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Exercise intervention under hypoxic condition as a new therapeutic paradigm for type 2 diabetes mellitus: A narrative review

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Abstract

This review aims to summarize the health benefits of exposure to hypoxic conditions during exercise in patients with type 2 diabetes mellitus (T2DM). Exposure to hypoxic conditions during exercise training positively changes the physiological response in healthy subjects. Exposure to hypoxic conditions during exercise could markedly increase skeletal muscle glucose uptake compared to that in normoxic conditions. Furthermore, post-exercise insulin sensitivity of T2DM patients increases more when exercising under hypoxic than under normoxic conditions. Regular exercise under short-term hypoxic conditions can improve blood glucose control at lower workloads than in normoxic conditions. Additionally, exercise training under short-term hypoxic conditions can maximize weight loss in overweight and obese patients. Previous studies on healthy subjects have reported that regular exercise under hypoxic conditions had a more positive effect on vascular health than exercising under normoxic conditions. However, currently, evidence indicating that exposure to hypoxic conditions could positively affect T2DM patients in the long-term is lacking. Therefore, further evaluations of the beneficial effects of exercise under hypoxic conditions on the human body, considering different cycle lengths, duration of exposures, sessions per day, and the number of days, are necessary. In this review, we conclude that there is evidence that exercise under hypoxic conditions can yield health benefits, which is potentially valuable in terms of clinical care as a new intervention for T2DM patients.

Key Words: Exercise; Hypoxia; Insulin-resistance; Metabolism; Type 2 diabetes mellitus;

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Weight loss

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Core Tip: Current research shows that exercise interventions performed under hypoxic conditions have positive effects on healthy subjects and athletes. Exercise intervention under hypoxic conditions can be beneficial as a new treatment for patients, including those with diabetes. This review summarizes recent studies on the potential cause-effect relationship for exercise interventions under hypoxic conditions in type 2 diabetes mellitus patients and discusses health benefits and risk factors.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a severe global public health problem. The worldwide diabetes prevalence in 2019 was estimated to be 463 million people, with a projected increase to 578 million by 2030 and 700 million by 2045^[1]. Diabetes is a primary cause of preventable lower limb amputations, blindness, and end-stage renal failure^[2]. It is also associated with increased cardiovascular complications and premature death^[3].

Insulin is the main hormone produced by pancreatic β -cells in the islets of Langerhans. It reduces blood glucose by stimulating glucose absorption into tissues, including fat and muscles. Insulin action refers to insulin signal cascade activation that is stimulated by insulin binding to its receptor, causing glucose and lipid absorption and metabolism, gene expression and protein synthesis, cell growth, and survival^[4]. Skeletal muscle is the leading glucose-uptake site^[5], one of the principal organs of insulin action, and is involved in glucose homeostasis regulation in healthy and diabetic conditions^[6]. In hyperinsulinemia, uptake of insulin-mediated blood glucose in skeletal muscle accounts for about 95% of whole-body-based glucose disposal during hyperglycemia^[5]. Glucose requires specific transfer proteins to be transported across the cell membrane^[7].

Glucose transporter 4 (GLUT4) is primarily responsible for this action^[8-10]. GLUT4 is the primary transporter of glucose in skeletal muscle^[9]. Increased GLUT4 expression in the skeletal muscle membrane is an essential indicator of exercise-related improvement^[11]. The carrying rate of glucose in skeletal muscle is the limiting stage for glucose uptake at rest, and the translation and expression of GLUT4 in response to exercise determine the acute regulation of glucose uptake^[11]. Previous studies have reported impaired insulin-stimulated glucose uptake and a decreased rate of glycogen synthesis in insulin-resistant muscles^[12,13]. The reduction of glycogen synthesis due to insulin-stimulated glucose transport disorder plays an important role in muscle insulin-resistance development^[14]. Therefore, skeletal muscle insulin-resistance has been regarded as a significant defect in T2DM^[12]. The precise mechanism underlying insulin-resistance in skeletal muscle has not yet been fully elucidated^[15]. According to previous reports, the decrease in insulin-stimulated glucose uptake in skeletal muscle is caused by the degradation of insulin signals and a defect in multicellular cascades, such as glucose transport inhibition, glucose phosphorylation, and the reduction of glucose-oxidizing glycogen synthesis, which plays a decisive role in the development of insulin-resistance in skeletal muscle^[16]. Thus, it has been reported that the decrease in insulin action in insulin-resistant skeletal muscle is related to the decrease in glycogen synthesis, caused by insulin-stimulated glucose transport disorder and decreased mitochondrial oxidation related to physical inactivity^[12,17,18].

It has been established that exercise intervention can enhance insulin action and glycemic regulation ability in individuals with T2DM, which may be due to the increased oxidation capacity of skeletal muscle, resulting in improved β -cell

function^[19-22]. Patients with T2DM do not release enough insulin to control glucose due to loss of cells, deterioration of their function, or both^[23]. Obesity increases the risk of T2DM^[24,25] partly by decreasing insulin sensitivity, *i.e.*, insulin does not cause a normal reduction in blood glucose.

Given the relationship between diabetes, increased cardiovascular disease, and decreased life expectancy^[26], the concept of effective treatment for diabetes is important. Exercise interventions promise to enhance glycemic control and cardiovascular condition^[19]. It is important to find a more effective strategy for treating this metabolic disease^[27]. Recently, many studies have investigated treatment of diabetes by widely applying hypoxic conditions, based on studies that showed that exercising at high altitudes reduced the risk of diabetes, cardiovascular disease, and obesity-related diseases, as compared to exercising at sea level^[27-31]. Hypoxic therapy is a novel treatment used as a common practice in many developed countries^[28,32-35]. Hypoxic therapies such as hypoxic exposure or hypoxic exercise intervention have been recommended to treat and prevent diabetes by affecting glucose uptake, insulin sensitivity, and vascular health^[27].

This narrative review aims to summarize any possible benefits of exposure and exercise under artificially generated hypoxic conditions in T2DM patients.

EFFECT OF HYPOXIC EXPOSURE ON PHYSIOLOGICAL RESPONSES

Short- or/and long-term exposure to hypoxic conditions causes extensive physiological changes^[36]. Normobaric (*i.e.*, simulated altitude) and hypobaric hypoxia (*i.e.*, real and simulated altitude) can reduce oxygen partial pressure in tissues and in blood. The acute compensatory response activates the sympathetic nerves and increases ventilation, and causes an altitude-dependent increased cardiac output upon exposure of inhabitants of low-lying areas to high altitudes^[37]. Hyperventilation is one of the essential processes involved in supplying sufficient oxygen to tissues^[38]. Moreover, peripheral chemical receptors in the carotid body react to reduced arterial partial pressure of oxygen^[39]. When a decrease in arterial oxygen saturation is detected by these receptors, the signal leads to sympathetic nerve activation and stimulation of ventilation, increasing the metabolic demand^[40]. Exposure to dry and cold environments may increase water loss as ventilation increases^[41]. As such, ventilation and cardiovascular reactions ensure that tissues' metabolic demands are met at rest and during exercise at high altitudes. Sustained exposure to hypoxia results in a reduced cardiac output to a similar level as under normoxia. These adaptive responses are facilitated by an increased stimulated red cell mass and further increases in ventilator responses to hypoxia^[36].

Intermittent hypoxia intervention has been studied over the past decades as a means of treatment for various health conditions^[42-44]. It has been suggested that exposure to mild hypoxia for 1 h, with or without simultaneous exercise, had an acute effect on insulin-resistance and blood glucose level in T2DM patients^[45,46]. In addition to these adaptations, exposure to the hypoxic environment positively affected body composition (*e.g.*, fat mass, percent body fat, and fat-free mass)^[28,30]. It has also been proven that several weeks of exercise under moderate hypoxia resulted in more weight loss in obese individuals than did exercising at the same or higher intensity under normoxia^[29,30,47,48]. Previous studies have also reported the beneficial effects of repeated exposure to intermittent hypoxic interventions for a few weeks, in the absence of other types of intervention, on fasting blood glucose and insulin levels^[49,50]. However, the fundamental mechanism underlying changes in glycemic control and insulin sensitivity due to hypoxia have been unclear^[51]. In addition to the insulin-dependent regulatory mechanism, it has been speculated that hypoxia may affect glucose uptake in a way similar to exercise^[51]. Therefore, exposure to hypoxic conditions is a new method of intervention for health-promotion and prevention or treatment of chronic diseases by improving body weight, cell metabolism, cardiovascular, and respiratory function (Figure 1)^[32,52].

HYPOXIC THERAPY FOR T2DM AND ITS APPLICATIONS

Review and meta-analysis suggest that exposure to hypoxic conditions during exercise can improve insulin sensitivity and enhance cardiovascular health more than exposure to normoxic conditions^[28,53-55]. Furthermore, exposure to hypoxic conditions has been shown to increase endurance performance in athletes^[56-58]. Exercising under hypoxic

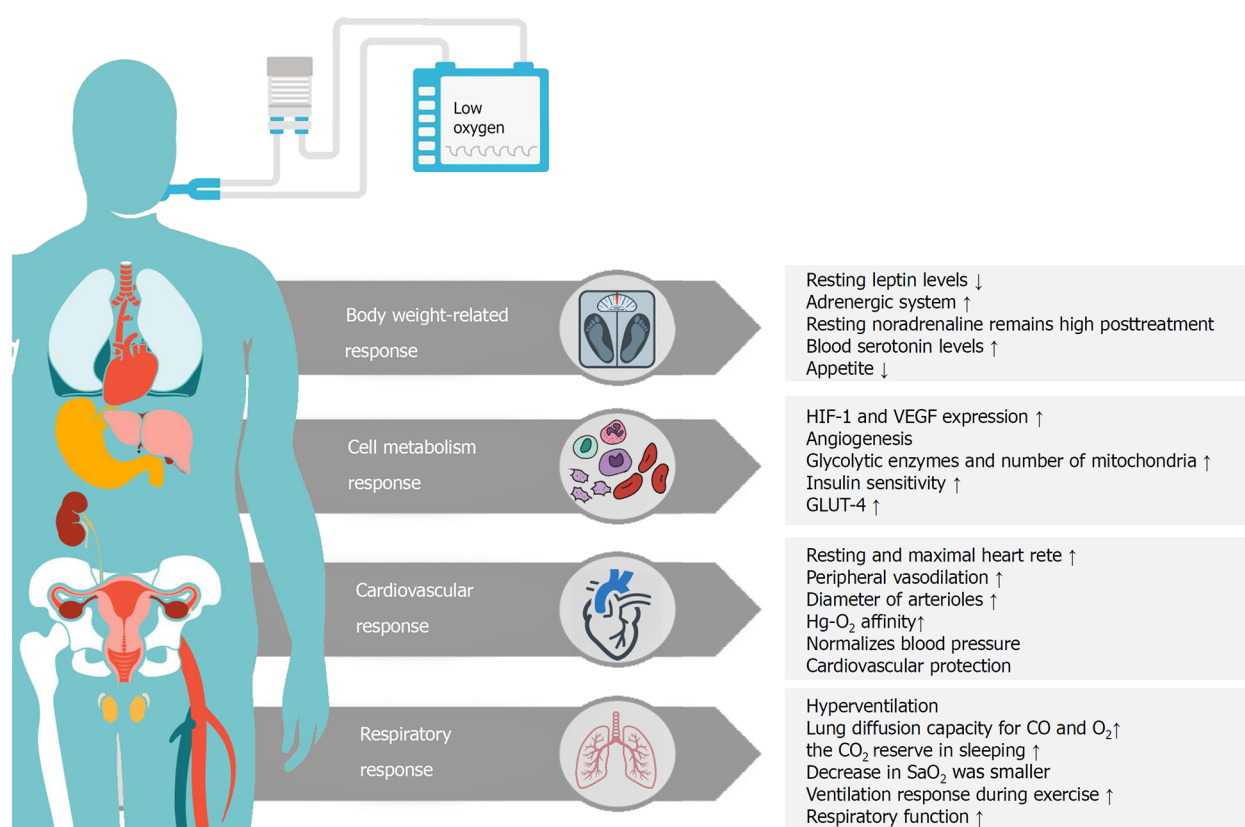


Figure 1 Effect of hypoxic exposure on the physiological response to exercise. Exposure to hypoxic conditions is a new intervention method for health-promotion and for preventing or treating chronic diseases by improving body weight, cellular metabolism, and cardiovascular and respiratory function. HIF-1: Hypoxic inducible factor-1; VEGF: Vascular endothelial growth factor; GLUT-4: Glucose transporter-4; Hg: Hemoglobin; O₂: Oxygen; CO: Carbon monoxide; C₂: Carbon dioxide; Sa₂: Arterial oxygen saturation.

conditions can enhance the exercise adaptations and exercise tolerance of T2DM patients^[27]. Previous studies of exposure to hypoxia during acute and chronic exercise in T2DM and insulin-resistant patients are summarized in detail in Tables 1 and 2.

To date, various technical equipment has been developed to create hypoxic conditions artificially. Artificially produced hypoxia can be obtained by changing barometric pressure (hypobaric hypoxia) or by changing the fraction of oxygen (FiO₂) (normobaric hypoxia). FiO₂ is always constant at sea level (ca. 21%), and barometric pressure decreases with higher altitude. Hypoxic conditions can be created by using a special chamber at rest or during exercise. Such an environment control chamber is shown in Figure 2.

Therapeutic effects of exercise intervention under hypoxic conditions on T2DM

Effects of exercise intervention under hypoxic conditions on glucose uptake and insulin sensitivity: Exposure to hypoxia increases glucose uptake in the skeletal muscles of healthy and obese adults^[59]. Brooks *et al*^[60] demonstrated that 3 wk of hypoxic exposure at an altitude of ca. 4300 m improves glucose turnover and decreases blood glucose in healthy males. Lippl *et al*^[61] showed that short-term hypoxic exposure (1 wk at an altitude of ca. 2650 m) decreased glycated hemoglobin (HbA1c) levels in obese males. Exposure to hypoxia can markedly improve glucose uptake, and exposure continuously improves blood glucose regulation over the long term.

A previous review article reported that regular physical activity and exercise could markedly increase peripheral glucose uptake and improve blood glucose regulation^[62]. It is necessary to clarify whether exercise and hypoxia can have positive combined effects in T2DM and whether patients with this condition can benefit from short- or long-term exposure to hypoxia during exercise. Mackenzie *et al*^[63] examined short-term hypoxic exposure during acute exercise on the glucose homeostasis in T2DM patients. They proved that glucose loss and sustained glucose infusion during cycling under hypoxic conditions were more significantly increased than under normoxic conditions^[46,63]. Glucose tolerance tests performed immediately after cycling showed that blood glucose regulation improved more under hypoxic conditions.

Table 1 Effects of acute exercise under hypoxia vs under normoxia in patients with type 2 diabetes mellitus

Ref.	Participants	Design and protocol	Exercise intensity	Main results
Mackenzie <i>et al</i> ^[63] (2011) ¹	<i>n</i> = 8; sex: Male; age: 58 ± 4.0 yr; BMI: 29.2 ± 6.7 kg/m ²	(1) 60 min rest in normoxia; (2) 60 min rest in hypoxia normobaric hypoxia (FiO ₂ : 14.6%, simulated altitude: ca.3100 m); (3) 60 min cycling in normoxia; and (4) 60 min cycling in hypoxia (normobaric hypoxia: FiO ₂ : 14.6%)	(3) and (4): 90% lactate threshold	Blood lactate: ↔ (1), (2); ↑ (3), (4). Blood glucose: ↔ (1); ↓ (2), (3), (4). Insulin sensitivity (during glucose tolerance test): (4) > (3) > (2) > (1)
Mackenzie <i>et al</i> ^[46] (2012) ¹	<i>n</i> = 8; sex: Male; age: 58.7 ± 2.2 yr; BMI: 28.3 ± 2.1 kg/m ²	(1) 60 min continuous cycling in hypoxia (normobaric hypoxia: FiO ₂ : 14.7%, simulated altitude: ca.3100 m); (2) 60 min interval training with passive recovery (5:5 min) in hypoxia (normobaric hypoxia: FiO ₂ : 14.7%); and (3) 60 min interval training with passive recovery (5:5 min) in normoxia	(1): 90% lactate threshold; (2): 120% lactate threshold; (3): 120% lactate threshold	HR and blood lactate: ↑ (1), (2), (3). Blood glucose decrease (pre- to post-exercise): (1) > (2). Glucose disappearance: ↑ (1); ↔ (2), (3). HOMA-IR index improved after 24 h: ↑ (1), (2); ↔ (3); after 48 h: ↑ (1); ↔ (3)
Brinkmann <i>et al</i> ^[76] (2017) ²	<i>n</i> = 8; sex: Male; age: 58.0 ± 15.0 yr; BMI: 33.0 ± 6.0 kg/m ²	40 min cycling: (1) Normoxia; (2) Hypoxia (normobaric hypoxia: FiO ₂ : 14%, simulated altitude: ca. 3400 m); and (3) Hypoxia (normobaric hypoxia: FiO ₂ : 14%) + hyperoxia (normobaric hyperoxia: FiO ₂ : 30%) intervals (5:5 min)	Blood lactate: 2.5 mmol/L	Blood lactate (post-exercise lower): (3) > (2). BORG RPE: ↔ (1), (2), (3). Pro-angiogenic factors: VEGF: ↑ (2), (3). Anti-angiogenic factor: endostatin: ↑ (2), (3)

¹Data are presented as mean ± SE.²Data are presented as mean ± SD. BMI: Body mass index; HR: Heart rate; BORG RPE: BORG rating of perceived exertion; FiO₂: Fraction of inspired oxygen; HOMA-IR: Homeostatic model assessment for the quantification of insulin-resistance; VEGF: Vascular endothelial growth factor.**Table 2 Effects of hypoxia vs normoxia chronic exercise in patients with type 2 diabetes mellitus or insulin-resistance**

Ref.	Participants	Intervention	Intensity	Frequency and duration	Main results
Wiesner <i>et al</i> ^[69] (2010) ¹	<i>n</i> = 45. NTG: sex: 8 male, 13 females; age: 42.1 ± 1.7yr; BMI: 32.5 ± 0.8. HTG: sex: 10 male, 14 females; age: 42.2 ± 1.2 yr; BMI: 33.1 ± 0.3	60 min running on a treadmill; normobaric hypoxia: simulated altitude: ca. 2740 m	VO _{2peak} : 65%	3 d/wk, 4 wk	Lactate levels at the anaerobic threshold: ↓ HTG; fasting insulin, HOMA-IR: ↓ NTG, HTG; body fat decreased: HTG > NTG; BP, LDL-c: ↔ NTG, HTG
Schreuder <i>et al</i> ^[66] (2014) ²	<i>n</i> = 19. NTG: sex: 5 male, 4 females; age: 52.0 ± 8.0 yr; BMI: 36.0 ± 6.5 kg/m ² . HTG: sex: 9 male, 1 female; age: 57.0 ± 6.0 yr; BMI: 30.9 ± 4.1 kg/m ²	45 min endurance training (cycling) + series of strength training exercises; normobaric hypoxia: FiO ₂ : 16.5%; simulated altitude: ca. 2100 m	HRR: 70%-75%	3 d/wk, 8 wk	VO _{2max} : ↑ NTG, HTG; BMI, BP, HOMA-IR, HDL-c, LDL-c, TC, TG, fasting glucose, HbA1c: ↔ NTG, HTG; Vasodilatory function: ↔ NTG, HTG

¹Data are presented as mean ± SE.²Data are presented as mean ± SD. NTG: Normoxia training group; HTG: Hypoxia training group; BMI: Body mass index; Fi₂: Fraction of inspired oxygen; HDL-c: High-density lipoprotein cholesterol; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostatic model assessment for the quantification of insulin-resistance; HRR: Heart rate reserve; LDL-c: Low-density lipoprotein cholesterol; VO_{2peak}: Peak oxygen uptake; VO_{2max}: Maximal oxygen uptake; BP: Blood pressure; TC: Total cholesterol; TG: Triglyceride.

Insulin sensitivity increased only after 24 h and 48 h after exercise under hypoxic conditions. It also reported that exercising at a continuous submaximal intensity under hypoxic conditions effectively increased glucose uptake and insulin sensitivity than interval training^[46]. Thus, previous research suggests that acute exercise under hypoxic conditions positively affects glucose uptake and insulin sensitivity in T2DM patients. The increase in glucose uptake during hypoxia has been thought to be due to the upregulation in the glycolytic energy pathway, which compensates for decreased energy production by the aerobic system^[64]. Katayama *et al*^[65] reported that the respiratory exchange ratio was lower during submaximal cycling exercise for 30 min at sea levels in healthy males than similar cycling under hypoxic conditions (at an altitude of ca. 2000 m). However, Schreuder *et al*^[66] found no change in insulin sensitivity and blood glucose regulation in T2DM patients after exercise training under normoxia or short-term hypoxia.

Previous studies were also conducted on insulin-resistance in healthy adults and T2DM patients. Haufe *et al*^[67] reported significant improvements in the values for the homeostatic model assessment of insulin-resistance (HOMA-IR) index in healthy males, only during exercise under hypoxic conditions. However, Lecoultré *et al*^[68] showed increased glucose and insulin concentrations and higher insulin-to-glucagon

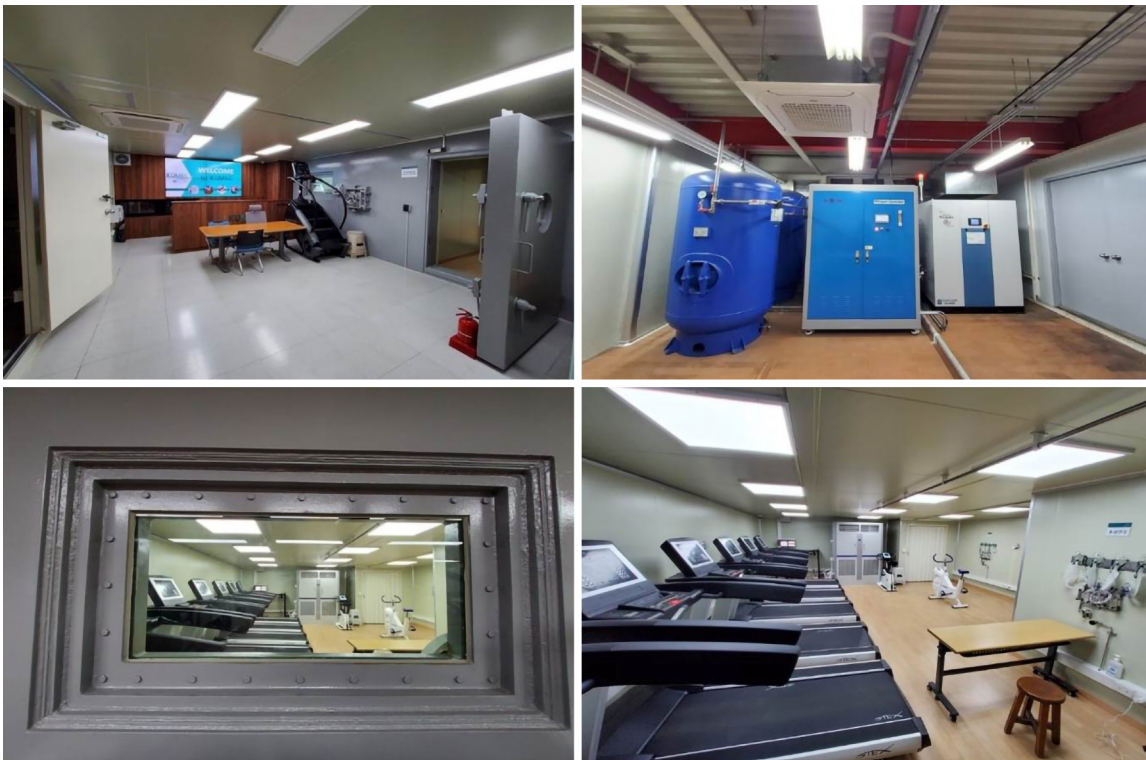


Figure 2 Environment control chamber. Various technical equipment has been developed to create hypoxic conditions. Artificially produced hypoxia can be obtained by changing barometric pressure (hypobaric hypoxia) or by changing the fraction of oxygen (FiO_2) (normobaric hypoxia). The FiO_2 is always constant at sea level (FiO_2 ca. 21%), and the barometric pressure decreases with higher altitude. The hypoxic conditions can be created using a special chamber at rest or during exercise.

rates after exercise training under hypoxic conditions, as compared to under normoxic conditions. Wiesner *et al*^[69] showed that exercise training performed under short-term hypoxia did not change the HOMA-IR index in overweight and obese subjects. However, the training workload was significantly lower in the hypoxic group than in the general group, and exercise under hypoxic conditions was a more efficient method. These previous studies also demonstrated improvements in the HOMA-IR index with reduced body fat in the hypoxia groups^[67,69]. Decreasing body fat helps to increase insulin sensitivity, particularly in T2DM patients, because there is a positive association between body fat, peripheral insulin-resistance, and pro-inflammatory conditions^[70].

Thus, the combination of short-term hypoxia exposure and exercise has a beneficial effect. Nevertheless, there is a lack of biochemical evidence in human research. Therefore, further studies are needed to clarify whether exercise under short-term hypoxia can effectively increase blood glucose uptake and insulin sensitivity, as compared to exercise under normoxia^[27].

Effects of exercise intervention under hypoxic conditions on skeletal muscle: The decrease in skeletal muscle capillarization can have a negative effect on blood glucose regulation, and a negative relationship between skeletal muscle capillary density and insulin concentration has been shown previously^[71]. Regular physical activity has been shown to have a positive effect skeletal muscle capillaries^[53]. Lundby *et al*^[72] concluded in a previous review that combining exercise and hypoxia may accelerate structural and functional adaptation. In contrast, prolonged exposure to hypoxia does not result in significant changes in human capillarization during rest^[72]. Mizuno *et al*^[73] reported that exposure to ca. 5300 m for 75 d did not change the ratio between capillaries and muscle fibers. However, because the reduction in fiber size can be adapted to hypoxic exposure, capillaries per region were increased at a similar altitude^[74]. Recent meta-analysis studies have shown that exercise under hypoxic conditions positively affects the skeletal muscle capillaries and function of the vascular dilator^[53].

A temporary increase in pro-angiogenic factors due to acute exercise may be related to the initiation and control of angiogenesis^[75]. Brinkmann *et al*^[76] found that acute exercise under hypoxia could lead to upregulation of serum pro-angiogenic factors, as compared to exercise under normoxia, in T2DM patients. Additionally, there are other

mechanisms that contribute to increased pro-angiogenic regulator release after exercise under hypoxic conditions. First, tissue hypoxia during exercise can be enhanced by environmental hypoxic conditions and is increased by activation of hypoxia-induced factor-1 α (HIF-1 α), which initiates expression of proteins related to angiogenesis regulation^[77]. However, responses to hypoxia in diabetes have been impaired, and hyperglycemia is a very important result in the HIF-1 α regulation^[78]. The second mechanism is increased sympathetic nerve activity and increased skeletal muscle blood flow and shear stress at the vessel walls, which induce intracellular signal transduction through mechanical stimulation of capillaries, thereby increasing angiogenesis *via* vascular formation^[79].

Effects of exercise intervention under hypoxic conditions on vascular health:

Exercise can help prevent disease progression and protect T2DM patients from secondary complications by improving long-term increases in skeletal muscle capillarization and vascular function. Patients with diabetes develop not only abnormal angiogenesis but also macroscopic and microscopic angiogenesis with endothelial dysfunction^[80]. The current meta-analysis suggested that exercise improves vascular dilation when performed under hypoxia than under normoxia^[53]. Exercise under hypoxic conditions is associated with a compensatory increase in blood flow to active muscles to meet the oxygen demand^[81,82]. Exercise-induced blood flow is important in inducing vascular adaptation. The combination of exercise and hypoxia can positively affect vascular adaptation in normoxic exercise training, particularly in T2DM patients who typically exhibit attenuated exercise-induced blood flow^[83]. However, Schreuder *et al*^[66] showed no effect of training on the vascular dilation in T2DM patients, both when exercise was performed in normoxia and hypoxia. These differences may be due to the different training protocols or oxygen concentrations used, and other possible adaptation mechanisms in T2DM patients^[84].

The effects of hypoxia and exercise may be related to subsequent increased blood flow to muscles, and high shear stress, nitric oxide (NO), and oxygen tension reduction^[81,83,85,86]. While the specific mechanisms that underlie the effects of exercising under hypoxia remain unclear, it has been demonstrated that exposure of endothelial cells to hypoxia increases^[87]. In this regard, the expression and activation of endothelial NO synthase (eNOS) as a potent vascular dilator can be increased and produce eNOS and NO levels. Therefore, exercise under hypoxic conditions is thought to have high potential to improve vascular health. However, further studies are needed to confirm that long-term exercise under hypoxia can improve skeletal muscle capillarization more significantly than exercise under normoxia in T2DM patients. Previous studies can also demonstrate how training protocols should be modified to induce effective adaptation of physiological variables. Schreuder *et al*^[66] have reported that the vascular dilation in T2DM patients could be positively affected by exercise training under short-term hypoxic conditions. However, additional studies should be conducted to apply various training protocols and oxygen concentrations.

Effects of exercise intervention under hypoxic conditions on body composition:

There are positive correlations between increased fat mass, insulin-resistance, chronic inflammation, and cardiovascular disease^[70]. Decreasing fat mass is one of the important goals in the treatment of overweight and obese patients with T2DM. Previous studies have reported that exercise under hypoxia can help reduce body weight and body fat mass in overweight and obese patients with T2DM^[27,88,89]. Kong *et al*^[47] showed that combined aerobics and strength training under hypoxic conditions (simulated altitude: ca. 2100-3200 m, FiO₂: 14.5%-16.5%) for 4 wk (11 sessions/wk) decreased weight more than under normoxic conditions in obese young adults. Wiesner *et al*^[69] reported that hypoxia exercise training for 4 wk improved body composition in obese men and women without diabetes and with insulin-resistance. Acute exposure to hypoxia (2 h) at a simulated altitude of 4300 m has been reported to decrease the leptin reaction to glucose uptake in healthy humans^[90]. The results of previous studies may be related to changes in hormones that control appetite. However, the effects of acute exposure to hypoxia on leptin levels and appetite in T2DM patients have not been demonstrated. Therefore, a future study on appetite regulation mechanisms is needed, considering that T2DM patients have leptin resistance^[91].

Effects of exercise intervention under hypoxic conditions on blood lipids and oxidative stress: Another perspective of the effect of exercise under hypoxic conditions is its effects on blood lipid variables in patients with diabetes. Simpson *et al*^[92] examined how exposure to hypoxic conditions during moderate exercise, as well as 16 d of rest in normoxia and continuous normobaric hypoxia (simulated altitude: ca. 3400

m, FiO_2 : 14%), changes total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels in healthy men. Exposure to hypoxic conditions during moderate exercise significantly reduced total cholesterol, HDL, and LDL levels. Schreuder *et al.*^[66] and Wiesner *et al.*^[69] reported no positive effect of exposure to hypoxic conditions during exercise on blood lipids variables in overweight and obese patients with T2DM and insulin-resistance. To date, there have been no studies providing evidence of an effect of exposure to hypoxic conditions during exercise on blood lipids.

T2DM patients may experience increased oxidative stress as free radicals increase, further exacerbating insulin-resistance or causing cardiovascular disease^[93]. However, more research is needed on whether exercise under short-term hypoxic conditions can reduce oxidative stress in T2DM patients and protect against secondary complications caused by free radicals than exercise performed under normoxic conditions. A single bout of interval training under hypoxic conditions (simulated altitude: ca. 4000 m, FiO_2 : 13%) has been reported to increase ventilatory responses in T2DM patients^[45]. These results demonstrate the potential of such training to benefit individuals with diabetes with autonomic regulation imbalances. Future research requires verification of the effectiveness of exercise under short-term hypoxic conditions in improving blood lipid levels and oxidative stress.

Possible health risks of exercise intervention under the hypoxic condition on T2DM

This narrative review describes some health risks that may arise when exercising under hypoxic conditions. The definition of the range of oxygen-availability under which exercise can be performed under hypoxic conditions without negatively affecting health needs to be defined. Previous studies have set short-term hypoxic conditions similar to simulated altitudes of up to ca. 4000 m for healthy participants and ca. 3400 m for T2DM patients. These hypoxic conditions did not result in health problems in previous studies. However, breathing air with rapidly reduced oxygen levels or prolonged exposure to very high altitude conditions increases the risk of neurocognitive impairment, myocardial infarction, and stroke^[94]. Clinical effects on the human body have not been apparent, but T2DM patients have been shown to respond to hypoxic conditions with low ventilation reactions^[95]. A previous study has suggested that cardiac output and heart rate is changed in T2DM patients upon exposure to hypoxic conditions^[84]. In particular, T2DM patients with neurological disorders could be negatively affected during exercise involving exposure to hypoxic conditions. In terms of body composition, exposure to long-term hypoxic conditions may facilitate reduction in body weight and fat mass, but exposure to extreme altitude (> 5000 m) has been shown to affect fat-free mass negatively^[96]. The effect of increased capillarization in skeletal muscle after exercise training under hypoxic conditions requires further study, and the clinical relevance of excessive abnormal angiogenesis in diabetes needs to be shown^[80].

Oxidative stress is exacerbated under hypoxic conditions by both intense and long-term exercise^[97]. The actual protocol for exposure to hypoxia has varied significantly across studies in terms of cycle length (*e.g.*, weeks), the duration of exposure (*e.g.*, minutes and hours), the number of exposures per day (*e.g.*, session), and the number of days. Exposure to extreme acute hypoxic conditions may be similar to the findings obtained with animal models of ischemia or reperfusion, with acute release of excessive free radicals and decreased antioxidant capacity^[98]. Oxidative stress can cause cell and tissue damage and be harmful to the human body. However, redox balance changes can play a positive role as a potential stimulus for adaptation to prolonged exercise^[99]. Previous studies have shown that regular moderate exercise can weaken oxidative stress associated with hypoxia^[100-103]. Therefore, there is potential health risks when T2DM patients exercise under hypoxic conditions. However, its value as an effective treatment method would be marked, if appropriate safety precautions are implemented.

CONCLUSION

Short- and long-term exposure to hypoxic conditions during exercise may improve glucose uptake and insulin sensitivity in T2DM patients more than when exercising under normoxic conditions. Additionally, exercising under hypoxic conditions could help reduce body weight and fat mass in overweight and obese patients with T2DM. Several previous studies have reported positive effects of exercise training under

hypoxic conditions on the bodies of T2DM patients. However, there is currently a lack of research on the long-term adverse effects of exposure to hypoxic conditions during exercise training in T2DM patients. Future studies should evaluate the potential benefits of exposure to hypoxic conditions during exercise, to design new intervention methods (normobaric hypoxia *vs* hypobaric hypoxia) for treating T2DM patients. Overall, exposure to hypoxic conditions during exercise in T2DM patients have the potential value of adaptation to stress stimulation in terms of clinical treatment, which can protect against pathological biology and other stresses in diabetes. Overall, the literature suggests that exposure to hypoxic conditions during exercise (simulated altitude of ca. 3000 m) is highly likely to improve the health condition of patients with diabetes. However, there is insufficient evidence for the safety of exposure to short-term hypoxic conditions during exercise in T2DM patients, and further research is needed to develop suitable interventions. Thus, exposure to hypoxic conditions during exercise should be performed with consideration of safety precautions, and patients should be advised by a medical doctor before undertaking exposure to hypoxic conditions.

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