IS ALTITUDE TRAINING AN EFFICIENT TREATMENT FOR OBESITY?

– Written by Olivier Girard, Davide Malatesta and Grégoire P. Millet, Switzerland

Worldwide, about half the adult population is considered overweight as defined by a body mass index (BMI – calculated by body weight divided by height squared) ratio in excess of 25 $kg.m^{-2}$. Of these individuals, half are clinically obese (with a BMI in excess of 30) and these numbers are still increasing, notably in developing countries such as those of the Middle East region[1]. Obesity is a disorder characterised by increased mass of adipose tissue (excessive fat accumulation) that is the result of a systemic imbalance between food intake and energy expenditure[2]. Although factors such as family history, sedentary lifestyle, urbanisation, income and family diet patterns determine obesity prevalence, the main underlying causes are poor knowledge about food choice and lack of physical activity[3]. Current obesity treatments include dietary restriction, pharmacological interventions and ultimately, bariatric surgery. The beneficial effects of physical activity on weight loss through increased energy expenditure and appetite modulation are also firmly established[3]. Another viable option to induce a negative energy balance, is to incorporate hypoxia per se or combine it with exercise in an individual's daily schedule[2]. This article will present recent evidence suggesting that combining hypoxic exposure and exercise training might provide a cost-effective strategy for reducing body weight and improving cardio-metabolic health in obese individuals. The efficacy of this approach is further reinforced by epidemiological studies using large-scale databases, which evidence a negative relationship between altitude of habitation and obesity. In the United States, for instance, obesity prevalence is inversely associated with altitude of residence and urbanisation, after adjusting for temperature, diet, physical activity, smoking and demographic factors[4].

OBESITY: WHAT IS THE NATURE OF THE PROBLEM?

A sedentary lifestyle is an independent risk factor for the development of some metabolic and cardiovascular disorders such as elevated blood pressure, coronary heart disease, dyslipidaemia, impaired glucose tolerance and insulin resistance. The latter seems to be linked to an impaired ability to oxidise lipids, particularly in severe obesity

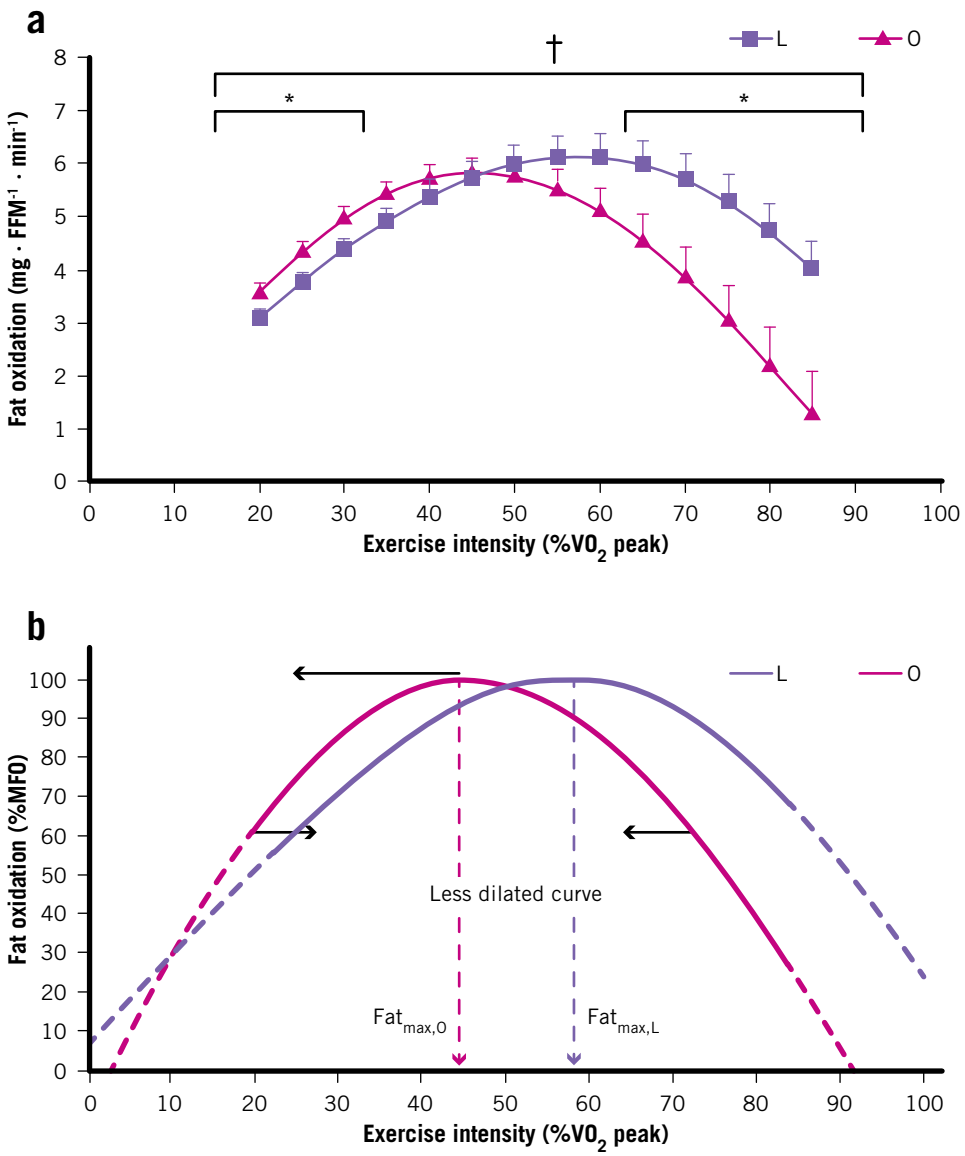

Figure 1: Mean fat oxidation rates in absolute [g/min (a)] and relative [% of MFO (b)] values determined with the sinusoidal model and during a submaximal incremental test in lean (L: purple, n=16) and obese (O: pink, n=16) individuals (adapted from Lanzi et al 2014).

Values are the means ± SE. VO_2 peak: peak oxygen uptake. * $p<0.05$ for differences with lean. A SIN model has been proposed to provide an accurate description of the pattern of fat oxidation kinetics (i.e. fat oxidation rates as function of exercise intensity) and to determine the exercise intensity (Fat_{max}) at which the rate of fat oxidation is maximal (MFO).

The SIN model includes 3 independent variables (dilatation, symmetry and translation) that account for the main expected modulations of the curve and can be adjusted separately to accommodate the fat oxidation rates measured during the graded exercise. These variables therefore precisely characterise and quantify the shape of the different fat oxidation kinetics that could occur. Moreover, dilatation appeared to be a sensitive marker of the ability to oxidise fat because this variable is correlated with Fat_{max} and MFO. Severely obese individuals present a lower Fat_{max}, a left-shifted and less dilated curve and a lower reliance on fat oxidation at high exercise intensities compared to lean individuals (b). FFM=fat-free mass, MFO=maximal fat oxidation, L=lean, O=Obese, SE=standard error, SIN=sine.

(BMI > 40 $kg.m^{-2}$)[5]. In fact, compared to lean men, severely obese individuals present a lower reliance on fat oxidation at high but not at low or moderate exercise intensities, likely reflecting an impaired muscular capacity to oxidise non-esterified fatty acids[6] .

Central to the development of these obesity-related diseases is chronic inflammation of the adipose tissue, which may enhance the oxidative stress in fat tissue[7]. Obstructive sleep apnoea is a breathing disorder that is characterised by repeated episodes of upper airway occlusion during sleep. This phenomenon may lead to oxidative stress through the production of reactive oxygen species, contributing to the development of inflammation[7]. Systemic and local inflammation associated with oxidative stress, adipokine dysregulation and increased sympathetic nervous activation contribute to endothelial dysfunction in obesity. Pro-inflammatory cytokines such as tumour necrosis factor-α or intreleukin-6 possibly released from macrophages, aldosterone, angiotensin II, leptin or other mineralocorticoid receptor agonists released from adipocytes, are all increased in metabolically unhealthy individuals and can decrease nitric oxide production and/or bioavailability. Thus, obesity is also associated with higher carotid intima-media thickness, lower vasodilation and carotid distensibility, which substantially increase the likelihood of developing neurodegenerative diseases such as mild cognitive decline and dementia[8].

Oxygen variation in organic systems may lead to substantial weight loss

TREATMENT FOR OBESITY – THE IMPORTANCE OF PHYSICAL ACTIVITY

Besides pharmacological treatments or dietary and nutritional interventions, incorporating physical activity into individuals' daily schedules is commonly prescribed for preventing and treating obesity. Continuous moderate-intensity training (50 to 70% of maximal heart rate) is most frequently recommended by current guidelines (American College of Sports Medicine; Donnelly et al[3]) for weight management for obese patients, while a dose-response relationship also seems to exist. Besides weight loss, it is firmly established that regular physical activity increases physical fitness, preventing the progression of vascular diseases and reducing cardiovascular morbidity and mortality – improving health substantially. For instance, 8 weeks of low-intensity training normalises carotid distensibility and endothelium-dependent vasodilation in the large conduit arteries of obese men[9]. Interestingly, high-intensity aerobic interval training, which may produce a greater shear stress, seems superior to 'traditional' continuous training for lowering blood pressure or improving endothelial function in metabolically unhealthy individuals[10].

WEIGHT LOSS AND WALKING PATTERN

Compared with lean individuals, the net energy cost of level walking (i.e. energy expenditure per distance unit) is usually higher in obese individuals[11,12]. As such, investigating the effect of decreased body mass on gait pattern, and its consequences on walking efficiency in this population, is undoubtedly clinically relevant. For instance, a 7% reduction in body mass over 3 months in obese women had a positive effect on gait kinematics, as evidenced by increases in walking speed, stride length and frequency, together with decreases in stance and double support times[13]. Messier et al[14] further reported that, in obese individuals with knee osteoarthritis, each pound of weight lost results in a four-fold reduction in the load exerted on the knee per step. More recently, it was demonstrated that otherwise healthy obese adolescents who engaged in a 12-week voluntary body mass reduction programme (-6%), reduced their net energy cost of level walking[15]. This may relate to an increase in muscle efficiency since, with body mass loss, less work in the lower limb muscles would be required to raise the centre of mass.

For weight reduction programmes aiming to induce a negative energy balance, spontaneous walking speed (i.e. the speed normally used during daily living activities) appears to be an appropriate walking intensity[16] and is normally slower in obese individuals than in their normal-weight counterparts[17,18]. At this speed, obese subjects walk with a more erect pattern and a relatively short step length, with reduced hip and knee flexion but increased ankle plantar flexion[17]. In severely obese individuals in particular, this may represent an active strategy to increase dynamic balance[16] and minimise knee loads[17], mechanical work[18] and energy cost during walking[19].

HEALTH BENEFITS OF HYPOXIC EXPOSURE

Systemic hypoxia (i.e. reduction in the ambient oxygen pressure), leading to decreased arterial oxygen pressure, elicits acute vasodilation in conduit arteries (arterial stiffness) and augmented blood flow in skeletal muscle vascular beds, which

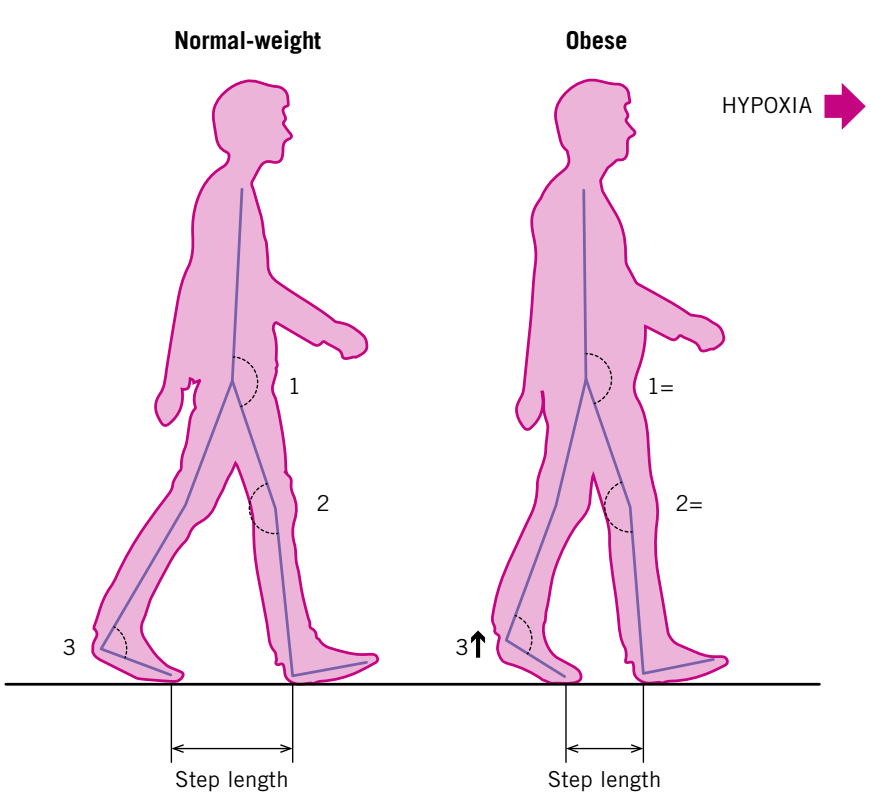

Figure 2: Effects of obesity on walking gait and postulated effects of weight reduction programmes (adapted from Wearing et al 2006).

Compared to normal-weight individuals, walking in the obese is characterised by a more erect posture and a relatively short step length. Despite their greater body mass, absolute joint torques at the hip (1) and knee (2) are relatively similar to those of normal-weight individuals, while those of the ankle joint (3) are approximately twice as large. Obese subjects also walk with reduced hip and knee flexion but increased ankle plantar flexion.

occurs despite an enhanced sympathetic vasoconstrictive activity[20]. Pioneering studies have reported that oxygen variations in organic systems may lead to substantial weight loss (as yet of undefined composition) and improve cardio-metabolic health, leading to the suggestion that sustained hypoxia may benefit weight management programmes for obese patients[2,21]. In addition, a phenomenon called 'altitude anorexia' has been described as a decrease in food intake and hypoxia-induced appetite reduction, as a consequence of the up-regulation of satiety-signalling peptides leptin or cholecystokinin, with a concomitant reduction in the hunger-stimulating hormone ghrelin[2]. Although it is possibile that hypoxia exposure per se may also result in increased energy expenditure, conflicting results exist in the literature[2].

SYNERGIC EFFECTS OF HYPOXIC AND EXERCISE STRESSORS?

Hypoxic exposure can also be combined with exercise training. Hypoxic training in the form of prolonged altitude sojourn first became popular with endurance athletes as part of their preparation for competition nearly 50 years ago. Altitude training protocols have largely evolved during the last 20 years: both 'classical' 'live high/train high' and 'live high/train low' interventions have the potential to improve convective oxygen transport capacity[22]. However, to what extent one method provides superior benefits to induce clinically relevant weight loss in obese individuals, and reach larger cardio-metabolic adaptations, remains to be determined. These two hypoxic training paradigms can be achieved with natural altitude (e.g. hypobaric hypoxia, as in Swiss Alps), and simulated altitude (e.g. normobaric hypoxia, as in Aspetar hypoxic facilities) or a combination of both. It has been passionately debated that the physiological responses to these two forms of altitude exposure could differ, with demonstrated evidence for severe responses (i.e. lower plasma pH levels, exaggerated oxidative stress and impaired nitric oxide bioavailability) associated with the hypobaric stimulus[23].

Chronic exposure to natural altitudes of 1500 to 2500m for several weeks, with individuals residing and enjoying mountainous scenery by the means of walking tours, is often incorporated in combined health practice for treating cardiovascular and respiratory disorders. In patients suffering from metabolic syndrome, Schobersberger et al[24] found reductions in resting systolic blood pressure at 3 days, within 3 weeks of altitude exposure at 1700 m, which persisted for up to 1 week after the sojourn. In another study with obese subjects, diastolic blood pressure was significantly lowered immediately after and 4 weeks following a 1-week stay at 2650m[25]. In the two aforementioned studies, however, the authors could not differentiate between altitude-specific and exercise effects (i.e. walking tours with no strict quantification of the associated load) because of the lack of control groups.

Owing to a potentially larger hypoxemia when physical activity is performed under hypoxic conditions, it is likely that body weight loss and improvement in metabolic health are larger than that by exercise or hypoxia alone. This is because the homeostatic perturbations induced by hypoxia are integrated via signalling pathways into alterations in gene expression and phenotype changes that are remarkably

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similar to changes induced by physical activity. In overweight subjects (BMI > 27 $kg.m^{-2}$) continuous hypoxic training (fraction of inspired oxygen = 15%), consisting of 90 minutes low-intensity endurance exercise three times a week for 8 weeks, leads to larger (+1.14 vs 0.03 kg) weight loss than similar training in normoxia[26]. Using a rather similar training paradigm, larger improvements in respiratory quotient and lactate at the anaerobic threshold, as well as in body composition, occurred in response to hypoxic, compared to normoxic training conducted for 4 weeks[27]. Strikingly, the beneficial results in the above study were obtained despite lower training workload and therefore mechanical strain in hypoxia. The clinical implication in obese patients with orthopaedic comorbidities would be that the mechanical load during aerobic exercise under hypoxic versus normoxic conditions can be significantly reduced to achieve the same metabolic effect. This may decrease the risk of orthopaedic injury and increase adherence to the training programme in overweight and obese individuals. This reduction in mechanical load was confirmed by Haufe et al[28], where healthy subjects training three times a week in hypoxia for 60 minutes over a 4-week period, had a lower workload for the same heart rate but a larger improvement in several metabolic risk factors (e.g. body fat content, triglycerides, fasting insulin) than the normoxic group. In addition, exercise combined with hypoxia can induce a reduction in appetite. In fact, Bailey et al[29] reported that 3-hour exposure to normobaric hypoxia while performing 50 minutes exercise at moderate intensity causes suppressions in appetite explained by decreased circulating plasma acylated ghrelin concentrations.

SUMMARY

Obesity is a major health burden, with almost half of the population being at risk in the Middle East and is accompanied by an increased risk of insulin resistance, diabetes, hypertension, cardiovascular diseases and various cancers. In order to tackle body fat accumulation and its clinical manifestation, innovative therapeutic approaches in combination with current treatments of obesity – i.e. mainly based on dietary restriction, pharmacological interventions and/or physical activity – are needed to improve body composition and substantially modulate obesity-associated metabolic risk factors. In this context, a combination of hypoxic exposure and exercise appears to be a promising approach. Indeed, owing to the augmentation of hypoxemia by exercise with hypoxia, several studies substantiate that body weight reduction and its effects on common cardiovascular and metabolic disorders associated with obesity are larger than that by exercise alone. Finally, Aspetar is fortunate to have world-class facilities both for residing (altitude dormitories including 25 hypoxic rooms) and exercising (e.g. ground walking in an oxygen-deprived tunnel[30]) in normobaric hypoxia. Not only is the combined use of these hypoxic facilities useful to improve athletic performance in team sports[31], but it could also help to promote this innovative strategy for the treatment of obesity, further positioning Aspetar as a centre of excellence for physical activity management through its Healthy Lifestyle Programmes.

References

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Davide Malatesta, Ph.D.
Senior lecturer

Grégoire P Millet, Ph.D.
Professor

Olivier Girard, Ph.D.
Research Scientist
University of Lausanne
Lausanne, Switzerland
Contact: oliv.girard@gmail.com