

## Impact of oxygen availability on body weight management

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### SUMMARY

Obesity is nowadays a major public health problem. The World Health Organization reported that globally 400 million adults are obese, and the situation seems to raise in the future. Furthermore, obesity is a major risk factor for a number of chronic diseases such as type 2 diabetes, cardiovascular diseases and the metabolic syndrome. Interestingly, several studies have reported that appetite suppression and body weight loss are frequently observed at high altitude. This observation has opened some possibilities for losing weight under hypoxia or living in altitude. Nevertheless, the triggering mechanisms for the decrease in energy intake in hypoxic conditions still remain unclear as well as the impact on body mass components. On the other hand, obese subjects often present a chronic inflammatory state on the adipose tissue that might have a strong relationship with onset and development of obesity-related diseases. Thus, it has been consistently reported that adipose tissue of obese subjects is poorly oxygenated and that this hypoxia state is a new potential risk factor for the chronic inflammation in obesity. In this sense, oxygen therapy is a common technique used in current medicine for the treatment of several diseases, while animal studies have demonstrated that treatment with hyperoxia produces some beneficial effects in different diseases related with lack of oxygen in several organs. In this article, we review the role of oxygen availability in body weight homeostasis and hypothesize the possible applicability of hypoxia and hyperoxia for the treatment of obesity and related disorders.

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### Introduction

Obesity is a common metabolic disorder associated with excessive fat accumulation, whose rates have dramatically increased in the recent decades [1]. Thus, in 2005 the World Health Organization established the prevalence of this disease in 400 million adults. Nevertheless, this situation seems unlikely to improve in the immediate future, even though the estimation of this organization is that by 2015 approximately more than 700 million adults will be obese [2]. It is known that over-nutrition and sedentary lifestyles are the main causes of this condition, leading to a positive balance between energy intake and energy expenditure. However, other factors such as genetic background, the dietary macronutrient composition, the distribution of energy expenditure or the individual's substrate oxidation can influence the energy balance equation in the human body [3]. Indeed, obesity is a major risk factor for a number of chronic diseases such as type 2 diabetes, cardiovascular disorders and the metabolic syndrome [4,5].

Several studies in humans have reported that appetite suppression and body weight loss are frequently observed at high altitude due to hypoxic conditions [6–8]. These observations are in agreement with a number of animal studies, where hypoxia exposure generated these features. Such findings have opened the door for

investigating the possibility of losing weight under hypoxia or living in altitude. Nevertheless, the capacity of animals to acclimate to a hypoxic environment make symptoms disappear in a short period of time and limits the use of hypoxia as a possible treatment of obesity.

On the other hand, obese subjects present a chronic inflammation of the adipose tissue [9], which is potentially considered to play an important role in the initiation and development of obesity-related diseases [10,11], and to enhance the oxidative stress of fat tissue [12–14]. Besides, it has been demonstrated that adipose tissue of obese subjects is poorly oxygenated [15,16]. These findings have led to a novel hypothesis suggesting that adipose tissue hypoxia is a triggering factor for the inflammation-related events in obesity [17]. Further studies have given strength to this theory demonstrating that adipose tissue hypoxia may provide cellular mechanism for macrophage infiltration, adiponectin reduction, leptin elevation, adipocyte apoptosis, endoplasmic reticulum stress and mitochondrial dysfunctions [18]. In this context, a recent study by Yin et al. [19] observed that hypoxia induced necrosis and apoptosis in 3T3-L1 adipocytes, suggesting that this cell death may promote lipolysis and release of free fatty acids into blood stream. Furthermore, cell studies have demonstrated that some inflammatory markers, such as TNF- $\alpha$ , which are increased in obese adipose tissue, are also involved in the hypoxic impairment of adipose tissue metabolism by increasing the HIF-1 $\alpha$  protein content [20,21].

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On the other hand, oxygen therapy is a common technique used in current medicine for the treatment of several diseases such as chronic obstructive pulmonary diseases [22], management of ulcers in diabetic patients [23] or cerebral ischemia [24]. Thus, some animal studies have demonstrated that treatment with hyperoxia produces beneficial effects in different diseases related with lack of oxygen within the affected tissue.

To contrast our hypothesis that oxygen may modulate fuel homeostasis and inflammation, we update the data regarding the role of hypoxia and hyperoxia in body weight management and hypothesize the possible applicability of both therapies for the treatment of obesity and related disorders.

## Hypoxia

### *Mechanisms involving hypoxia and body weight homeostasis*

A number of studies have demonstrated the effects of hypoxia in relation to body weight regulation. Concerning human studies, during high altitude sojourns appetite suppression and decreased food intake have been commonly described [6–8], as characteristic symptoms of acute mountain sickness together with nausea, vomiting, headache, lethargy, irritability, and sleep disturbance [25]. Thus, appetite suppression and decreased food intake often produce an imbalance in the energy equation that leads to weight loss and changes in body composition [26]. These outcomes depend on the duration of the exposure and the altitude reached. Evidence suggests that the altitude limit for the maintenance of body weight is approximately 5000 m, where appetite and food intake return to normality once acclimatized, while above 6000 m, anorexia becomes pronounced as the time spent at this altitude increases [26,27]. However, the mechanisms responsible for the decrease in energy intake in hypoxic conditions still remain unclear. Some of the suggested mechanisms involve changes in leptin, glucagon-like peptide 1, protein synthesis, intestinal absorption, and hypoxia-regulated genes, and are described below.

### *Leptin*

It is known that circulating leptin levels increase due to hypoxia and this event has been one of the keys for understanding the appearance of some of the accompanying symptoms. In humans, several studies have measured leptin at high altitude. Thus, Shukla et al. [6] studied the effect of high altitude exposure (4300 m) on circulating levels of leptin in 30 lowlanders and found a significant increase over baseline levels. In another study by Tschop et al. [28], mean serum leptin levels in 20 male mountaineers increased significantly after active ascent to 4559 m and were higher in those subjects with elevated loss of appetite. These authors also measured leptin levels in 18 volunteers at 490 m and at 4559 m after transportation by helicopter, to eliminate the exertion factor. An increase in serum leptin levels was found in individuals with loss of appetite, but not in volunteers without loss of appetite. Snyder et al. [29] demonstrated that exposing 25 healthy humans to 17 h in a normobaric chamber simulating approximately 4100 m, caused a significant elevation in plasma leptin levels corroborating that this release-mechanism occurs even at short periods of time and indistinctly at hypobaric or normobaric hypoxia.

In animal studies, similar results have been achieved in both continuous or intermittent hypoxic environments [30,31]. Interestingly, in a study performed in pregnant ewes that were maintained at high altitude (3820 m) throughout the gestation period (100 days approx.), periaxillary adipose leptin mRNA was significantly up-regulated compared with the control group, as was placental leptin expression. This observation suggests that leptin is a

hypoxia-inducible gene not only at a direct-breathing level, but also at the fetus level [32]. Thus, animal studies in different settings have set up that loss of appetite and weight loss do also appear during hypoxia at normal altitude levels, ruling out other high altitude-related factors such as cold, overexertion, stress and limited food supply.

Additional studies have shown that the ob gene contains hypoxia response element (HRE) sites that can be bound by hypoxia inducible factor 1 (HIF-1) in 5'-untranslated region [33,34]. Furthermore, it is known that adipocyte leptin expression is regulated by body adiposity, food intake, hormones and hypoxia [33,35]. Moreover, cell culture studies revealed that leptin expression is induced by hypoxia in human preadipocytes [36,37].

Nevertheless, a recent study in humans have suggested that leptin may not be the main player for hypoxia-induced anorexia [38]. Thus, an interesting study in leptin-receptor-deficient mice demonstrated a reduction in caloric intake under hypoxic conditions [39], suggesting that leptin does not have a direct role on the appearance of hypoxia-induced anorexia, and that other pathways may be involved.

### *Glucagon-like peptide 1*

Glucagon-like peptide (GLP-1) plays an important role in the mediation of satiety and appetite regulation [40]. This protein inhibits food intake and reduces the feeling of hunger in the postprandial state [41–43]. However, heretofore only Snyder et al. [29] have investigated the effect of normobaric hypoxia on plasma GLP-1 levels in humans. Thus, over 17 h they found no changes in fasting or 20 min postmeal GLP-1 levels and a small increasing trend in absolute GLP-1 levels at 40 min postmeal. However, further experimental investigations are needed to corroborate this study.

### *Protein synthesis*

Another hypothesis that has been put forward to explain this phenomenon involving weight loss with low oxygen availability, is the direct effect of hypoxia on protein synthesis. Thus, a decrease in whole-body insulin sensitivity and muscle-specific glucose utilization was observed under conditions of acute exposure to intermittent hypoxia in lean C57B1/6J mice [44]. This finding suggests that muscle can develop insulin resistance in hypoxic conditions and could explain the loss of muscle mass during high altitude sojourns.

### *Intestinal function*

In hypoxic conditions, malabsorption of food or changes in intestinal permeability have usually been hypothesized as another possible explanation for the metabolic changes associated to hypoxia. Thus, Boyer and Blume [45] reported a fat absorption decrease in climbers at 6300 m. Nevertheless, most of the studies that actually measured energy digestibility at high altitude have reported that this function is well maintained. Thus, Kayser et al. [46] observed a digestion efficiency of  $96.2 \pm 2.0\%$  in subjects during a 1-month stay at 5000 m. In another study, energy digestibility of subjects at normoxia was  $94.2 \pm 1.3\%$  [7]. When the same subjects were placed in a hypobaric chamber simulating altitude of 7000 m, their digestion efficiency was  $94 \pm 2.9\%$ .

A new hypothesis has been proposed since Kleessen et al. [47] reported changes in intestinal microbiota and signs of immunological stress during exposure to very high altitudes.

### *Hypoxia-regulated genes*

HIF-1 is considered to be a key regulator of O<sub>2</sub> homeostasis [48]. It is a heterodimer protein composed of an inducibly-expressed HIF-1 $\alpha$  subunit and a constitutively-expressed, and not regulated directly by O<sub>2</sub>, HIF-1 $\beta$  subunit. In normal oxygen conditions, HIF-1 $\alpha$  is constantly synthesized and degraded via proteosomal

system [49] and this process is inhibited under hypoxic conditions [50]. Consequently, HIF-1 $\alpha$  is stabilized and translocated to the nucleus where it heterodimerizes with the  $\beta$ -subunit forming HIF-1. Finally, this protein dimer recognizes HRE to induce target gene expression [51]. This last mechanism may occur in white adipose tissue of obese, where hypoxic conditions are established [15,16,52], leading to the production of inflammation-related adipokines and probably to an inflammation state within the tissue [17], and therefore to the expansion of adipose tissue. Regarding to this, HIF-1 $\alpha$  protein is usually undetectable in tissues with normal oxygen concentration. However, in inflamed tissues oxygen concentrations are often lower, consequently leading to an increase of HIF-1 $\alpha$  and therefore to the expression of HIF-1 sensitive genes [51].

HIF-1 target genes include those encoding proteins involved in angiogenesis, cell proliferation and survival, apoptosis, vascular tone, and glucose and energy metabolism [53]. The effect of hypoxia on the expression and secretion of a number of candidate genes, particularly those related to the inflammatory response, have been widely investigated in both animal and cultured adipocytes studies. In this sense, the production of IL-6 and adiponectin, two adipokines implicated in the development of insulin resistance, is up-regulated and down-regulated, respectively, in obesity and in response to hypoxia [12,54,55]. Besides, phosphorylation of insulin receptor- $\beta$  and insulin receptor substrate-1 has been shown to be reduced via HIF-1-dependent mechanisms in animal and human adipocytes [56]. These findings strongly suggest that adipose tissue hypoxia may play a central role in the induction of insulin resistance [57].

#### *Effects of hypoxia on body composition*

The exposure to acute hypoxia seems to increase energy expenditure, leading to a negative energy balance and therefore to weight loss. However, currently controversy still exists regarding what type of body mass component, either fat or fat-free, is mainly affected. Other factors such as physical activity duration and altitude reached could be involved.

#### *Fat-free mass*

Several studies have shown that muscle mass depletion is responsible for the weight loss induced by hypoxia. In this context, Boyer and Blume [45] measured body weight loss of an expedition to Everest and found that during residence above 5400 m, there was a significant decrease in arm and leg circumferences, suggesting that muscle catabolism contributes significantly to weight loss at high altitude. In an animal model, an interesting study was carried out by Morel et al. [58], who measured body composition in rats exposed to hypobaric hypoxia, simulating an altitude of 5500 m and demonstrated a dramatic reduction of fat-free mass gain, suggesting that perhaps exposure to hypoxia does not lead directly to a muscle mass loss but to a lower fat-free mass gain. In 1996, Bigard et al. investigated the effect of a high-protein diet in rats chronically exposed to a simulated hypobaric altitude (6000 m). Interestingly, the high-protein diet was not able to minimize the altitude-induced decrease in skeletal muscle growth and also obtained a lower relative muscle weight [59].

In this sense, in a pilot study performed by our group, we investigated the effect of acute intermittent hypoxia (8% oxygen) on diet-induced obese rats. Results showed that this exposure to normobaric hypoxia led to a significant decrease of muscle mass (gastrocnemius muscle) compared with control group, while no changes were observed in fat mass stores. It is important to emphasize that, during hypoxia exposure, rats were still fed a high fat diet, so perhaps this factor led to a lower mobilization of fat stores.

#### *Fat mass*

In hypoxic conditions, several studies have shown that the major part of weight loss is due to loss of fat mass [8]. Indeed, in a study carried out by Westerterp et al. [7], the loss of fat mass in subjects at 6542 m of altitude represented  $74 \pm 15\%$  of the total body mass lost. Reynolds et al. [60] in subjects exposed to 9 weeks at altitudes between 5300 and 8848 m, demonstrated a preferential loss of adipose tissue. Interestingly, this fat mass loss did not only affect climbers but even participants who remained at base camp, suggesting that exertion is not a determinant factor.

#### *Intermittent hypoxia in animal models*

Several animal studies have demonstrated that exposure to intermittent hypoxia also leads to weight loss. In a series of studies, weight loss was observed in the hypoxic group independently of time, hypoxia/normoxia cycles, oxygen levels and normobaric or hyperbaric hypoxia (Table 1). As in humans, the exposure to this environment in animals leads to appetite suppression and decreased food intake. These symptoms occur only at the beginning of the exposure, demonstrating an adaptation process of approximately 3–5 days duration. Nevertheless, since the research target was not focused on weight regulation but to simulate pulmonary diseases such as obstructive sleep apnea, body weight was measured only at baseline and endpoint, and no measurements of muscle or adipose tissue were carried out.

In our pilot study mentioned above, the aim was to eliminate the short-term adaptation of rats to hypoxia by implementing a new intermittent hypoxia model. We observed that, when administering cycles of 4 days hypoxia/3 days normoxia air (8 h/day), rats did not become acclimated to the hypoxia environment during the 4 weeks the experiment lasted. Thus, each new hypoxia exposure triggered appetite suppression and led to a continuous reduction in body weight gain for 3–5 days (Fig. 1). Muscle mass (gastrocnemius muscle), but not apparently fat mass, was significantly decreased at endpoint, perhaps because of the full-time administration of a high fat diet. These results differ from some published studies where either white [61] and brown [62] fat mass were significantly decreased and muscle was not affected after the exposure to hypoxia.

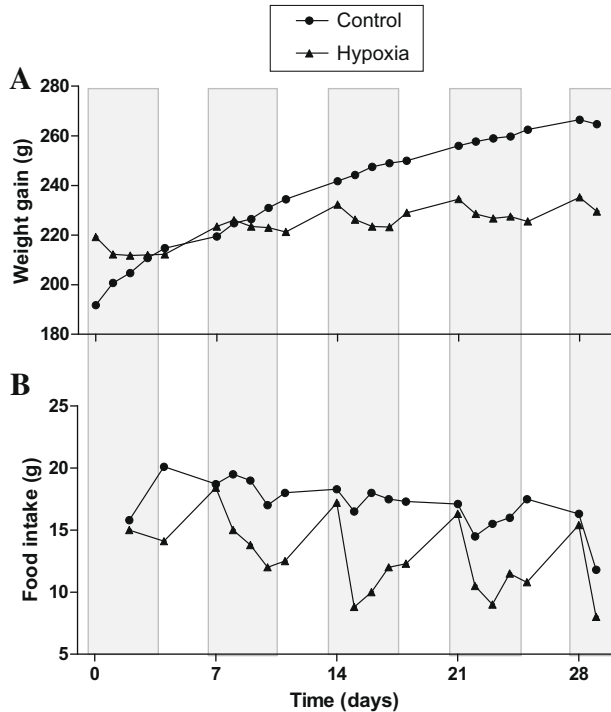
#### *Hypoxia: hypothesis and discussion*

With regard to the studies mentioned above, the mechanisms for the regulation of body weight due to hypoxia exposure remain unclear. It is known that appetite is suppressed in hypoxia and therefore leading to reduction of body weight. Nevertheless, both human and animal studies have produced contradictory results regarding what type of body mass component is mainly affected. Some studies have demonstrated that hypoxia leads to depression in muscle tissue growth. It has been attributed to a decrease in energy intake at first days of hypoxia exposure, and perhaps to specific effects that hypoxia per se might induce on muscle protein metabolism [59]. These results are consistent with those of our own pilot study.

On the other hand, a number of human studies have consistently demonstrated that a reduction of fat mass is the main cause of weight loss due to hypoxia. These rather contradictory results may be due to several experimental factors such as oxygen concentration, time exposure, physical activity, acclimation time, or dietary macronutrients composition. Further studies, taking these variables into account, will be needed to explain the involved mechanisms. In this sense, we postulate that hypoxia exposure may be a possible treatment of obesity and support this is an important issue for future research.

**Table 1**  
Models of intermittent hypoxia inducing a decrease in body weight in rodents.

Author	Animal	Hypoxia-normoxia cycles	Hypoxic intensity	Hypoxia duration
Allahdadi et al. [98]	Sprague–Dawley rats	20 s/20 s	5% O <sub>2</sub>	7 h day <sup>-1</sup> ; 14 days
Chen et al. [99]	Sprague–Dawley rats	30 s/30 s	4–6% O <sub>2</sub>	8 h day <sup>-1</sup> ; 5 days week <sup>-1</sup> for 5 weeks
Dematteis et al. [100]	C57BL/6 J mice	30 s/30 s	4% O <sub>2</sub>	8 h day <sup>-1</sup> for 1, 14 and 35 days
Dunleavy et al. [101]	Wistar rats	30 s/30 s	6–8% O <sub>2</sub>	8 h day <sup>-1</sup> ; 5 days week <sup>-1</sup> for 3 weeks
Joyeux-Faure et al. [102]	Wistar rats	40 s/20 s	5% O <sub>2</sub>	8 h day <sup>-1</sup> ; 35 days
Polotsky et al. [103]	– C57BL/6 J mice – C57BL/6 J-Lep <sup>ob</sup> mice	30 s/30 s	5% O <sub>2</sub>	– 5 days (short term) – 12 weeks (long term)
Zoccal et al. [104]	Wistar rats	5 min/4 min	6% O <sub>2</sub>	8 h day <sup>-1</sup> ; 10 days



**Fig. 1.** Four weeks of cycle hypoxia (8% O<sub>2</sub>) and normoxia exposure. (A) Weight gain in control and hypoxia groups; (B) food intake. Grey columns represent 4 days of hypoxia and white columns 3 days of normoxia for the hypoxia group.

## Hyperoxia

### Applicability of hyperoxia in different clinical indications

#### Hyperoxia in humans

Oxygen is used in current medicine as a treatment for several diseases and wounds. There are two clearly-defined therapies commonly used in clinical trials: (i) hyperbaric oxygen therapy (HBOT) and (ii) normobaric oxygen therapy (NBOT). The first one (HBOT) involves the inhalation of 100% oxygen in a chamber at pressures greater than at sea level. This method is commonly used in the treatment of cardio-respiratory system diseases [63]. In addition, there are several clinical applications for oxygen therapy recognized by the Undersea and Hyperbaric Medicine Society (Table 2) [64]. Several studies in humans have demonstrated the beneficial effects of HBOT. Thus, Bennett et al. [65] investigated the effects of HBOT for treating late radiation tissue injury (LRTI), observing an improved outcome in tissues affected such as the head, neck, anus and rectum. Besides, there was no such evidence of any important negative effect on neurological tissues. In a review by the same authors, they provide evidences that HBOT improved local tumour control, mortality and recurrence for cancers of the

**Table 2**  
Clinical indications for hyperbaric oxygen therapy.

- Air gas embolism
- Carbon monoxide poisoning
- Clostridial myonecrosis
- Crush injury
- Decompression sickness
- Enhancement of healing in problematic wounds
- Exceptional blood loss
- Necrotising soft tissue infection
- Osteomyelitis (refractory)
- Radiation tissue damage (osteoradionecrosis)
- Skin graft and flaps (compromised)
- Thermal burns
- Adjunctive hyperbaric therapy in intracranial abscess

head and neck, and uterine cervix [66]. However, adverse effects including oxygen toxic seizures and severe tissue radiation injury were also reported. A recent study has evaluated the effect of HBOT in 30 patients with myofascial pain syndrome (MPS), which observed an important improvement [67]. In relation to wound healing, multiple studies have demonstrated the beneficial effects of HBO treatment [68] (Table 3). Thus, in diabetic patients, ulcers are treated with daily 100% oxygen exposure at 2–2.5 ATA for 90–120 min daily [68,69].

On the other hand, normobaric oxygen therapy (NBOT), which involves administering more than 21% oxygen at same pressure than sea level, has also been commonly used for the treatment of several pathological disorders. Over the past few years, multiple studies have documented NBO's neuroprotective effects. In this sense, early NBO therapy salvages acutely ischemic brain tissue, reduces pathological brain infarct volumes, improves neurobehavioural scores, attenuates diffusion-weighted brain MRI abnormalities, and extends the reperfusion time window for effective thrombolytic therapy in acute ischemic stroke [70–72]. In a pilot study, a transient improvement in acute ischemic stroke was observed in patients treated with high-flow oxygen [73]. Thus, Tisdall et al. [74] studied the treatment of traumatic brain injury (TBI), associated with depressed aerobic metabolism and mitochondrial dysfunction, with NBOT, who observed an increased aerobic

**Table 3**  
Beneficial effects of hyperbaric oxygenation in wound healing.

1. Decreased local tissue edema
2. Improved cellular energy metabolism
3. Improved local tissue oxygenation
4. Improved leukocyte-killing ability
5. Increased effectiveness of antibiotics
6. Enhanced uptake of platelet-derived growth factor-BB
7. Promotion of collagen deposition
8. Promotion of neoangiogenesis
9. Enhanced epithelial migration



metabolism, suggesting that NBOT has the potential to improve outcome after TBI.

*Hyperoxia in animals*

Additionally, some animal studies have demonstrated that treatment with hyperoxia might produce beneficial effects in different diseases. Positive results were obtained when HBOT was administered in rats with induced hepatic ischemia, which led to a significant decrease in the number of cells undergoing apoptosis [75]. Another investigation showed a protective effect of HBOT in rat brain tissue against ischemia reperfusion injury [76]. In a study by Erzin et al. [77], 100% oxygen HBOT treatment applied for 7 days was significantly effective in reducing the severity of colitis, preventing weight loss and reducing NO activities in rats. An interesting study by Efrati et al. [78] assessed the effect of NBOT (100% oxygen) on hemorrhagic shock-induced renal failure in rats. This trial evidenced a significant decrease in intrarenal hypoxia and less deterioration of renal functions in a 12–48 h treatment.

Nevertheless, an excess of the exposure to hyperoxia in time and/or concentration of oxygen can lead to deleterious effects, some of them affecting body weight regulation. Some studies in mice confirmed that serum leptin levels increased dramatically during acute hyperoxia exposure, together with several pro-inflammatory cytokines and hormones in lung and other tissues, such as TNF- $\alpha$ , IL-6, MCP-1, insulin and corticosterone [79,80]. In this sense, this finding further supports the idea of leptin upregulation in response to acute infections and sepsis, which exerts direct effects on T-lymphocyte proliferation and macrophage phagocytosis [81]. Barazzone-Argiroffo et al. [79] also observed severe weight loss, suggesting that hyperoxia could exert a direct effect on adipose tissue via oxygen toxic metabolites or an indirect effect via other mediators secreted by the lung or other organs. Thus, animal models have demonstrated that the generation of reactive oxygen species is directly related to high oxygen concentration exposure [78,82]. Long term adverse effects have also been observed in neonatal rats, where hyperoxia exposure led to cardiovascular and renal affections in the adult rat [83].

It is important to highlight that hyperoxia studies in animals mentioned above have been carried out at high concentrations of oxygen and/or over long time periods. They thus represent aggressive treatments and therefore lead to the appearance of some side effects. Hence, they are not representative of those respiratory oxygen therapies applied in humans, where oxygen concentration

and/or time exposure are lower [69,84]. In this sense, studies in humans reveal that prolonged high oxygen exposure is reported to induce cough, shortness of breath, decreases in vital capacity and increases in alveolo-capillary permeability [85].

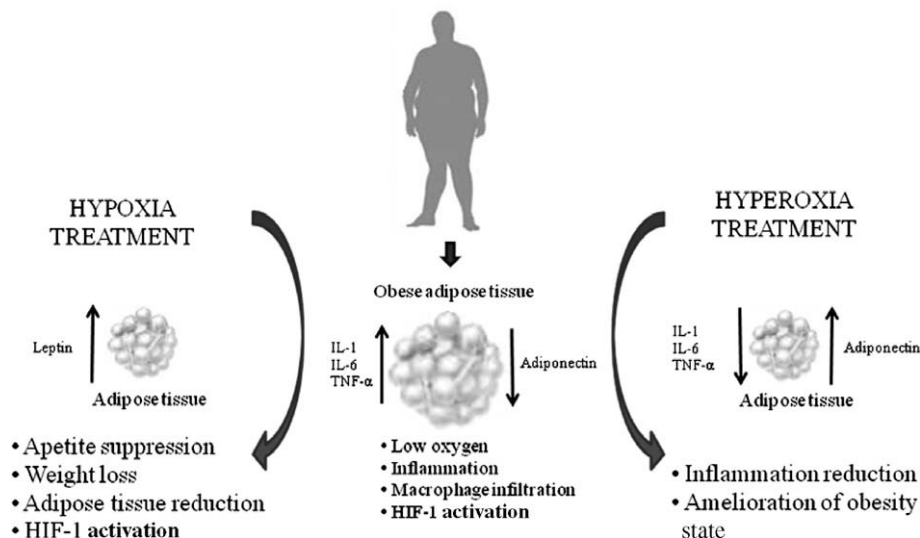
*Hyperoxia-induced genes*

Regarding the effects of NBOT in animal models, several groups have observed significant increases in the expression of some inflammatory genes, such as IL-6, IL-1 and TNF- $\alpha$  [86–90]. Nevertheless, these effects were not evident until the animals had received at least 48 h of hyperoxia, suggesting that inflammation is a function of the duration of oxygen exposure. Hence, Desmarquest et al. observed a decrease in TNF- $\alpha$ , IL-1 $\beta$  and IL-6 expression in alveolar macrophages exposed 48 h to hyperoxia [91]. This effect seems to be consistent with HBOT studies carried out in *ex vivo* cell cultures. In this sense, macrophages were isolated from patients with Crohn's disease treated with 90 min of HBOT after the exposure. They secreted less IL-1, IL-6 and TNF- $\alpha$  than cells obtained prior to the treatment [92]. Lahat et al. [93] also observed a decrease in the secretion of TNF- $\alpha$  in macrophages of rats exposed to HBOT for 90 min. In a study by Benson et al. [94], IL-1 $\beta$  and TNF- $\alpha$  synthesis was inhibited by a 90-min HBOT exposure in macrophages. Nevertheless, a longer exposure led to a wane of the inhibitory effect, concluding that the effect of HBOT depends upon the duration of exposure. These findings are also in agreement with studies demonstrating that HBOT attenuates pro-inflammatory cytokine production in animal models of systemic inflammation. Thus, Yamashita and Yamashita [95] observed that HBOT reduced inflammatory cytokine induction by improving liver ischemia. In another study, TNF- $\alpha$  levels were reduced in rats after the treatment of an inflammatory state with HBOT [96]. Yang et al. [97] also demonstrated the inhibition of TNF- $\alpha$  production in a rat model of intestinal injury treated with HBOT.

On the other hand, in reviewing the literature, no data were found regarding the effect of hyperoxia on adipocytes in both *in vivo* and *ex vivo* cell cultures. In this sense, we think further research regarding the effects of hyperoxia on inflammatory markers of adipocyte cells needs to be developed.

*Hyperoxia: hypothesis and discussion*

In recent years, it has been observed that adipose tissue becomes poorly oxygenated in obese subjects [53]. For instance, an



**Fig. 2.** Hypothetical benefits of hypoxia and hyperoxia treatments in obese adipose tissue. The figure shows those genes whose expression are (in hypoxia) or might be (in hyperoxia) up-regulated (↑) or down-regulated (↓) in human adipocytes.

interesting study carried out by Kabon et al. [16] demonstrated that subcutaneous tissue oxygen tension in obese patients was significantly lower during surgery and postoperative periods. Furthermore, recent studies suggest that adipose tissue hypoxia provides cellular mechanisms for chronic inflammation and macrophage infiltration in white adipose tissue in obesity [12,55], playing an important role in the initiation and development of obesity-related diseases [11,13].

The studies reviewed above suggest that oxygen availability may improve oxygen utilization of body tissues. As hypoxia in obese adipose tissue is linked to an increase in pro-inflammatory cytokine release, amelioration of this hypoxic state through hyperoxic therapies could reduce this pro-inflammatory environment and contribute to lose weight and improve insulin resistance. The applicability of hyperoxia in different clinical conditions and the results obtained in animal models, demonstrating that the exposure to hyperoxia can ameliorate hypoxia state within some tissues, support this hypothesis. Therefore, the exposure to hyperoxia might be a novel method for the treatment of obesity and its associated diseases together with a dietary approach and physical exercise programs. However, further research is necessary to establish the optimum selection and timing of this therapy and the lack of deleterious effects, as well as the implication of cell structures such as mitochondria [105].

## Final conclusion

A comprehensive review of the scientific literature shows that oxygen availability may play an important role in the regulation of body weight and energy homeostasis. In this sense, both increase and decrease respiratory oxygen concentration could be applied as a therapeutic approach for the management of obesity and associated comorbidities. In one hand, hypoxia has been shown to reduce appetite and adipose tissue mass at certain circumstances. On the other hand, hyperoxia could ameliorate the hypoxia state within obese adipose tissue and reduce local inflammation (Fig. 2). Future studies should be performed to validate these hypotheses and provide information about the mechanisms involved.

## Conflict of interest statement

The authors declare not having any personal or financial support or involvement with organizations with financial interest in the subject matter or any actual or potential conflicts of interest.

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