

Review

Exposure and Exercise Training in Hypoxic Conditions as a New Obesity Therapeutic Modality: A Mini Review

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Obesity is an important health problem caused by positive energy balance. Generally, low calorie dietary intake combined with regular exercise is the most common modality to lose bodily fat in obese people. Although this is the first modality of choice for obesity treatment, it needs to be applied to obese patients for at least 12 weeks or more and it does not provide consistent results because it is difficult to suppress increased appetite due to exercise. Recently, many researchers have been applying hypoxic conditions for the treatment of obesity, as many studies show that people residing in high altitudes have a lower percentage of body fat and fewer obesity-related illnesses than people living at sea level. Hypoxic therapy treatment, including hypoxic exposure or hypoxic exercise training, is recommended as a way to treat and prevent obesity by suppression of appetite, increasing basal metabolic rate and fat oxidation, and minimizing side effects. Hypoxic therapy inhibits energy intake and appetite-related hormones, and enhances various cardiovascular and metabolic function parameters. These observations indicate that hypoxic therapy is a new treatment modality for inducing fat reduction and promoting metabolic and cardiovascular health, which may be an important and necessary strategy for the treatment of obesity. As such, hypoxic therapy is now used as a general medical practice for obesity treatment in many developed countries. Therefore, hypoxic therapy could be a new, practical, and useful therapeutic modality for obesity and obesity-related comorbidities.

Key words: Obesity, Hypoxia, Appetite regulation, Body weight

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INTRODUCTION

Obesity is currently an important social and health problem. It is caused by a positive energy balance via greater dietary intake than energy consumption in resting, physical activity, and exercise.^{1,2} According to recent estimates from the World Health Organization, 39% of individuals aged 18 years or older (≥ 1.9 billion adults) were overweight and 13% (600 million adults) were obese in 2014.³ Obesity via excessive fat accumulation is caused by increased dietary energy intake compared to energy consumption

such as basal metabolic rate, diet induced thermogenesis, non-exercise activity thermogenesis, and exercise. This excessive fat increase is claimed to be associated with other factors, such as obesity-induced environmental conditions, oxidative stress, inflammation, and genetic factors.^{4,5} Chronic inflammatory responses, which are common among obese people, induce a variety of obesity-related diseases and increase oxidative stress in adipose tissue. Also, obesity is recognized as one of the major causes of various chronic diseases or disorders such as cardiovascular disease, insulin resistance, hypercholesterolemia, type 2 diabetes mellitus, nonalcoholic fatty liv-

er, and metabolic syndromes.⁶

The combination of low calorie dietary intake and exercise is the most common modality for losing body fat in obese people. This combined intervention is the first step used in obesity treatment; however, this method should be tested for at least 24 weeks or more, it does not inhibit increased appetite due to exercise, and the results are inconsistent with a relatively large number of positive and negative results.^{7,8} If no reduction in body weight or body fat mass is observed after more than 12 weeks of combined intervention via low calorie diet and exercise, prescribing a drug treatment (e.g., stimulators of thermogenesis, absorption/digestion blockers, and appetite suppressants) can be considered with some limitations and considerations.⁹⁻¹¹ However, few drugs are available for obesity treatment, and their effect is limited with benefits fading when the drugs are stopped. Since drug treatments inherently have more risks, pharmacologic therapy should be used only in patients in whom the benefit justifies the risk.¹¹ As a last resort, patients with morbid severe obesity associated with comorbidities and/or various surgeries (e.g., gastrectomy, gastric bypass surgery, and gastric banding surgery) may be available as therapeutic methods associated with clinically significant and relatively long-term sustained weight loss.^{7,12} However, pharmacotherapy and surgery for the treatment of obesity are not recommended except for cases of severe morbid obesity because of the various adverse health effects.^{13,14}

Nowadays, many researchers are widely applying hypoxic conditions for the treatment of obesity based on the results of studies that people residing in high altitude have a lower percentage of body fat and obesity-related illness than people living at sea level.^{2,15} Hypoxic therapy is a novel obesity treatment method that is used as a general medical practice in many developed countries.⁷ Hypoxic therapies such as hypoxic exposure or hypoxic exercise training have been recommended as way to treat and prevent obesity by appetite suppression and minimization of side effects.^{1,16} Also, the increased oxygen delivering capacity of the blood is positively correlated with basal metabolic rate, and the enhanced oxygen transporting ability to working muscle by natural high altitude or artificial hypoxic condition contributes to improvement of fat oxidation and the reduction of body fat.¹⁷⁻²⁰ Several previous studies have investigated the therapeutic benefits of exposure or exercise in vari-

ous altitude or hypoxic conditions in obese patients.^{1,7,16,18,21-25} Therefore, this review summarizes recent evidence suggesting that exposure or exercise training under hypoxic conditions might be a valuable and viable obesity therapeutic modality.

HYPOXIC CONDITION AND APPETITE

When lowlanders are exposed to a natural high-altitude environment, sustained reduction in appetite and reduced dietary intake occur. This phenomenon is called “altitude anorexia,” and is considered to be a consequence of acute altitude sickness occurring at the early stage of exposure to a high-altitude environment.²⁶⁻²⁸ However, previous studies suggest that hypoxemia per se provokes appetite changes.^{29,30} While the underlying mechanism for the modulation of appetite changes by natural altitude or artificial hypoxic conditions is not clearly understood, the change of appetite regulating hormones induced by hypoxic conditions is attracting attention as a major factor for appetite change and reduced dietary intake.^{21,31,32} Leptin, the most common representative hormone associated with energy expenditure and appetite, is a hormone predominantly made by adipose cells that help to regulate energy balance by inhibiting hunger and is probably associated with reduced appetite and food intake observed at natural altitude or artificial hypoxic conditions.¹⁶ To date, various hormone and adipocytokines seem to affect appetite, dietary intake, and satiety (Table 1). Changes in several hormones and adipokines associated with appetite such as glucagon-like peptide-1 (GLP-1)^{33,34}, ghrelin^{29,30,35}, leptin^{33,36,37}, pancreatic polypeptide (PP)³⁸, and peptide YY (PYY)^{30,33} were demonstrated to be associated with exposure or exercise in various altitudes or hypoxic conditions.

In this regard, Wasse et al.³⁰ examined the effect of resting and exercising in hypoxia (simulated 4,000 m; FiO₂, 0.127) on energy intake, appetite, and plasma concentrations of acylated ghrelin and PYY. They concluded that acute exposure to normobaric hypoxic conditions induced a decrease in energy intake that may be associated with a reduction in plasma acylated ghrelin levels, and exercise also reduced acylated ghrelin levels but did not seem to interfere with the reduction found in hypoxic conditions. Debevec et al.³⁹ evaluated whether daily moderate intensity exercise with a hypoxic condition (simulated 4,000 m; FiO₂, 0.127) for 10 days changed

Table 1. Appetite-related hormones and adipocytokines that are estimated to be affected by hypoxic conditions

Hormone or adipocytokine	Function
GLP-1 (↑)	GLP-1 is thought promote satiety through several mechanisms, including slowing gastric emptying and enhancing insulin biosynthesis and secretion. Also, it decreases blood sugar levels in a glucose-dependent manner by enhancing the secretion of insulin.
Ghrelin (↓)	The hunger hormone ghrelin is a peptide hormone produced by ghrelinergic cells in the gastrointestinal tract that functions as a neuropeptide in the central nervous system and plays an important role in regulating the distribution and rate of use of energy.
Leptin (↑)	The hormone of energy expenditure leptin is a hormone predominantly made by adipose cells that helps to regulate energy balance by inhibiting hunger. Leptin is opposed by the actions of the hormone ghrelin and both hormones act on receptors in the arcuate nucleus of the hypothalamus to regulate appetite to achieve energy homeostasis.
PP (↑)	PP is a polypeptide secreted by PP cells in the endocrine pancreas predominantly in the head of the pancreas and it functions to self-regulate pancreatic secretion activities (endocrine and exocrine); it also has effects on hepatic glycogen levels and gastrointestinal secretions. PP has been shown to be reduced in conditions associated with increased food intake and elevated in anorexia nervosa.
PYY (↑)	PYY inhibits gastric motility and increases water and electrolyte absorption in the colon. It may also suppress pancreatic secretion and has been shown to reduce appetite. PYY works by slowing gastric emptying; hence, it increases efficiency of digestion and nutrient absorption after a meal.

↑, increased secretion response by hypoxic condition; ↓, decreased secretion response by hypoxic condition; GLP-1, glucagon-like peptide-1; PP, pancreatic polypeptide; PYY, peptide YY.

appetite-related hormone levels and enhanced metabolic health. Consequently, exercise training with exposure to hypoxic conditions significantly changed appetite, appetite-related hormones, and augmented metabolic outcomes. However, they reported that gut permeability and glucose uptake were unchanged via exposure to hypoxic conditions regardless of exercise. Bailey et al.²⁹ examined the influence of continuous and interval exercise while exposed to a hypoxic condition (simulated 2,980 m; FiO₂, 0.145) for a short time (2.6 hours) on plasma concentrations of GLP-1, PYY, acylated ghrelin, and appetite in healthy normal weight men and they demonstrated that exposure to the hypoxic condition for a relatively short time can induce a decrease in plasma acylated ghrelin concentration and appetite. In addition, the response to appetite by exercise did not appear regardless of exercise modality. Mekjavic et al.³³ assessed the effect of normobaric hypoxia (simulated 2,800 to 3,400 m) on metabolism, gut hormones, and body composition in aerobic trained men and they reported that the hypoxic condition

was likely correlated with increased noradrenaline fasting, fasting leptin, and reduced energy intake, especially hypoxic exposure without exercise training resulting in a reduced energy intake and a negative energy balance. Debevec et al.³¹ evaluated the effect of independent hypoxic exposure and combined hypoxic exposure and bed rest induced inactivity for 16 days on appetite modulation-related parameters in healthy males, and they reported that exposure to simulated $\geq 4,000$ m normobaric hypoxic condition and/or inactivity by bed rest did not induce remarkable changes on the subject report on appetite or ad libitum intake. Matu et al.⁴⁰ investigated dietary energy intake, appetite, gut hormone, and substrate oxidation responses to breakfast ingestion and exercise at simulated moderate (simulated 2,150 m, 15.8% O₂) and severe (simulated 4,300 m, 11.7% O₂), altitudes compared with sea level. As a result, they reported that exercise during acute exposure to a simulated severe altitude inhibited appetite, acylated ghrelin concentration, and energy intake in comparison with sea level; however, exercise during exposure to simulated moderate altitude did not influence these variables compared with sea level. Most previous studies associated with changes of appetite and appetite-related hormone for exposure or exercise to hypoxic conditions were performed on healthy normal weight males.

In a study of obese subjects, Lippl et al.¹⁶ examined the effect of hypobaric hypoxic conditions on body weight at high altitude (at low altitude, day 1; at the end of a 1-week stay at 2,650-m-high altitude, day 7 and day 14; 4 weeks after returning to low altitude, day 42) and they reported that significant decrease of weight, calories per day, and significant increase of basal metabolic rate and leptin concentration was found on day 14 compared to day 1. Based on these results, they concluded that obese subjects lose weight at high altitude with reduced dietary energy intake and a higher metabolic rate and plasma leptin levels rise in natural high-altitude environment despite reduced body weight.

In summary, although the mechanism of appetite suppression via hypoxic condition has not yet been elucidated, exposure and exercise training in the hypoxic condition seems to induce reduced appetite and energy intake via a decrease in ghrelin and increase in leptin, PYY, PP, and norepinephrine. However, these comprehensive summaries suggest that various results are obtained depending on specific exposure conditions within that hypoxic environment



Figure 1. Practical application of hypoxic therapy for obese patients.

(e.g., the degree of hypoxic stimulation and exposure time, frequency, duration) or exercise training condition (e.g., exercise type, intensity, time, duration) to the hypoxic environment and difference according to characteristics. In addition, research on appetite suppression by hypoxic conditions in obese subjects is very limited and the physiological mechanisms are poorly understood overall. Therefore, there is a need for well-designed studies on appetite, energy intake, and appetite-related hormones by exposure and exercise training in hypoxic conditions.

HYPOXIC THERAPY FOR OBESITY AND ITS APPLICATIONS

Again, one of the new alternatives to address obesity is hypoxic therapy, which was recently used as a general medical modality and is well positioned in the field of alternative medicine.⁷ It is recommended that hypoxic therapy, such as hypoxic exposure or hypoxic exercise training, is a way to treat and prevent obesity (Fig. 1). Currently, we have identified that the inhibition of several appetite-related hormones by hypoxic conditions decreases appetite and dietary energy intake, causing the loss of body weight and percentage body fat. Furthermore, the use of hypoxic conditions can increase energy expenditure and basal metabolic rate by oxygen variation in organic systems.^{20,21,32} These findings suggest that hypoxic conditions can be used as a new modality to play a pivotal role in the treatment of obesity. In this section of the review, we focus on the therapeutic effects of hypoxic conditions and their potential applications.

Therapeutic effects of hypoxic condition exposure on obesity

The decrease in body weight and/or percentage body fat is thought to be caused by various factors; however, acute mountain sickness (AMS) is one representative cause of high altitude or hypoxic condition induced body weight loss via reduced appetite and its related reduced dietary energy intake.¹⁶ Obesity has been reported as one of the factors causing AMS and obese subjects are more susceptible to AMS and their frequent comorbidity, the prevalence of AMS in obese subjects, is reported to be three times higher than that in people with normal body mass index (BMI).²¹ Also, obese people have a higher frequency of pulmonary hypertension than normal body weight subjects.⁴¹ Hence, the hypoxic condition appears to be a double-edged sword with both positive and negative aspects. Hypoxic therapy applied using appropriate methods is considered to be a potential therapeutic modality in the treatment of metabolic and cardiovascular diseases caused by obesity. Urdampilleta et al.⁷ and Verges et al.⁴² summarized the compensatory mechanisms and responses to hypoxic conditions as shown in Table 2.

In general, hypoxic exposure, one of the modalities of hypoxic therapy, is a passive exposure to the hypoxic condition lasting from a few minutes to hours that is repeated daily over several days.^{7,21} Hypoxic exposure modality is mainly used by various intermittent hypoxic exposure (IHE) methods, which are interspersed with exposure to normoxic conditions or moderate hypoxic condition levels. Intermittent exposure to hypoxic conditions for 1 week is practically beneficial in weight loss.^{16,43} The exposure to actual high alti-

Table 2. Mechanism of compensation for exposure to hypoxic conditions by Urdampilleta et al.⁷ and Verges et al.⁴²

Physiological response	Compensatory mechanism
Body weight-related response	Decreased resting leptin levels Increased adrenergic system Resting noradrenaline remains high posttreatment Increased blood serotonin levels Appetite is suppressed.
Cellular and metabolic response	Increased HIF-1 and VEGF expression Angiogenesis Increased glycolytic enzymes and number of mitochondria Improved insulin sensitivity Increases GLUT-4
Cardiovascular response	Increases resting and maximal heart rate Increases peripheral vasodilation Increases diameter of arterioles Increases Hg-O ₂ affinity Normalizes blood pressure Cardiovascular protection
Respiratory response	Hyperventilation Increases lung diffusion capacity for CO and O ₂ Increases the CO ₂ reserve in sleeping Decrease in SaO ₂ was smaller. Ventilation response during exercise increased. Improves respiratory function

HIF-1, hypoxic inducible factor-1; VEGF, vascular endothelial growth factor; GLUT-4, glucose transporter-4; Hg, hemoglobin; O₂, oxygen; CO, carbon monoxide; CO₂, carbon dioxide production; SaO₂, arterial O₂ saturation.

tude and artificial hypoxic condition probably influences the loss of body weight via several appetite-related gut hormones and adipocytokines, energy substrate utilizing change, higher energy metabolic rate, reduced perception of hunger feeling together with reduced dietary food intake and various endocrine factors.¹⁶ Also, exposure to hypoxic conditions has been reported to be associated with greater weight loss in subjects with a higher BMI.⁴³ Hypoxic inducible factor-1 expression changes by hypoxic condition changes helps to regulate mitochondrial function.⁴⁴ Therefore, it is considered that the hypoxic exposure modality is a useful therapeutic method for obese subjects.

Until now, few studies have investigated the therapeutic effects of hypoxic condition exposure on obese subjects. In diet-induced obese mice models, Ling et al.⁴⁵ reported that hypoxic exposure of the IHE method was shown that it compared with normoxic conditions in that IHE reduces body weight by enhancing liver leptin expression and increasing plasma leptin level, and the IHE method

also increases plasma erythropoietin and insulin level and decreases plasma cholesterol and glucose level and thereby may effectively prevent obesity induced fatty liver disease. For healthy males, Brooks et al.⁴⁶ reported that adaptation to the 4,000-m-high altitude by the IHE method was found to decrease blood glucose, induce higher glucose turnover, and result in enhanced insulin sensitivity at rest and during exercise. Mackenzie et al.⁴⁷ concluded that acute exposure to hypoxic conditions can be attributed to enhanced short-term glycemic control via hypoxia-induced glucose tolerance improvement after 4 hours of hypoxic exposure that may be due to improved peripheral insulin sensitivity in patients with type 2 diabetes mellitus. Kelly et al.⁴⁸ investigated the influence of acute hypoxia induced by natural high altitude on hormone and metabolism response to ingested glucose in young and healthy subjects and they concluded that acute exposure to high-altitude environments seems to increase glucose utilization as an energy source and results in a rapid metabolic response with associated hormonal changes. In a study of obese people, Lippl et al.¹⁶ reported a decrease in body weight and diastolic blood pressure and an increase in basal metabolic rate and leptin levels after 4 weeks of exposure to 2,650 m for 1 week in obese subjects, but there was no control group in this study. They concluded that the physiological mechanism for this is still unclear, but hypobaric hypoxic condition appears to play an important role.

In summary, there are very few studies focusing on the therapeutic effects of exposure to hypoxic conditions on obese subjects. The hypoxic exposure modality seems to be effective for obese subjects with reduced body weight via increased basal metabolic rate, insulin sensitivity, and leptin levels.

Therapeutic effects of exercise training in hypoxic condition on obesity

Combining hypoxia and exercise such as trekking at altitude or intermittent hypoxic training (IHT) using artificial equipment might be of therapeutic use for obese subjects. The IHT method, the living low and training high approach, commonly involves shorter hypoxic exposures such as approximately two to five sessions of < 3 hours per week over a 4 to 12 week time period.^{1,8,18} Especially, the IHT method is one of the most effective nonpharmacologic therapies that activates the natural immune action of the

body itself by repeatedly performing exercise training in an intermittent hypoxic environment and it is the most used hypoxic therapy for obesity treatment and health promotion.⁴⁹ Although the hypoxic environment provides the subject with lower exercise load and hence lower mechanical stimuli, exercise training in hypoxic conditions may lead to change in body composition by decreased percentage of body fat and enhanced metabolic and cardiovascular function compared with normoxic training. Therefore, hypoxic training can be helpful in weight management programs for obesity subjects.^{21,23,25,50} Hypoxic training such as IHT is known to induce body weight loss via reduction of dietary energy intake as a consequence of a decrease in ghrelin and an increase of leptin or cholecystokinin, two satiety signaling hormones.^{21,50-52} The effects of hypoxic training can lead to inconsistent results depending on hypoxic exposure state with exercise condition (type, intensity, duration, and time, etc.). Because hypoxic conditions play an important role in the pathogenesis and principles of obesity and its associated complications, the relevant evidence must be carefully assessed for the therapeutic use of hypoxic conditions for the treatment of obesity.

Previous studies related to the effect of hypoxic training as an obesity therapeutic modality have been reported since the 2000s. Netzer et al.²² examined the influence of low intensity exercise for 90 minutes at 60% of the maximal heart rate, 3 days a week for 8 weeks, in either ambient 15% O₂ or 21% O₂ in two groups of 10 subjects with a BMI > 27 kg/m². They concluded that 8 weeks of moderate exercise three times per weeks for 90 minutes in ambient 15% O₂ hypoxic conditions induced greater body weight loss (-1.14 vs. -0.03 kg) in obese subjects compared with normoxia. Similarly, Haufe et al.²⁵ classified 20 healthy males as one of two groups that performed similar exercise training in ambient 15% O₂ and 21% O₂ environmental conditions and then all subjects performed exercise three times for 60 minutes over a 4-week time period with measured heart rate at 3 mmol/L lactate level at pretraining exercise testing. They reported a greater improvement in percent body fat, triglycerol, fasting insulin level, area under the curve for insulin level and homeostatic model assessment index during an oral glucose tolerance test, despite the absolute exercise load under the hypoxic condition was lower compared to that in normoxic conditions (hypoxia vs. normoxia, 1.4 vs. 1.7 W/kg). Wiesner et al.²³

conducted a single-blind study to examine the hypothesis that exercise training in hypoxic conditions (n = 24; FiO₂, 15%) would have a greater improvement in body weight loss and metabolic risk-related parameters compared to exercise training in normoxic conditions (n = 21; FiO₂, 21%). As a result, they reported that exercise training in hypoxic conditions induces better improvement in the response of health-related fitness, body composition, and metabolic risk-related parameters despite lower absolute exercise load compared to normoxic conditions.

As with the above studies, exercise training in hypoxic conditions can reduce absolute exercise load and mechanical stress can be particularly beneficial for obese patients with orthopedic comorbidities. More recently, Kong et al.²⁴ randomly assigned subjects to either a normobaric hypoxia group (FiO₂, 16.4%–14.5%) or normobaric training group (FiO₂, 21%) and all subjects experienced 16-hour normoxia and 6-hour hypoxia or 22-hour normoxic training weekly. Then, they investigated whether IHT at the normobaric hypoxic condition combined with low-caloric diet had an additive effect on weight loss compared with normoxic training in obese young adults. As a result, IHT with low caloric diet had an additive improvement on body weight loss compared to normoxic training (-6.9 kg or -7.0% vs. -4.3 kg or -4.2%). Park and Lim¹ determined the effectiveness of aerobic exercise under hypoxic conditions for 6 weeks on body composition, blood pressure, arterial stiffness, and blood lipid level in 30- to 60-year-old women. For this, obese women above 30 kg/m² in BMI and percentage body fat volunteered to participate in the study as participants and were divided into three groups including a normoxic training group, 16.5% O₂ hypoxic training group, and 14.5% O₂ hypoxic training group. In the results, they demonstrated that the hypoxic training regime had a positive effect and good possibility for efficiency on body composition, blood pressure, arterial stiffness, and blood lipid level in middle aged obese women compared with normoxic training. Lee and Kim¹⁸, by applying the hypoxic training intervention period longer (total 12 weeks), investigated the effects of aerobic training in hypoxia on fat metabolism during resting and exercising and the body composition of people with obesity (body fat ≥ 25% for men and ≥ 30% women). They concluded that aerobic training in hypoxia reduces body fat and increases high-density lipoprotein cholesterol in obese subjects more greatly than training in normox-

ia under the same exercise conditions.

To summarize, the complex treatment of excessive adiposity could be improved by prescribing low or moderate intensity exercise under moderate hypoxic conditions to obese subjects to reduce fat accumulation and avoid muscle depletion. In the future, various investigations should include whether the stay in moderate hypoxia alone without exercise increases weight loss compared to hypoxic training and if such a regimen would still be safe.

CONCLUSION

Exposure and exercise under hypoxic conditions in conjunction with decreased appetite, improved metabolism, enhanced utilization of fatty acids, and body weight loss are considered an interesting and important therapeutic modality for obesity treatment. Specifically, IHE and IHT, which are regimens that involve intermittent exposure or exercise in hypoxic conditions, have a very important clinical value in promoting general health and prevention. However, hypoxia appears to increase obesity-related health risk factors due to susceptibility to AMS and their frequent comorbidities. Hence, hypoxic conditions appear to be a double-edged sword with both positive and negative aspects. In other words, with optimal doses, hypoxic therapy might become a potential new obesity treatment strategy. Future investigation should verify whether exposure and exercise to hypoxic conditions could be a new therapeutic modality for obesity and obesity-related comorbidities and elucidate the underlying mechanisms and signaling pathways.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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