid fat ratios, regardless of baseline body mass (Table 1).

From what is currently known, one may conclude that combined energy restriction and exercise in the non-obese is beneficial. Both time-restricted feeding and classic caloric restriction ameliorate body composition in the non-obese when submitted to resistance exercise. Short-term fasting and mild endurance exercise has also proven to have beneficial effects on body composition, which may be promising in terms of application on a larger scale, both in obese and non-obese subjects.

Body composition and obesity-related co-morbidities

Several basic studies have shown that combining energy restriction with exercise induces beneficial metabolic reprogramming in skeletal muscle⁵⁶. In this light, failure to achieve reductions in body or fat mass does not necessarily imply lack of amelioration of specific features of obesity-related co-morbidities. MRI analysis on resistance-exercised patients with NAFLD for 8 weeks did not reveal reductions in body and fat mass, although resistance exercise resulted in amelioration of the disease²⁷ (Table 1, data on lean mass was not reported). The authors suggested that combined interventions with energy restriction would lead to loss of fat mass in this setting. Interestingly, the restriction exercise intervention decreased the HOMA-IR index (indicating increased insulin sensitivity) in these patients²⁷. More recently, it has been shown that alternate day caloric restriction in combination with resistance as well as endurance exercise in obese participants ameliorates the response to insulin^{21,23,57,58}. Similarly, time restricted feeding combined with resistance exercise has been shown to significantly increase sensitivity to insulin³¹. Since insulin efficiently inhibits protein breakdown in muscle at plasma insulin concentrations of 15–30 mU/mL⁵⁹⁻⁶², combinations of exercise

with energy restriction in type 2 diabetic participants, should therefore favor muscle synthesis, by reducing fat mass and thus increasing the action of insulin in muscle.

Towards unravelling the mechanisms underlying sparing of lean mass and muscle quality, insights from human and animal studies

A wealth of basic studies has shown that combining energy restriction with exercise leads to drastic metabolic as well as structural remodeling in skeletal muscle. Rodents submitted to food withdrawal for 3 days⁶³ or longer-term intermittent food withdrawal for 1 month⁶⁴ combined with endurance exercise show amelioration of whole-body metabolism^{63,64} and increased endurance⁶⁴. The amelioration of whole-body metabolism is associated with increased phosphorylation of muscle AMP-activated protein kinase (AMPK) at Thr172 and with upregulation of peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1 α ⁶³. Fasting/food deprivation and exercise both induce the autophagy process in muscle, which preserves muscle integrity and strength. In obese rats, high-intensity interval training after myocardial ischemia-reperfusion injury induced beneficial body composition changes and led to increased muscle PGC-1 α expression and increased phosphorylation of mTOR at Ser2481 associated with restored muscle atrophy⁶⁵. Muscle endurance and strength is tightly associated with a healthy mitochondrial pool within the myofibers. Endospasmin 2, an autophagy-related factor, has recently been shown to be crucial for mitochondrial quality and muscle endurance in mice (measured by treadmill running at a speed equivalent to 70% of the mouse's previously assessed maximum heart rate. Time to exhaustion and total run distance were determined)⁶⁶. Autophagy-induced proteolysis in muscle increases circulating levels of alanine, an essential amino acid required for gluconeogenesis. Thus, muscle autophagy during fasting prevents hypoglycemia and is under control of AMPK, since muscle-specific ablation of AMPK in mice results in a block of autophagy during food deprivation accompanied by reduced muscle mitochondrial function⁶⁷. In humans, short-term (14–21 days) calorie restriction has been shown not to decrease the basal rate of muscle protein synthesis in overweight and obese middle-aged men^{68–70}. In the longer term though, moderate calorie restriction has been found to increase the rate of muscle protein synthesis^{71,72}. These data suggest that caloric restriction related loss of muscle mass involves increased proteolysis (mediated by autophagy) instead of suppressed synthesis of muscle protein. With regard to strength training, it has recently been shown in mice that high-intensity interval training restores glycolipid metabolism and mitochondrial function in skeletal

muscle of mice with type 2 diabetes⁷³. In humans mitochondrial quality control during exercise recovery has been shown to be an autophagy-linked process associated with increased phosphorylation of both AMPK at Thr172 and the autophagy marker UNC51-like kinase (ULK1) at Ser317⁷⁴. To maintain muscle performance, mechanically damaged cytoskeletal proteins in response to 75%–80% of maximum voluntary force resistance exercise are degraded by chaperone-assisted selective autophagy (CASA)⁷⁵. CASA complexes anchor to the Z-disk of the sarcomere through interaction with the actin-crosslinking protein FLNC (filamin C, γ). This interaction stimulates recognition of unfolding protein domains within the filamin rods by the CASA complex during contraction of the actin network⁷⁵. The autophagy-muscle repair process during combined fasting and exercise interventions has been studied in rodents⁷⁶ and humans^{77–79}. Interestingly, mice exercised on a treadmill (12 m/min for 2 h, 10° inclination) showed a suppressed (24 h) starvation-induced autophagy accompanied by reactivation of the mammalian target of rapamycin (mTOR) signaling including Akt, accompanied by a synergistic increase of AMPK phosphorylation⁷⁶. AMPK activation has also been shown in 66 h food-deprived rats exercised twice daily on a horizontal treadmill for 30 min at 10 m/min⁶³ and in humans after 15 h of fasting and cycling for 1 h at 70% Wmax⁸⁰. Post-exercise reactivation of eukaryotic elongation factor 2 (eEF2), resulting in increased protein translation, upon a 6-week supervised training program (3 \times /wk, 60–120 min) in combination with fasting during training has been suggested to facilitate muscle repair⁷⁹. In contrast to the study in mice of Zheng et al.⁷⁶, one study in humans showed that autophagic signaling through ULK 1 induced by exercise (single 60 min-bout of cycling at 50% VO_{2max} or until fatigued) following a 36 h fasting period remained unaltered⁷⁸. However, in line with the study of Zheng et al.⁷⁶, human participants trained based on maximum oxygen uptake, muscle citrate synthase activity and oxidative phosphorylation protein levels showed repressed ULK 1-induced autophagy after a 36 h fasting period⁸¹. These results may imply that short-term repression of autophagy with combined energy restriction and exercise may thus increase muscle mass, an aspect that needs further evaluation.

Considerations

The main aim of this review was to report the current knowledge in the literature of the effect of various interventions on body composition in obese subjects, with a comparison to those in non-obese subjects. It becomes increasingly clear that outcomes of body composition in the obese can vary from those in the non-obese with various interventions (e.g., resistance exercise), which must be considered, and stresses that results from

interventions in non-obese individuals cannot predict outcomes obtained in obesity. There is a lack of data directly comparing different exercise/dietary interventions that target loss of fat mass and preservation of lean mass/strength in the obese versus the non-obese. Regarding the obese, three interventions stand out that may be considered for application in a therapeutic context: combined endurance/resistance exercise, caloric restriction with endurance exercise and caloric restriction with resistance exercise, all favoring loss of fat mass and sparing of lean mass and muscle strength (Table 2). Research involving both animal models and humans has revealed that combinations of energy restriction and exercise may influence autophagy to increase sparing of muscle⁷⁶⁻⁷⁹, but whether this influences muscle functionality remains to be investigated. In practice, training programs that are tailored for each obese individual should be employed, since individuals respond differently to specific training regimes related to their genetic background³⁷. This should be accompanied by energy restriction guidelines that produce satisfactory outcomes related to body composition, muscle strength and any specific co-morbidities. One recent study explored genetic associations with outcomes of an intervention of short-term combined fasting and exercise in 107 male participants (obese and non-obese) and found a trending association between a single nucleotide polymorphism (snp rs35767) in the gene encoding insulin-like growth factor 1 (IGF-1) and reduced body mass loss following the intervention²⁹. Studies involving increased numbers of participants should be performed to reach significance and similar genetic analyses in different training/nutritional interventions involving larger cohorts of participants could help predict which type of exercise is individually most suitable.

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Competing interests

The authors declare that they have no conflict of interests.

Ethics approval

With regard to the authors' own studies discussed in this work: Human studies: written informed consent for participation and publication of related data was obtained from all volunteers and the study on outcomes was approved by the Medical Ethical Committee from Erasmus MC, Rotterdam, The Netherlands (nWMO-2014).

Animal studies: studies on animals by the authors discussed in this work were carried out in accordance with the current recommendations of the European Commission for the care and use of laboratory animals. The protocols were approved by the Committee on the Ethics of Animal Experiments of the University of Campania "Luigi Vanvitelli" and the Italian Ministry of Health (authorization 704/2016 PR pursuant to article 31 of legislative decree 26/2014).

Author contributions

AG and ES equally contributed to the design of the draft and the literature search, as well as the manuscript writing, RS, FC, AC, AL1 (Assunta Lombardi), MM, and AL2 (Antonia Lanni) contributed to the literature search as well as the manuscript writing, PdL contributed to the design of the draft and the literature search, as well as the manuscript writing and editing.

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