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Review

Hypoxic training: Clinical benefits on cardiometabolic risk factors

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ABSTRACT

Objectives: The main aim of this review was to evaluate the effectiveness of hypoxic training on the modulation of cardiometabolic risk factors.
Design: Literature review.
Methods: An electronic search encompassing five databases (PUBMED, EMBASE, MEDLINE, CINAHL, and SPORTDiscus) was conducted. A total of 2138 articles were retrieved. After excluding non-relevant articles, duplications and outcomes not related to cardiometabolic risk factors, 25 articles were chosen for review.
Results: Body weight and body composition were reported to be significantly improved when hypoxic training (≥1700 m) was used in conjunction with exercise regimes, at least three times a week, however extreme altitudes (>5000 m) resulted in a loss of fat-free muscle mass. Fasting blood glucose levels generally improved over time (≥21days) at moderate levels of altitude (1500 m–3000 m), although reductions in blood glucose tolerance were observed when subjects were exposed to extreme hypoxia (>4000 m). Resting systolic and diastolic blood pressure levels improved as much as 26 mmHg and 13 mmHg respectively, with hypoxic training (1285 m–2650 m) in medicated, stable hypertensive subjects. Effects of hypoxic training when used in combination with exercise training on cholesterol levels were mixed. While there were improvements in total cholesterol (−4.2% to −30%) and low-density lipoprotein (−2.6% to −14.3%) reported as a result of hypoxic training, available evidence does not substantiate hypoxic training for the improvement of high-density lipoprotein and triglycerides.
Conclusion: In conclusion, hypoxic training may be used as an adjunct treatment to modify some cardiometabolic risk factors. Measurement of hypoxic load may be used to individualize and ascertain appropriate levels of hypoxic training.

1. Introduction

Obesity and metabolic syndrome are pressing worldwide epidemics that are growing at alarming rates, with one in three individuals being at risk of these conditions.[1] It has been suggested that early detection and implementing suitable lifestyle modifications to reduce risk factors such as weight, blood pressure, blood glucose and lipids, may reduce comorbidities and mortality rates.[1,2] Hypoxic training, commonly referred to as altitude training, refers to the use of normobaric or hypobaric hypoxia (reduced oxygen concentration, <20.93%), in an attempt to emulate altitude acclimatization to attain improved athletic performance. Normobaric hypoxic training incorporates the use of masks and chambers, whereas hypobaric hypoxic training involves ascending to elevated environments. Hypoxic training can be conducted in normobaric or hypobaric conditions with the use of masks, chambers or by ascending to elevated environments. Following the 1968 Mexico City Olympics Games (held at an altitude of 2300 m), poor results were observed in endurance events, which led to the popularization of hypoxic training. The effectiveness of hypoxic training to improve performance however, varied among different sports.[3,4] The use of hypoxic training has been suggested to be beneficial in clinical conditions such as coronary artery disease and chronic obstructive pulmonary disease,[5] despite not commonly used. The purpose of this review was to determine the effectiveness of hypoxic training on cardiometabolic risk factors, which included body weight and body composition, blood glucose, blood pressure, and blood lipid levels.

2. Methods

A computerized search of scientific articles was conducted using PUBMED, EMBASE, MEDLINE, CINAHL, and SPORTDiscus databases. Keywords used included hypoxic and altitude used in combination with metabolic conditions, cholesterol and therapy.

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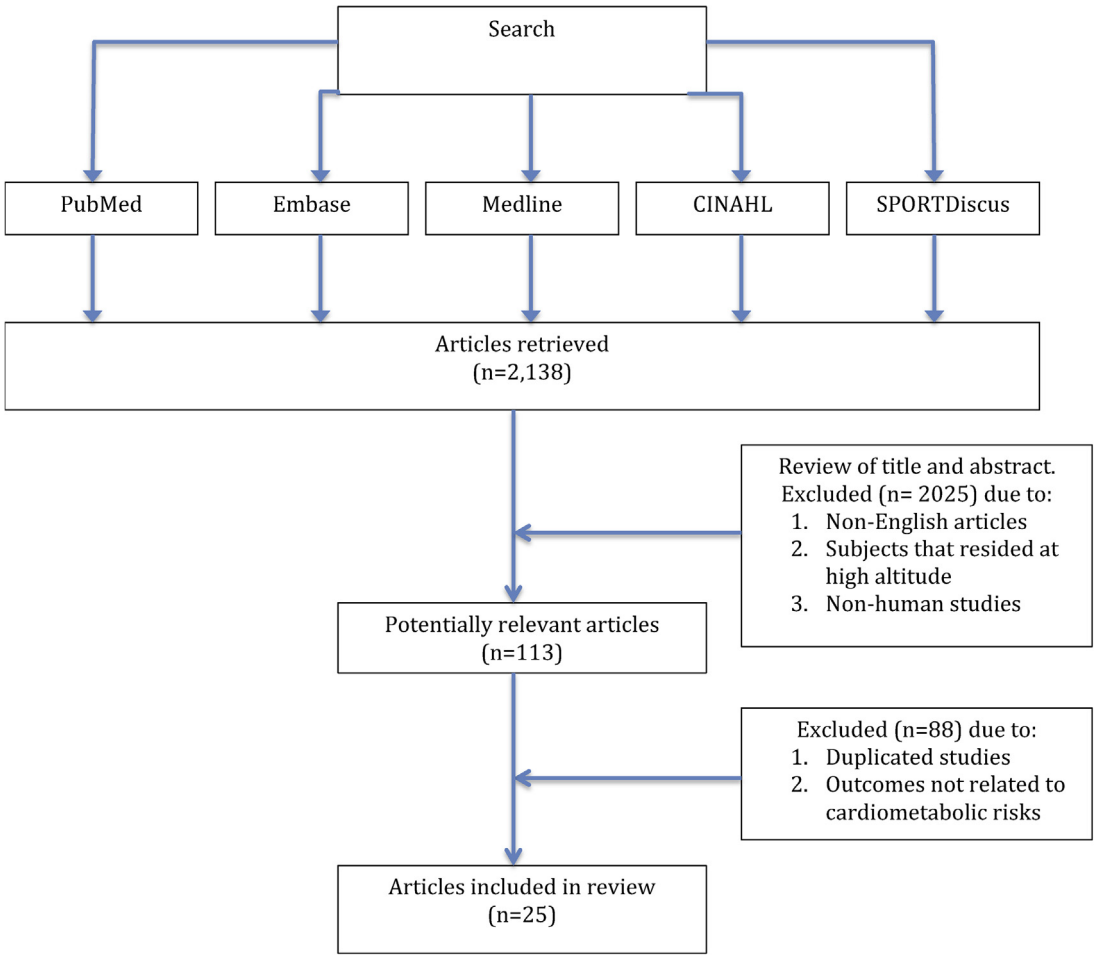

Fig. 1. Selection of studies for review.

Studies were included if they met the following inclusion criteria: (1) randomized controlled trials, case controlled trials or case reports performed on adult humans; (2) use of hypoxic/altitude training ≥1000 m; and (3) measurements used that could relate to therapeutic use. Studies were excluded from this review if they contained the following: (1) non-English articles; (2) subjects that resided at high altitude; and (3) outcomes that were not related to cardiometabolic risk factors. A total of 2138 articles were found, of which, 113 met the inclusion criteria. After applying the exclusion criteria, 25 articles were accepted and included in this review (Fig. 1).

3. Results

The main findings of the reviewed studies are presented in Table 1.

Assessment of body weight and body composition was measured using various tools including scales, bioimpedance analysis systems and skin folds. A moderate altitude of at least 1700 m resulted in significant reduction in body weight in two studies[6,7] of between 1.5% and 3.3%. Of those two studies, one study[6] had control subjects performing the same training protocol at normoxic conditions, and body weight was not found to be significantly reduced compared to the control group. No clinically relevant differences could be detected between the study groups, most likely indicating that any changes noted had to do with the exercise rather than the exposure to moderate altitude. Bailey et al.,[8] also found that body weight was not reduced with supplementing hypoxic training with exercise, however, subjects noted an increase in lean body mass of 1.4 (±1.5 kg), which would account for the lack of reduction of body weight observed. Wiesner et al. also found improvements in fat free mass and body composition in patients with obesity.[9] Although body weight reduction was not seen in healthy subjects[8] at altitude, patients with obesity[7,9] and metabolic conditions (impaired fasting glucose or type 2 diabetes mellitus)[6] saw reductions in body weight without significant loss of fat free mass. Intermittent hypoxic training used in conjunction with moderate exercise three times a week[8] was sufficient to bring about significant increase in lean body mass, however, in order for body weight reductions to occur continuous exposure of at least one week at minimum of 1700 m of altitude[6,7] is required. Exercise intensities used in conjunction with hypoxic training that brought about positive outcomes in body composition and bodyweight ranged from 55 to 85% heart rate max. Extreme altitude (>5000 m) has shown to have an adverse effect on fat free mass due to excessive hypoxic stress, as shown with the study by Wagner.[10] Overall, the use of moderate levels (≥1500 m) of hypoxic training as a supplement to exercise training resulted in improvements in body composition and body weight.

In healthy subjects, acute exposure to high altitude ≥3000 m resulted in a reduction in insulin sensitivity in some studies,[10–14] although glucose metabolism was enhanced, as shown in two studies[9,15] that reported a 36%–60% improvement in glucose uptake. Chronic exposure of ≥21 days, at moderate levels of altitude (1700 m–2740 m)[6,9] demonstrated improvements in fasting glucose levels.[6,9] However, chronic exposure at extreme high altitudes (>5000 m) resulted in a reduction of insulin sensitivity, with

Table 1
Changes in body weight, body composition, blood glucose, blood pressure and cholesterol to hypoxic training.

Author	Sample	Hypoxia		Hypoxia pattern	Effects
Auer et al. (2004)[21]	138+60	Altitude	1285 m	2.5 (±0.4) h	↓SBP & DBP in both groups, hypertensive group ↓ >normotensive group
	Normotensive+hypertensive				HR ↑ in both groups
Bailey et al. (2000)[8]	18+14	FiO_2	16%	20–30 min/day, 3 days/week, 4 weeks	↑ lean body mass in H group, ↓ resting total cholesterol, HDL,LDL, ↓ maximal SBP in H
	H+C				
Bailey et al. (2001)[26]	18+14	FiO_2	16%	20–30 min/day, 3 days/week, 4 weeks	↓ total cholesterol, HDL, LDL in both groups, ↓ triacylglycerols in C, ↑ triacylglycerols in H
	H+C				
Braun et al. (2001)[11]	12	Altitude	4300 m	16 h	↓ insulin sensitivity, ↑ plasma epinephrine
Foster et al. (2005)[25]	9+9	FiO_2	12%	30 min intermittent hypoxia/session	↔ SBP & DBP
	Short duration hypoxia+long duration hypoxia			10 sessions over 10 days	
				Short duration hypoxia-5 min on/5 min off for 1 h	
				Long hypoxia-30 min	
Fukuda-Matsuda et al. (2007)[22]	30	Altitude	1000 m–3400 m	4 h	↑ mean BP, ↑ heart rate
Greie et al. (2006)[6]	36+35	Altitude	1700 m	3 weeks	↓ body weight, body fat, waist-circumference, fasting glucose, total cholesterol, LDL, plasma fibrinogen, SBP, DBP in both groups, ↔ waist to hip ratio, oral glucose tolerance test, HDL in both groups
	H+C				
Haufe et al. (2008)[30]	10+10	FiO_2	15%	60 min/day, 3 days/week, 4 weeks	↓ body fat, triglycerides, fasting insulin, ↑ glucose tolerance
	H+C				
Houssiere et al. (2006)[18]	24	FiO_2	10%	3 min	↔ SBP, DBP & blood lactate
Kelly et al. (2010)[15]	4+4	Altitude	4300 m	15 min	↓ glucose response, ↑ glucose metabolism, ↔ insulin sensitivity
	H+C				
Lecoultre et al. (2010)[12]	7+7	Altitude	3000 m	3 days/week, 4 weeks	↑ blood glucose and insulin, ↓ glucose metabolic clearance, ↑ insulin to glucagon ratio in H
	H+C			2 sessions of interval training. 1 session of continuous training	
Lippl et al. (2010)[7]	20	Altitude	2650 m	1 week	↓ body weight and DBP, ↔SBP,
Louis et al. (2009)[13]	13	FiO_2	5%	25 hypoxic events/h for 5 h	↓ insulin sensitivity, ↔ cortisol levels, ↑ sympathetic activity
	Crossover				
Minvaleev (2011)[27]	16	Altitude	2000 m–3000 m	10 days	↓ total cholesterol, LDL, triglycerides ↑HDL
Mori et al. (1999)[23]	6	Altitude	4000 m–6000 m	40 min/day, 2 days/week, 3 weeks	↑ peak SBP, ↓ blood lactate at peak exercise
Oltmanns et al. (2004)[14]	14 Crossover	SaO_2	75%	30 min	↑ epinephrine, ↓ glucose tolerance
Pialoux et al. (2008)[29]	41	Altitude	3000 m–4800 m	10 min at 3000 m, 3 h at 4800 m	↑ plasma triacyglycerol, cholesterol
Ruiz et al. (2006)[28]	11	Altitude	2340 m	332 min	↑ triglycerides, ↔ total cholesterol, ↓ LCL & HDL
Sandoval et al. (2002)[17]	29	FiO_2	13%	Duration of 4× incremental exercise test	↑ glucose & insulin
	Crossover				
Shave et al. (2004)[19]	4+4 H+C	FiO_2	15%	125 min	↔ SBP & DBP
Siqués et al. (2009[24]	346+50 H+C	Altitude	3550 m	12 months	↑ SBP & DBP
Snyder et al. (2008)[20]	25	FiO_2	12.5%	17 h	↑ BP
Valletta et al. (2011)[16]	1	Altitude	1564 m–4095 m	70 h	↑ blood glucose levels
Wagner (2010)[10]	8	Altitude	Sea-level to 8848 m	40 days	↓ cholesterol, triglycerides, fat-free mass ↑ insulin
Wiesner at al. (2009)[9]	24+21	Altitude	2740 m	60 min/day, 3 days/week, 4 weeks	↔ SBP, DBP, insulin sensitivity, total cholesterol, HDL, LDL, triglycerides ↑ fat-free mass
	H+C				

H: hypoxic group, C: control group, SaO_2: oxygen saturation, BP: blood pressure, SBP: systolic blood pressure, DBP: diastolic blood pressure, HDL: high density lipoprotein, LDL: low density lipoprotein.

100% increase in insulin levels.[10] Investigations that included individuals with metabolic syndrome,[6] hypoxic training at moderate altitude (1700 m) gave rise to significant improvements in fasting glucose levels ($p < 0.05$). However, in a case study, a patient with type 1 diabetes found increased fasting glucose levels of 60% despite maintaining caloric intake.[16] The increase in blood glucose level was reported to be gender specific, with females affected more than males.[11,17] Impaired blood glucose regulation occurred when hypoxic training was performed with high intensive training of incremental durations of maximal aerobic power and ventilatory threshold,[12] whereas with moderate intensity of exercise, glucose tolerance and insulin sensitivity depended on level of altitude where moderate levels produced increased glucose metabolism[6] while higher altitude (>3000 m) resulted in impairment in blood glucose regulations.[10,11,16]

Most studies[18–20] measuring the effects of acute hypoxic training (<1 day) on blood pressure resulted in no change in systolic blood pressure (SBP) and diastolic blood pressure (DBP). However, in one study,[21] both SBP and DBP reduced significantly following hypoxic training, 26 mmHg and 8 mmHg respectively, while increases in SBP and DBP were reported another study.[22] Chronic exposure to hypoxic training for ≥three weeks resulted in mixed findings, with one study reporting reductions in SBP and DBP ($p < 0.05$)[6] two studies[23,24] reporting increase in both SBP and DBP, and no change in one study[9]. Higher levels of altitude ≥4000 m increased both SBP and DBP,[22–24] while at moderate levels of altitude (1700 m–2740 m), blood pressure levels either maintained or improved.[6,7,9,19,21] Although improvements in SBP and DBP were not evident in healthy subjects,[9,18–20,22–25] patients diagnosed with hypertension resulted in 8–13 mmHg[6,7,21] reduction in DBP and up to 26 mmHg[21] reduction in SBP at altitudes of 1285 m–2650 m.[6,7,21] With patients with obesity (BMI ≥ 30 kg/m^2), one week of exposure to altitude of 2650 m resulted in DBP reduction of 13.9%,[7] however, no change in blood pressure were observed with non-hypertensive patients with obesity.[9]

Total cholesterol levels reduced from as little as 0.5%–30% in five out of eight studies,[6,10,26–28] although one study[29] reported a significant increase of 4.5% at 4800 m and 4.3% at 3000 m. Most studies that measured low-density lipoprotein (LDL) levels reported reductions, however, only three studies[6,26,27] reported significant reductions of between 10% and 14.29%. Those studies[6,26,27] also reported reduction in total cholesterol levels (6%–13%). Levels of high-density lipoprotein (HDL) reduced significantly (−6.6% to −12.5%) in one study,[26] increased by 6.35% in another study,[27] and remained the same in two studies.[9,30] Comparing controlled studies, triglyceride levels were reported to increase by 1.3%–10% in two studies[6,26] while another study[30] reported a decrease of 18%. Triglyceride levels rose significantly between 20.8% and up to two folds immediately after hypoxic training while triglycerides levels taken after fasting produce varying results. Two studies reported improvements in fasting triglycerides (−13.4% to −18%)[27,30] while two studies reported no significant changes[6,9] and one study reported increase of 10%.[26] In patients with metabolic syndrome, hypoxic training resulted in reduction in total cholesterol of 8%,[6] while in elite endurance athletes the opposite occurred with cholesterol increasing by up to 4.5%.[29] Overall, while there was some evidence for using hypoxic training to improve total cholesterol and LDL, however, there is currently insufficient evidence to justify the use of hypoxic training to improve HDL and triglyceride levels.

4. Discussion

There are various mechanisms that may explain the improvement of body composition and the reduction of body weight associated with hypoxic training. Firstly, the two studies that found reductions in body weight subjected their subjects to natural moderate altitude i.e. mountainous environments. Other variables such as temperature, humidity level and hypobaric conditions may affect the subject to a larger extent, as compared to mere differences in oxygen concentration. Dehydration, which is associated with these conditions, may result in the loss of body weight. It was reported that during acute exposure to high altitude, fluid loss could be as much as 3 l.[31] Hence, to determine the effectiveness of hypoxic training, future studies should attempt to minimize fluid loss and ensure the participants are euhydrated. A second mechanism would be the increase in basal metabolic rate at hypoxic conditions. An increased metabolic rate can be the result of improved substrate utilization and mitochondrial oxidative capacity[32] via signalling pathways that stimulate GLUT-4 transport. Training at hypoxic conditions would also allow a higher relative intensity to be achieved, which would reduce the mechanical strain of higher workloads while gaining similar benefits.[9] Hypoxic conditions have also been associated with an increase in leptin levels,[20] which would result in appetite suppression and hence reduced body weight and improvement in body composition. Through the activation of hypoxia-inducible factor (HIF) gene via hypoxic exposures, pathways leading to increased activation of leptin occur, resulting in reduction of caloric intake. This may be beneficial in the treatment of patients with obesity where caloric intake is excessive. In addition, epinephrine levels increased as a result of hypoxic training,[33] which may give rise to increased glycolysis.

The differences in effects of blood glucose levels may be attributed to the varying levels of hypoxia used in combination with different levels of intensities of exercise. Adverse blood glucose regulation was noted in most studies with either acute exposure to high altitude (>4000 m)[11,13,14,16] or high intensive training. However, in chronic exposure to hypoxic conditions (≥3 weeks) with moderate levels of exercise intensity showed favourable blood glucose status[6,9,15] however, in one study[6] the control group (200 m) also demonstrated a favourable change in fasting blood glucose. This would suggest positive adaptive changes in blood regulation would require extended exposure to moderate levels of hypoxia. It would also suggest that patients with issues with blood regulation should monitor their blood glucose status when participating in hypoxic training involving high exercise intensities or high levels of hypoxia. Secretion of epinephrine has been suggested to be responsible for the rise in blood glucose levels and reduction in insulin sensitivity,[14,15] however in one study, epinephrine levels remained unchanged despite a rise in blood glucose, indicating alternative metabolic signalling pathways.[17] Additionally hormones such as oestrogen may affect the response to hypoxic training as seen with gender differences in glucose response to hypoxic training.[17] Current studies favour a chronic, moderate level of hypoxic training (1500 m to 2500 m) used with moderate level of exercise intensity (55%–65% HR_{max}) to improve blood glucose regulation. Future studies into blood glucose regulation after acute hypoxic training at appropriate hypoxic load, used in combination with moderate levels of exercise intensity would be useful to determine if glucose regulation may benefit from moderate hypoxic training.

Resting SBP and DBP may be affected by various factors such as temperature, atmospheric pressure and humidity.[34] Besides hypoxia, such factors may contribute to changes in blood pressure especially with studies that used mountainous exposure as a form of hypoxic training.[6,7,21,22,24] Moreover, only two[6,24] of those studies had a control group at a normoxic environment. The increase in both SBP and DBP at higher altitudes may be attributed by the higher hypoxic stress imposed on the body, causing heightened sympathetic responses including increased secretion of hormones like epinephrine and noradrenaline.[14,35] However, it was theorized[36] that this response may be blunted

due to hyperventilation, which is often associated with hypoxia. The inverse response may occur resulting in a drop in vascular resistance and thus, a reduction in blood pressure.[36] Long-term reduction in resting blood pressure may be explained through hypoxia signal transduction pathways.[37] Gene products activated by this pathway that may affect blood pressure includes vascular endothelial growth factor and nitric oxide synthase.[37] Prescription of appropriate levels of exercise intensity at altitude should be observed, as exercise is associated with increase in SBP.[38] It was suggested that hypoxic training levels or exercise intensity be reduced in situations where SBP was greater than 220 mmHg or DBP greater than 140 mmHg. Alternatively, in the presence of symptoms associated with elevated blood pressure, exercise intensity should be reduced where SBP and DBP exceed 180 and 120 mmHg respectively.[39]

While epidemiological studies have reported increased total cholesterol amongst high altitude dwellers,[40] our review found that hypoxic training was actually able to significantly reduce total cholesterol[6,10,26–28] in subjects who were dyslipidemic, obese and with metabolic syndrome. One striking difference between those studies and epidemiology is the inclusion of an exercise regime with concurrent hypoxic training, which would affect findings. However the amount of reduction beyond the effects of exercise had been inconsistent and numbers of controlled studies are few. HDL and LDL levels have been strongly associated with cardiovascular risk.[41] Even though no clear conclusions can be drawn on the beneficial effects of hypoxic training on HDL, it can be concluded that hypoxic training does not increase LDL levels, evident by none of the studies recording any significant increase in LDL levels. In theory, triglycerides level should reduce due to lipid oxidation through the transcriptor coactivator PGC1α[42] that is controlled by hypoxia inducible factor −1 that is activated during exposure to hypoxia. However, this has not been demonstrated in studies reviewed, as seen in mixed results obtain. Contrasting results may be due to improper optimization of hypoxic load.

5. Limitations

The first and most major limitation of studies included in this review would be the exclusion of studies not written in English. Research into the use hypoxic training initiated in the former Soviet Union as early as the 1940s and since then, there were numerous publications.[43] Unfortunately, most of these studies are published in Russian and hence, excluded from this review. Secondly, inconsistency of parameters made comparisons between studies challenging. For example, to measure blood glucose regulation, two studies[13,14] conducted the intravenous glucose tolerance test, while other studies measured levels of insulin[10,12] and response to an oral glucose load. Even in the two studies[13,14] that used intravenous glucose tests, parameters reported differed, with insulin sensitivity, disposition index, glucose effectiveness and glucose effectiveness at zero insulin recorded in one study,[13] while dextrose infusion rate was recorded in the other study.[14] Thirdly, controlled studies were few which increased the variability of results that could be attributed to other factors such as effects of exercise.[21,22,25] Next, different studies used varying altitudes in combination with different levels of exercise intensity. Lastly, it would be remiss to not address the confounding effect that exercise training would have on the cardiometabolic variables we have reported in this review. No study included in this review reported the coefficient of determination (r^2) which would allow us the opportunity to report on the specific effect of hypoxic training.

One way to ensure consistency in relative hypoxic stimulus and exercise intensity would be to measure the hypoxic load. Urdampilleta et al.[44] suggested measuring the hypoxia stimulus charge (HSc) (HSc = blood oxygen concentration × time, where HSc = SpO_2% × time in minutes). However, one significant limitation of using HSc is that exercise intensity is not taken into consideration. Exercise training is commonly prescribed together with hypoxic training and hence, it should be accounted for when measuring hypoxic load. We therefore propose hypoxic load equals average percent heart rate max divided by SpO_2 multiplied by time in minutes (hypoxic load = avg %HRmax/SpO_2% × time in minutes), to ensure a consistent relative hypoxic stimulus, with relative exercise intensity taken into account. Empirically, this formula could be validated by measuring the mRNA of genes known to respond to hypoxia, such as hypoxia-inducible 1 (HIF-1), at a given hypoxic load. Subjects given the same hypoxic load with varying exercise intensities or levels of hypoxia should result in the same amount of gene expression. This is vital because response to hypoxic training would vary between individuals.[45] Therefore measuring hypoxic load may be useful in determining relative hypoxic intensity, or dose response of hypoxia training, and enable individualization of hypoxic stimulus.

6. Conclusion

Despite a somewhat limited number of studies included in this review, there are promising benefits with the use of moderate levels of hypoxic training in relation to some metabolic risk factors; body weight and composition, blood glucose and blood pressure. However, prolonged hypoxic exposure is required for adaption to occur to observe these beneficial effects. Beneficial effects to cholesterol levels are still inconclusive and it is anticipated that future research will assist in determining dose response of hypoxic training. Hypoxic training may be used as a treatment option to supplement exercise training to modulate certain cardiometabolic risk factors although it is unlikely the use of hypoxic training for clinical benefits will be commonly prescribed in clinical populations in the near future. There are however, a number of contraindications to participation in hypoxic training, this includes individuals with a history of acute or chronic mountain sickness,[46] acute and somatic viral diseases, impaired respiratory function/chronic obstructive pulmonary disease, hypoxaemia and pregnancy. Individuals practicing altitude training should also ensure proper hydration as limited research[47] has reported an increase in sweat rate with altitude training. Close monitoring of patients are necessary to ensure safe and therapeutic benefits of hypoxic load.

Competing interests

All authors declare that non-financial competing interests in the preparation of this manuscript.

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