# Hypotheses for fat tissue supercompensation after exercise cessation

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Please cite this article as:
Victor Silveira Coswig *et al.*, Hypotheses for fat tissue supercompensation after exercise cessation. *Hypothesis* 2016, 14(1): e4, doi:10.5779/hypothesis.v14i1.509

Received: 2016/05/11;
Accepted: 2016/08/30;
Posted online: 2016/09/26

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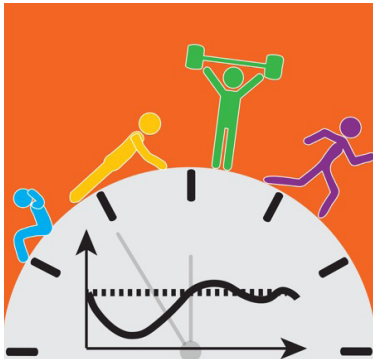

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**ABSTRACT** General Adaptation Syndrome and the supercompensation model are frequently applied theoretical concepts in exercise science. Metabolic changes in response to an exercise stimulus can promote compensatory effects on different systems, including organic tissues and energetic substrates. It has already been established that specific exercise protocols can promote compensatory effects in muscles, bone mass, and encephalic mass. Curiously, fat tissue has shown the same pattern of compensatory effects when the stressor is liposuction, and to the best of the authors' knowledge, yet there is no specific investigation about exercise-based stimulus and compensatory effects on fat. Our hypothesis indicates that since fat is an important tissue and the primary energetic substrate for moderate-intensity continuous exercise, this kind of exercise could promote a compensatory and adverse effect like an obesogenic factor, after recovery and detraining. A wide debate should begin about exercise recommendations and the prescription of exercise programs, especially when weight and fat loss are the main goal. This biological response to exercise should be investigated further to determine whether this compensatory effect influences fat oxidation and deposition.

**INTRODUCTION** General Adaptation Syndrome (GAS), proposed by Selye[1], refers to non-specific systemic physiological reactions in response to different applied organic stressors. Following this definition, three stages (alarm, resistance, and exhaustion) are suggested. The alarm reaction is the response to stimulus that activates a "fight or flight" reaction by the sympathetic nervous system and induces high body resource mobilization. The resistance phase indicates a compensatory parasympathetic response intended to return the nervous system to normal levels. Finally, the exhaustion phase is characterized by a loss of resistance capacity, which keeps the alarm phase chronically active and can lead to health problems if not resolved.

As muscular exercise is considered a potential stressor, Selye's theory has become a basic theoretical concept in sports science, especially for training program periodization, in order to explain positive physiological adaptations or overtraining issues after workload applications. In the 1950s, Yakovlev[2] proposed a supercompensation model, in which the applied load could be associated with the first and second GAS stage. After workload, there appears an acute phase of reduced work capability and a subsequent recovery to baseline values. When the GAS exhaustion stage is not induced and recovery is completed, a compensa-

tory effect is expected with an increased work capability, known as the "supercompensation" phase.

In this sense, compensatory effects were widely demonstrated from different stressors related to exercise protocols and in two distinct situations: specific tissues and energetic substrates. Exercise protocols have shown a compensatory impact in bones[3], skeletal muscles[4] and cardiac muscles[5], and hippocampus size[6]. On the other hand, phosphagen (ATP and PCr) storage[7], intramuscular lipid[8], total lipaemic response[9], muscle glycogen[10] and brain glycogen[11] storages have also shown exercise-induced supercompensation. In addition, the compensatory effects of invasive strategies like liposuction on fat tissue were previously demonstrated in humans[12] and rodents[13]. Considering this, we suggest that adipose tissue, an important energy storage for future needs that played an important role in human evolution[14] and a primary energetic source for moderate intensity (60-65% $VO_2$max, known as $FAT_{max}$ intensity zone) aerobic exercises[15,16], could also be subject to supercompensation during the detraining period after moderate-intensity continuous exercises (MICE). From that, it became important to point out that aerobic energy supply for MICE is derived especially from fat oxidation[17], which could play a role as a stressor agent on fat tissue and, consequently, induce supercompensation after exercise cessation, which could be strongly related to specific tissue insulin sensitivity[18,19]. In other words, MICE would improve insulin sensitivity in adipose tissue and, after exercise cessation, it could remain (including in gene expression level), leading to greater fat storage due to insulin action. However, this type of exercise effort has been widely suggested as the main exercise strategy for weight control and fat loss[20]. In addition to the low efficiency of MICE for fat loss[21], it has been shown that a high percentage of the worldwide population does not adhere to this type of physical activity[22].

Alternatively, high intensity intermittent training (HIIT[23]) and high intensity resistance training (HIRT[24]) could be applied in order to avoid fat supercompensation, since these exercise protocols have a low effect on fat oxidation during exercise and greater anaerobic activation, which could improve fat mobilization during the acute detraining phase and should induce compensatory effects on different pathways[23,24].

Considering that exercise has already been established as one of the most important factors positively impacting health, the exercise-induced adipose tissue compensatory effect should be considered. This topic is relevant since it could change basic theoretical concepts, which could influence exercise guidelines for health and physical fitness, since currently MICE protocols are widely recommended for lipid profile, diabetes and fat loss[20]. Following this hypothesis, detraining and recovery periods should be carefully analyzed in order to avoid compensatory lipogenesis and adipogenesis.

**HYPOTHESIS** The hypotheses presented here are related to the effect of exercise prescription, and subsequent cessation, on adipose tissue and lipid profile. Until now, exercise prescription for aerobic fitness, metabolic and cardiovascular health and weight loss involved mainly MICE protocols[20] to raise fat mobilization, transport, and uptake during effort[16]. On the other hand, this type of exercise appears to be insufficient to promote fat loss[21]. In addition, most studies measured fat metabolism from training responses, while investigations during detraining periods are limited and recent[25-27]. In this sense, three perspectives are suggested as hypotheses: 1) MICE/$FAT_{max}$ exercise protocols are important stressor agents for fat tissue mobilization and can induce compensatory effects, independently of fat loss but dependent on exercise-protocol, which involve obesogenic responses during detraining periods. 2) This compensatory effect is not just an expected weight regain response to exercise cessation, but a reaction that causes changes in metabolic and gene expression to supercompensate fat tissue to higher levels by obesogenic mechanisms. 3) Insulin sensitivity is the main mechanism of the fat compensatory effect after cessation and exercise modes that do not promote this change could be alternative strategies to fat loss with reduced (or no) fat overshoot.

The evidence to support the hypotheses are discussed in three parts. First, by specific data on adipose compensation, second by additional data on energetic substrates and tissue compensation, and finally possible mechanisms to explain the hypotheses are proposed.

**SUPPORTING EVIDENCE FOR ADIPOSE TISSUE COMPENSATION** Fat tissue compensatory effect appears to be well established after liposuction surgeries as a stressor agent in humans, which could be attenuated by physical activity (40 min MICE protocol combined with strength training) in order to avoid this fat regain[12]. On the other hand, it is important to consider that, aside from the weight control promoted by exercise practice,

the lipogenic gene expression did not change after liposuction[12] or physical activity[28], and if gene expression plays any role in body fat control, then this signaling compensatory effect could remain and generate future fat regain with exercise interruption.

Considering humans, it has been shown that long-term physical activity cessation in previously highly endurance-trained subjects induced compensatory fat mass gain (~6.5kg), decreased HDL cholesterol, and increased BMI, leptin and LDL cholesterol even with reduced caloric intake[29]. Similarly, obese children who performed four months of a 40 min MICE protocol and then were subsequently detrained for an additional four months showed increased visceral fat mass and additional cardiac risk factors after the detraining period, with no differences in dietary intake energy for either the training or no training groups[30]. Healthy adults who reduced their daily steps [from 10,501 (8,755-12,247) steps to 1,344 (1,272-1,416) steps] presented with increased risk factors to chronic diseases such as decreased insulin sensitivity, attenuation of postprandial lipid metabolism, decreased fat free mass, and increased intra-abdominal fat mass[31]. Unfortunately, to the author's knowledge, fat tissue compensatory effect was not directly investigated in humans.

In contrast, results about the compensatory effect on animal adipose tissue after exercise cessation is not recent. Dohm *et al.*[32] demonstrated increased fat accumulation and higher lipogenic rate in rats after only 2 weeks of exercise interruption. Similar metabolic changes were found after two weeks of detraining in rats that had exercised with a MICE protocol over six weeks for 50 min/day, 6 days/week at 20m/min, regardless of whether they were in a control group or fed a high fat diet[33]. The authors concluded that two weeks of detraining "results in a rapid state of lipid deposition" that could represent a "pre-obese" state. In addition, it seems that chronic endurance training could cause an adaptive response that reduces lipolysis in both visceral and subcutaneous adipocytes[34], which would reduce the efficiency of the MICE protocol in reducing adipose storage. Recently, advances were made regarding the responses of adipose tissue during the detraining process, and the mechanisms are being explored in animal models. Responses to cessation of daily wheel running were investigated in rats after 5 hours and 173 hours of the wheel locking, and the results showed a rapid increase in adipose tissue after acute reduction in physical activity and an impairment in fat oxidation by decreased energy requirements[35].

Additionally, Sertie *et al.*[25] investigated metabolic changes and adipose cellularity after the cessation of physical activity. In this twelve-month intervention with a MICE protocol, rats were divided into three groups: 1) a control group with no physical activity; 2) a trained group that performed the exercise program for 12 weeks and; 3) a detrained group that exercised for 8 weeks and then detrained for 4 weeks. The detrained group showed increased adiponectin gene expression (related to an increased amount of newly differentiated adipocytes), increased $PPAR_{\gamma}$ gene expression (favorable to adipogenesis), recovered de novo lipogenesis (after reduction during training), higher fatty acid synthase and malic maximal enzymatic activities, higher weight gain during the last four weeks, and greater adipocyte size than the control group. The authors concluded that four weeks of detraining raised obesogenic responses in white adipose tissue.

To explain these processes, Sertie *et al.*[27] compared a control group to a detrained group of rats that exercised for 8 weeks and then detrained for 4 weeks. To measure rates of glucose uptake and oxidation related to lipogenesis, procedures involved isolated adipocytes with and without insulin. The findings indicate higher glucose uptake and oxidation in the detrained groups when adipocytes were stimulated with insulin. The relationship of these findings to fat mass compensation could be related to higher lipogenic capacity that raises glucose oxidation to supply energy for triglyceride synthesis and storage. While exercise improves the ability of adipocytes to uptake and oxidize glucose, it appears to generate advantageous situations for compensating fat tissue at exercise cessation, which could explain obesogenic responses[27].

## SUPPORTING EVIDENCE FOR ENERGETIC SUBSTRATES AND TISSUE COMPENSATION

As compensatory effect on adipose tissue was previously discussed, additional data are presented in order to discuss the impact of exercise protocols on different energetic substrates and tissue compensation.

### ENERGETIC SUBSTRATES COMPENSATION

Primary energetic sources during exercise involve stored muscular phosphagens (ATP and PCr), stored glycogen and oxidation of carbohydrates, and free fat acids (FFA) to ATP resynthesis[17]. These

energetic sources have shown compensatory effects related to exercise demonstrated by several studies[6,7,8,9].

In intense exercise and short-term efforts, depletion of ATP and PCr stores take place quickly, resynthesize in short recovery intervals, and the subsequent diminished levels of these energy sources mean a loss of anaerobic power[36]. Increased levels of PCr were identified after HIIT type exercise[7], a clear evidence of supercompensation. Six adult men performed 30 min at 30-35% $VO_2$peak followed by 60 min of passive recovery after three 30s all-out cycling bouts, interspersed by 4 min of passive recovery. Before the fourth bout, PCr values were higher than rest values. The authors referred to this as the "overshoot" phenomenon that could be explained by an increased production of PCr via mitochondrial creatine kinase during recovery. Similar responses were found in Type II fibers after 166s of intense intermittent electrical simulation with vascular occlusion[37]. Muscle biopsies occurred 20s, 60s, 5 min, and 15 min after stimulus, and at this last time-point, PCr content was significantly higher than resting values. In addition, Parra *et al.*[38] compared 14 sessions in short (7 days a week for 2 weeks) and long (6 weeks, with 2 days of rest between sessions) HIIT designs in ten male subjects. The sessions were comprised of 30s all-out cycling sprints and 12 min rest-periods. After the training period, resting PCr concentrations were higher than pre-training values only for the short-program group, which suggests that PCr adaptations (as well as PFK, HAD, PK, and CK) are more successfully induced with shorter periods than with rest distribution.

On the other hand, six months of endurance or resistance training did not induce compensatory effects on resting ATP and PCr muscle content in elderly adults[39]. This result could be explained, firstly, by the post-training measure that occurred only 10 days after exercise cessation. Secondly, the proposed exercises were not focused on these energetic sources since endurance training appears to have a higher aerobic contribution while resistance training appears to be more glycolytic[26], as expected following the specific adaptation to imposed demand (SAID) principle.

Considering glycogen concentrations, the compensatory effect appears to be better established than phosphagens and the term "glycogen supercompensation" is already frequently used in sports science, both in humans and in animal models[40]. Specifically, in animal models, glycogen supercompensation is discussed in regards to time course and different sites of storage. From a long term point of view, the glycogen compensatory effect was significantly different only in the last week, compared to the baseline, the 4th, and the 8th weeks in rats that swam 60 min/day at 80% and 90% of lactate threshold, six times a week, for 12 weeks[41]. The exercise-induced compensatory effect on glycogen concentration was also found in additional tissues[11] when two conditions were applied for glycogen responses. First, rats ran at 20m/min$^{1}$ for 60 min/day, five days a week for three weeks, and results demonstrated higher glycogen concentrations in the muscle (soleus) and brain (cortex and hippocampus) than in sedentary rats. Second, the effect of exhaustive exercise (20 m/min$^{1}$ until exhaustion) was also tested and results demonstrated that, in addition to muscle (soleus and plantaris) and liver, the compensatory effect occurred in the whole brain, including the cortex, hippocampus, hypothalamus, cerebellum, and brainstem. Another important finding was that for different sites, glycogen presented at a different time course after exhaustive exercise, and happened earlier in the brain (~6 h) followed by skeletal muscle (~24 h) and the liver (~48 h).

In humans, the supercompensation effect on muscle glycogen concentrations were also shown[40,42,43]. Higher muscle glycogen levels were found after five days of a depletion protocol (120-min cycle exercise at 65% $VO_2$peak followed by 1-min sprints at 120% $VO_2$peak to exhaustion), completed by volunteers from the US Navy and Marine Corps Special Operations[40]. Glycogen levels were higher and were maintained longer in the group that executed the depletion protocol. In addition, daily moderate-exercise practice (20 min cycling at 65% $VO_2$peak) did not reduce supercompensation effects after a depletion protocol in fourteen healthy men. Glycogen concentration of the exercised limb was 10 times higher 6 hours post exercise protocol and 30 times higher after 5 days[43]. Additionally, more intensive protocols (7x30s all-out cycling sprints between 12 min rest-periods) also induced glycogen supercompensation after 14 sessions independent of distribution (2 weeks vs. 6 weeks) of resting periods[38].

Even closer to the main hypothesis, the intramuscular lipids paradox in endurance trained subjects is presented[44]. This theoretical concept refers to a greater insulin sensitivity that could be related to elevated intramuscular triglyceride deposition in highly endurance-trained athletes[45]. Instead, research failed to show a direct relationship between these adaptive responses[44,45], higher rates of intramuscular triacylglycerol synthesis

rate and concentration[8], and raised total lipaemic response[9] after endurance type exercise was already established.

In summary, it seems that the primary energy sources present a supercompensatory effect in response to exercise. It is important to point out that these responses are different between substrates, have different time course behavior, and are directly dependent on exercise intensity, duration and mode.

TISSUE COMPENSATION Exercise-induced compensatory effects on organic tissues have been documented in bone mass, skeletal and cardiac muscles, and the hippocampus. Initially, the nervous system appears to be responsive to physical activity levels, since fit elderly humans present with higher volumes in the hippocampal region (verified by magnetic resonance imaging measures), which is accompanied by an improved memory[46]. Based on that result, to investigate the effect of exercise on brain tissue, Erickson *et al.*[6] compared aerobic based exercises (40 min at 60-75% of maximal HR reserve) to stretching control conditions (13–15 on the Borg Rating of Perceived Exertion scale) after 6 months and 12 months. The main findings indicate that aerobic exercise increased hippocampus volume (~2%) of elderly humans, which could be mediated by greater levels of brain-derived neurotrophic factor, and was associated with spatial memory improvements.

Considering human skeletal muscles, hypertrophy responses are already strongly evidenced in response to exercise programs, especially with heavier loading [~80% of one-repetition maximum (1RM)] resistance training but not after MICE $FAT_{max}$ protocols[47]. Aerobic exercise at higher intensities (70-80% HR reserve, 30-45 minutes) could induce skeletal muscle hypertrophic responses[48]. In this context, HIRT (8 weeks of 3 sets of 8 reps with 2 min rest period) improved free-fat mass, regional strength and muscle mass, and was associated with functional improvements in institutionalized frail nonagenarians[4].

Actually, this kind of adaptation appears not to be exclusive to high loads. To investigate training-mediated hypertrophic gains for quadriceps, Mitchell *et al.*[49] compared different resistance training protocols: 30% 1 RM and 80% 1RM, 3 days per week. The main findings indicate that there were no differences between 30% and 80% of 1RM, when three sets were performed until momentary muscular failure.

Additionally, muscular changes are not exclusive to skeletal muscles. Human cardiac muscle showed remodeling responses that may be not only pathological, but also physiological, and occur after systematic training, indicating heart-related physical benefits[5]. Specifically for left ventricular responses, it has been demonstrated that strength and endurance trained athletes present distinct morphological forms[50]. Based on this finding, raised left ventricular wall thickness (concentric heart hypertrophy) is related to strength training, and raised left ventricular chamber dilatation (eccentric heart hypertrophy) is related to endurance training[5].

In addition, data from different meta-analyses can also provide some indication about exercise-related compensatory gains in human bones[51-53]. It is important to highlight that: 1) regular walking has positive effects on bone mineral density (BMD) on the femoral neck of postmenopausal women[51]; 2) resistance exercise and high impact combination protocols appear effective in preserving BMD in postmenopausal women[52]; and 3) high-intensity progressive resistance training increases lumbar spine BMD in premenopausal women[53].

In summary, similar to energetic substrates, the compensatory effect in response to exercise appears to occur in different organic tissues, including encephalic mass, muscles and bones. As previously indicated, these responses are different between tissues and have a supercompensation rate and time course behavior dependent on exercise protocols.

**MECHANISMS TO SUPPORT HYPOTHESIS**

Considering the previously discussed data, there remains the discussion about biological mechanisms that could support our hypothesis *(FIG 1)*. It is already known that MICE induces raised lipoprotein lipase (LPL) activity[33,54], lipolysis rate[55] and insulin sensitivity[27,56], which promote greater fat mobilization and glucose uptake. On the other hand, detraining did not immediately reverse these responses. Actually, after two or three weeks of exercise cessation, LPL activity[33,54] and insulin sensitivity did not decrease to baseline levels[18,19]. In addition, it was shown that resting energy expenditure and non-exercise thermogenesis were reduced during five weeks of detraining[56,57] and are related to reduced lipolysis rate[26,55]. These metabolic changes after exercise cessation create a favorable environment for lipogenesis and adipogenesis[25,33] in order to restore energy stores by compensating fat mass[25,58]. In addition, these mechanisms could be related to the “lipostatic hypothesis” (based on liposuction actions but extrapolated for

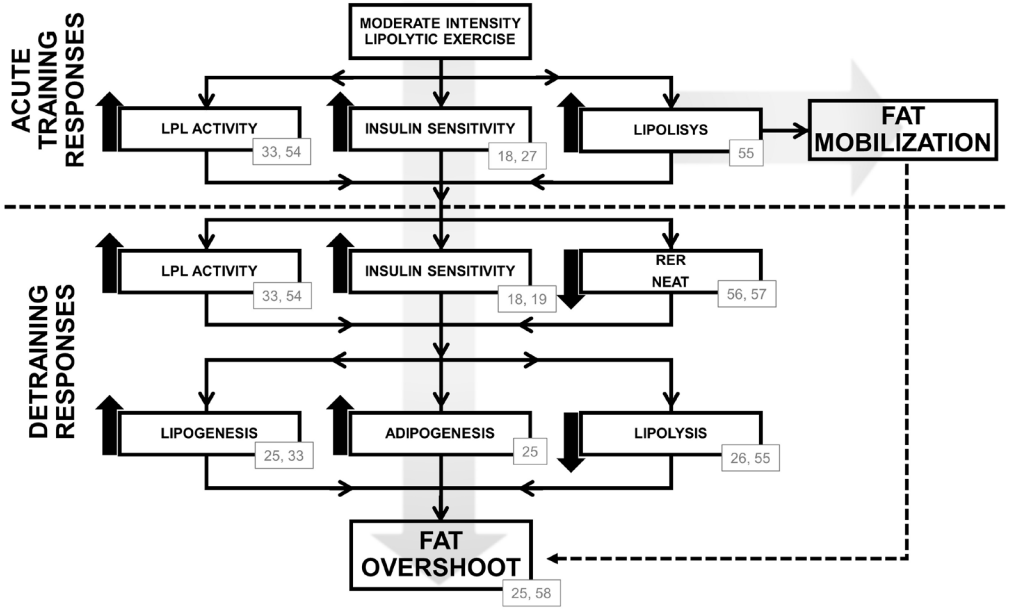


**Figure 1 |** Mechanism to support hypothesis of compensatory effect on fat tissue after acute MICE and detraining. RER: Resting energy expenditure; NEAT: non-exercise activity thermogenesis; Up arrows: Increasing response; Down arrows: Decreasing response; Up and down arrows combined: No change

general fat loss), in which adipose tissue reduction challenges the body fat regulatory system, causing possible changes in some humoral factors and decreasing sensory nerve outflow[59]. These changes could induce sympathetic nervous system outflow from brain to brown adipose tissue, adrenal medulla and remaining white adipose tissue decreasing lipolysis and increasing adipogenesis[59].

In order to reduce fat mass and avoid fat compensatory effect, we presented the hypothesis that high-intensity anaerobic exercises, such as HIIT[23] and HIRT[60], could be alternative strategies *(FIG 2)* to MICE. The main issue to consider in this case would be to avoid acute improvements in insulin sensitivity[61,23], and the expected acute responses in glycogenolysis rate[10], metabolic stress and muscle damage[62]. Detraining after HIIT or HIRT could induce a glycogen overshoot[10]. In addition, after a period of HIIT or HIRT, outcomes such as fat loss induced by augmented lipolysis in response to raised levels of resting energy expenditure[60,64], as well as increased resting thermogenesis, excessive post-exercise oxygen consumption and free fat mass[20,64,60] could be expected. In summary, even with improvements in insulin sensitivity after cessation of high-intensity anaerobic exercise occurs, elevated lipolysis rate during the detraining period would balance any fat gain, inducing no compensatory effect on adipose tissue.

**CONCLUSION** MICE protocols are aerobic in nature, and fat oxidation provides the predominant energy contribution to total energy expenditure due to its moderate-intensity characteristics. Further, the optimal zone for fat oxidation ($FAT_{max}$) appears to be close to 60-65% of $VO_2max$[16]. This type of exercise has been suggested for weight control and fat loss, but adults who add MICE to diet and behavior therapy showed no more than a 3kg loss after 12 and 24 months[21]. In addition to the inefficiency of MICE for fat loss, it appears that the recommended 150 min per week[20] is not enough to affect weight loss and prevent weight gain[24]. As a big part of the population worldwide does not reach this level of physical activity[22],

it appears to be unlikely that recommended levels for weight loss (250-300 min/week[1,20]) would have great adherence.

To avoid this, alternative exercise protocols have been proposed to induce a greater impact on weight and fat loss with different metabolic demands, which could prevent the compensatory effect on fat tissue and redirect it to different pathways. One example is HIIT, a modality that involves short duration efforts (10s to 5 min) at intensities higher than anaerobic threshold interspersed by active or passive pauses[65]. This model of exercise is a promising method with regard to weight loss[66,64] and with proper prescription, could avoid the lipolytic characteristics of MICE[69,68] and the negative effects we hypothesize.

From a practical point of view, if confirmed, fat compensatory effects after MICE should be considered in physical activity and fat loss guidelines. The need for regularity of this form of exercise should be reinforced, since MICE exercise has extremely positive effects on health. On the other hand, patients with dyslipidemia should be aware of raised blood triglyceride levels after cessation of a MICE protocol. In addition, exercise mode and intensity effects on specific-tissue insulin resistance is presented as a relevant issue, related to compensatory effects, to be investigated specially in obese and diabetic patients.

Finally, the authors are not suggesting the avoidance of physical activity (MICE), even if there is a known cessation period, since there are uncountable benefits from the practice. However, compensatory effects should be considered when training plans or exercise suggestions are made. Further randomized controlled trials will be needed to test this hypothesis and nutritional behavior after exercise in different intensities should be considered. Different exercise model (including MICE) time-course responses should also be compared, with a specific focus on exercise cessation and insulin sensitivity as a key point. END

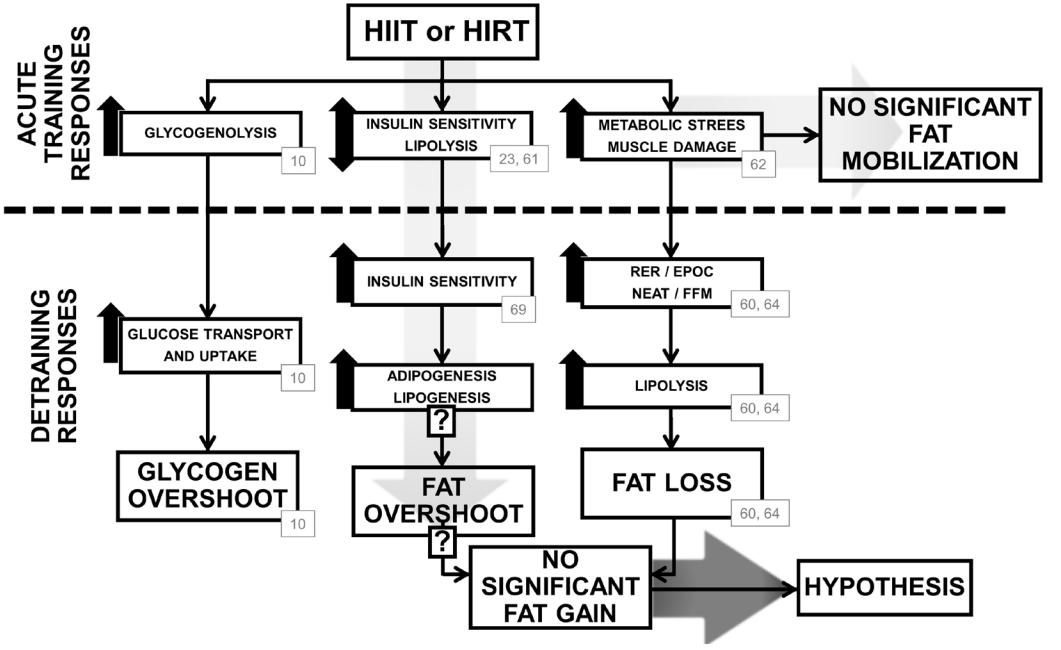


**Figure 2 |** Mechanism to support hypothesis of alternative exercise modes to avoid compensatory effect on adipose tissue. RER: Resting energy expenditure; NEAT: nonexercise activity thermogenesis; EPOC: excessive post-exercise oxygen consumption; FFM: free fat mass; Up arrows: Increasing response; Down arrows: Decreasing response; Up and down arrows combined: No change.

## CONFLICTS OF INTEREST

Authors declare no conflicts of interest.

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