



# Training under normoxia and normobaric hypoxia in patients with type 1 diabetes

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## Abstract

Apart from insulin, physical exercise is a crucial component of therapy in patients with type 1 diabetes mellitus (T1DM). The benefits of physical activity in such patients include improved insulin sensitivity, lowered blood glucose, reduced body fat and improved cardiovascular function and physical performance. Hypoglycemia is a crucial issue in the peri-training period in insulin-treated patients. Proper preparation for exercise is the key to reducing the risk of hypoglycemia. The selection of the training type and the patient's knowledge of the effect of such training on glycemia are also significant.

Physical exercise under normobaric hypoxia in the training rooms is also available commercially and is becoming increasingly popular. Under such conditions, the air consists of 15.4% oxygen and 84.5% nitrogen, which corresponds to the conditions at an altitude of approximately 2,500 meters above sea level. Hypoxia induces the production of the hypoxia-inducible factor (HIF-1), which regulates the expression of over 100 genes. It modulates key metabolic pathways to optimize glucose utilization by increasing cell sensitivity to insulin, more efficient glucose uptake from the blood and activating effect on glycolytic enzymes. Additionally, HIF-1 shows beneficial effects on the lipid profile, vascular endothelium and performance as measured by the maximal oxygen uptake ( $VO_{2max}$ ).

The aim of this paper was to review and summarize the most recent studies on the effects of exercise on glycemic control and physical performance under normoxia and normobaric hypoxia in patients with T1DM.

**Key words:** type 1 diabetes; exercise; hypoxia; resistance training; aerobic training

## Introduction

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease resulting from the irreversible destruction of insulin-producing pancreatic beta cells, which results in absolute insulin deficiency and lifelong exogenous insulin administration [1].

The possibility of preventing and inhibiting the loss of beta cells as well as identifying the genetic and environmental factors that cause T1DM are under intense research. The number of individuals with T1DM was estimated to be approximately 8.42 million worldwide in 2021 with an increasing trend in incidence each year. The estimated increase in prevalent cases is expected to reach 13.5–17.4 million in 2040, which is double the current number of patients [2].

Glycaemic control in patients with diabetes is necessary to prevent the development of microangiopathic complications (in the form of nephropathy,

retinopathy and neuropathy) and macroangiopathic complications, which are clinical manifestations of atherosclerosis, such as myocardial infarction and stroke [3]. In addition to intensive insulin therapy, behavioural treatment, which consists of a proper diet and physical activity, is crucial for the appropriate treatment of T1DM. Adequate regular exercise improves insulin sensitivity and glycaemic control and reduces the risk of complications, including those involving the cardiovascular system [4].

The health benefits of training under normobaric hypoxia in patients with T1DM are reported in the literature [5]. Hypoxia leads to the production of the hypoxia-inducible factor (HIF-1), which regulates the expression of over 100 genes. HIF-1 improves tissue function at low oxygen availability through increased expression of glucose transporters and glycolytic enzymes. It also shows the beneficial effect on skeletal muscle adaptation to endurance training.



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The aim of this paper was to review and summarise the most recent studies on the effects of exercise on glycaemic control under normoxia and normobaric hypoxia in patients with T1DM.

## The role of physical exercise in T1DM

Exercise is one of the essential elements of therapeutic management in patients with type 1 and type 2 diabetes mellitus, regardless of age. For many years, only aerobic training was recommended to patients with diabetes. Recent papers have contributed to a better understanding of exercise, including resistance training, in patients with T1DM. The latest guidelines of the American Diabetes Association recommend both aerobic and resistance training for most adults with diabetes. According to the guidelines, patients should engage in at least 150 minutes of moderate-to-vigorous-intensity aerobic activity per week for at least 3 days per week with no more than 2 consecutive days without activity so as not to lose improved insulin sensitivity due to exercise. In addition, patients should engage in 2–3 sessions/week of resistance exercise on non-consecutive days [6].

The benefits of physical activity in patients with T1DM include improved insulin sensitivity, lower blood glucose, reduced body fat, and improved cardiovascular function and physical performance. Even low-intensity training of short duration has anti-inflammatory properties and may lead to a protective response against the autoimmune process directed to  $\beta$ -cells [7]. It can prolong the remission of T1DM, which is the initial period of the disease characterised by a reduced need for exogenous insulin [8, 9].

During exercise, oxygen consumption increases in proportion to the increase in load until it reaches a stable level that cannot be higher by increasing the load. This value is referred to as maximum oxygen consumption ( $VO_{2max}$ ) and is considered the best measure of a patient's physical fitness. During 2–3 monthly training sessions,  $VO_{2max}$  can increase by as much as 15%. This increment is higher in those who do not regularly train, and the maximum value is reached by individuals aged 20–29 years. In this age group, the mean  $VO_{2max}$  values are 34–42 mL/kg/min in men and 31–37 mL/kg/min in women. The value of  $VO_{2max}$  decreases with age (e.g. 31–38 mL/kg/min for men and 28–33 mL/kg/min for women aged 30–39 years) [10].

When choosing the type and intensity of exercise, the risk of hyperglycaemia and hypoglycaemia should be assessed. The release of catecholamines during vigorous exercise ( $> 85\%$  of  $VO_{2max}$ ) can increase hepatic glucose production and cause post-exercise hyperglycaemia. In turn, moderate-intensity exercise (40–60% of

$VO_{2max}$ ) is associated with a higher risk of hypoglycaemia, especially if the patient does not take appropriate preventive measures.

Regular exercise has many benefits not only related to carbohydrate metabolism. It can contribute to the reduction of body weight, triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) [4]. Increased physical fitness due to training is associated with a reduced risk of developing dyslipidaemia, coronary artery disease, and stroke [11]. Physically active patients with T1DM are less likely to develop retinopathy and microalbuminuria compared to those who are physically inactive [12].

## What type of exercise is the most beneficial for patients with T1DM?

### *Aerobic training*

Aerobic training (AT) includes repetitive and continuous movements of large muscle groups with at least moderate intensity [rating of perceived exertion (RPE) range: 4–6] [13], including activities such as walking, cycling, jogging, and swimming with moderate intensity. In patients with T1DM, this type of training is associated with increased muscle strength, improved mobility, balance and endurance, and reduced insulin requirements [14].

Prolonged moderate-intensity exercise (RPE range: 4–6) leads to the activation of lipolysis, glycogenolysis, and gluconeogenesis, which results in an increased supply of substrates for oxidative phosphorylation in contracting muscles, leading to substrate exhaustion and an increased risk of post-exercise hypoglycaemia [15]. One day after such physical activity, counter-regulatory hormones, including epinephrine and glucagon, are blunted, which is another risk factor for hypoglycaemia [16]. Aerobic exercise increases the number of insulin receptors in skeletal muscle and adipose tissue, improves their function, and increases the total number of cellular glucose transporters (GLUTs), leading to better glucose uptake and a faster decrease in blood glucose concentration during exercise [17]. Aerobic training improves vascular endothelial function in patients with long-term T1DM who are at increased risk of diabetic angiopathy. AT may also reduce triglyceride and LDL cholesterol levels, waist circumference, and body weight [18]. Aerobic training leads to an increase in mitochondrial density in skeletal muscle, improved vascular compliance and reactivity, cardiac minute volume, and pulmonary function [19, 20]. In the healthy population, insulin release is decreased during AT, while glucagon secretion is increased, which results in relatively stable glycaemia [21]. In patients with T1DM, exogenous insulin levels in the blood are not physiologically regulated during physical activity, which

occurs in healthy individuals. This phenomenon puts patients at risk for hypoglycaemia. In addition, the patient's blood glucose concentration depends mainly on the time elapsed since the injection, the amount and type of insulin, and the meal size [22].

Furthermore, the liver produces less glucose in patients with T1DM during exercise due to a higher concentration of insulin circulating in the blood, which blocks hepatic gluconeogenesis [23]. For this reason, during training, patients with T1DM should be educated about the amount of carbohydrates consumed before exercise and in the peri-training period, and insulin doses should be modified accordingly. During aerobic exercise, particularly if it was not planned and the patient did not reduce insulin dose, a decrease in the glucose level occurs more frequently and more rapidly compared to resistance training, and the patient needs to consume additional carbohydrates, which may not translate into better glycaemic control and possible weight reduction.

### ***Resistance (anaerobic) training***

Resistance training (RT) consists of physical activities in which specific skeletal muscles are activated due to the high load generated by external resistance (during weight lifting, using elastic resistance bands and workout machines) [24]. When performed regularly, RT increases muscle strength and muscle mass, which allows better blood glucose uptake, thus improving glycaemic control [25].

Additionally, RT is associated with increased adiponectin levels, which is associated with improved insulin sensitivity. Resistance exercise provides greater glycaemic stability than continuous moderate-intensity aerobic exercise and causes a smaller initial decrease in blood glucose during training. However, it is associated with a longer decrease in post-exercise glycaemia than aerobic exercise, and hence improved glycaemic control and lower insulin requirement during such a training session. Some studies found improved glycaemic control in patients with T1DM during RT as opposed to aerobic training [26, 27]. It may have been due to the fact that many studies were related to RT in conjunction with aerobic training and the duration of RT. A longer training period (e.g. 32 weeks) resulted in increased muscle mass, thus leading to a reduction in glycosylated haemoglobin (HbA<sub>1c</sub>) levels [28]. The results of a recent meta-analysis of 5 studies evaluating the effect of RT in patients with T1DM showed a beneficial effect on glycaemia (decreased HbA<sub>1c</sub> levels) [29]. Proper RT improves exercise capacity as assessed by an increase in  $VO_{2max}$  without an increase in the maximum heart rate ( $HR_{max}$ ), which suggests its beneficial effect on the cardiorespiratory system [30].

### ***Combining resistance training with aerobic training***

Combining RT with aerobic training in a single training session produces the most favourable results. The exercise order in patients with diabetes is essential — RT before aerobic exercise provides a more stable glycaemic profile and thus a lower tendency to hypoglycaemia during aerobic exercise and a lower need for carbohydrate intake. To achieve stable glycaemia, training should start with resistance exercise followed by aerobic training [31]. This sequence of exercise results not only in stable glycaemia but also in a reduction in the duration and severity of hypoglycaemia within the 12-hour period after training [32].

### ***Eccentric training***

Eccentric training increases muscle strength and endurance and improves glucose tolerance, similarly to concentric exercise [33]. Eccentric movements occur when the loaded muscle lengthens and muscle attachments move away from each other (e.g. work of the thigh extensor muscles when descending while performing squats, running downhill, and lowering on a bar). Unlike walking uphill, which is concentric endurance exercise, walking downhill puts less strain on the cardiovascular system. However, it causes a relatively high load on the contractile units of the muscles. Therefore, walking downhill can be a valuable training method for patients with diabetes and low physical fitness [34, 35].

Exercise with a predominance of eccentric movements causes muscle microdamage, which may help to improve glucose tolerance in individuals without diabetes. It can be related to faster recovery of muscle fibres after eccentric exercise. The life cycle of skeletal muscle cells is short and is characterised by cell death and regeneration. Younger muscle fibres offer a greater permeability to plasma glucose across sarcolemma, which results in faster glucose uptake by muscles [36]. This type of exercise can also lead to improved insulin sensitivity, accelerated metabolism of triglycerides, weight reduction, and reduced low-grade inflammation [37].

There are few studies on the effect of eccentric exercise on glycaemic control in patients with T1DM. It can be assumed that since glycaemic control improves in healthy individuals, the influence of eccentric training may also be beneficial in T1DM patients.

### **Hypoglycaemia**

Hypoglycaemia, i.e. a decrease in blood glucose level below 70 mg/dL in exercising patients with T1DM, is a common phenomenon [38]. Surveys of patients with T1DMs showed that hypoglycaemia was the strongest

factor preventing them from engaging in regular physical activity. Both patients and physicians need to be aware that the risk of hypoglycaemia increasing during, shortly after, and up to 24 hours following exercise due to increased insulin sensitivity.

A history of severe hypoglycaemia, which requires the assistance of another person, in the preceding 24 hours is an absolute contraindication to exercise [39]. It is caused by counterregulatory hormones released during severe hypoglycaemia that are not effective enough during another hypoglycaemic episode that can occur soon after the previous episode.

Education about modification of insulin therapy and diet (including adequate carbohydrate supplementation in the peri-training period) in relation to exercise is essential for patients to feel safe and not to abandon physical activity due to the fear of hypoglycaemia [40]. If the training takes place in the afternoon or evening, the risk of nocturnal hypoglycaemia can be minimised by reducing the daily basal insulin dose by approximately 20% and reducing the meal bolus insulin [41]. Low insulin levels combined with normoglycaemia or moderate hyperglycaemia seem most beneficial during exercise in T1DM patients [42]. This can be achieved by appropriately reducing the insulin dose before the meal, after which physical activity is undertaken — the less trained the patient, the greater the reduction should be ( $\leq 75\%$ ). Another element that reduces the risk of hypoglycaemia is associated with planning exercise not earlier than 1.5–2 hours after a meal and insulin administration so that physical activity can occur after reaching hormone peak levels. A short 10-second sprint at maximum intensity (RPE range: 8–10) before, during, or after a moderate-intensity exercise session is also beneficial [43]. The levels of catecholamines and growth hormone (GH) increase immediately after sprint. They activate hepatic glucose production and inhibit glucose uptake in skeletal muscles, thus reducing the risk of post-exercise hypoglycaemia [44, 45]

It seems that in terms of glycaemic control with a low risk of hypoglycaemia, resistance exercise or aerobic exercise of high intensity is a good alternative for patients with T1DM [46].

The use of a continuous glucose monitoring (CGM) systems also contributes to the reduction of the risk of hypoglycaemia. Such systems report blood glucose levels in real time and improve patient safety during training by tracking the glucose levels [47].

## Physical exercise in hypoxia

Hypoxia is a state in which oxygen is available to tissues, organs, or the whole body in insufficient amounts

to maintain adequate homeostasis. This condition can occur due to physiological and pathological causes. In high-mountain conditions, at over 2000 metres above sea level, a decrease in haemoglobin oxygen saturation occurs due to a decrease in the barometric pressure and the partial pressure of oxygen in the blood [48].

This physiological response was initially applied mainly to the training of athletes, pilots, and mountain climbers to adapt to altitude and improve their performance by enhancing erythropoiesis [49]. At the time, training was performed under natural conditions during group meetings, mostly at 1500–2500 metres above sea level.

According to some data, being under moderate hypoxia ( $\leq 2500$  m above sea level) can have a beneficial effect on the cardiovascular system by reducing the risk of myocardial infarction and stroke. Studies found that people living at higher altitudes had lower blood pressure and LDL-C levels than those living in low-altitude areas [50, 51]. Cardiovascular and respiratory benefits are also obtained under artificial hypoxia combined with exercise not only in healthy individuals but also in patients with cardiovascular and respiratory diseases. Due to its inhibitory effect on appetite caused by increasing serotonin and leptin levels, hypoxia combined with exercise is used in obesity treatment programs [52].

For wider use of training under hypoxia, it is possible to induce it artificially in a normobaric hypoxic room, in which the barometric pressure is not changed as opposed to the oxygen content in the air, which then consists of 15.4% oxygen and 84.5% nitrogen. These values correspond to the conditions at around 2,500 meters above sea level. However, the atmospheric pressure remains unchanged [14].

Currently, such rooms are also commercially available in sports facilities, including gyms. Training under normobaric hypoxia leads to the production of hypoxia-inducible factor HIF-1 $\alpha$ , which is a modulator of cellular and systemic responses to hypoxia. HIF-1 regulates changes in the expression of over 100 genes responsible for muscle hypertrophy or blood glucose stability. HIF-1 $\alpha$  is a key regulator of metabolism, erythropoiesis, angiogenesis, and apoptosis [53].

Adequate exposure time and training type are crucial factors determining the activation of adaptive mechanisms to hypoxia. Currently, hypoxia and its use in medicine are of increasing interest. However, no clear guidelines are available for the management of particular diseases [54].

Under hypoxia, induction of HIF-1 leads to the increased expression of vascular endothelial growth factor (VEGF), which is a potent angiogenic molecule. VEGF stimulates endothelial cell proliferation and differentia-



tion, prevents apoptosis of muscle and endothelial cells, and regulates vasodilatation.

Impaired pro- and anti-angiogenic mechanisms underlie immune diseases, carcinogenesis, and neovascularisation disorders, such as retinopathy and nephropathy. However, the literature data on the role of VEGF in patients with diabetes are inconsistent. In patients with T1DM, the severity of late complications is often associated with increased VEGF levels (diabetic retinopathy). In turn, VEGF deficiency may be related to impaired formation of collateral circulation in chronic coronary syndrome [55]. Diabetes can co-exist with increased angiogenesis (proliferative retinopathy and the vascular wall, which potentially causes destabilisation of the atherosclerotic plaque) and impaired neovascularisation, which translates into impaired healing of diabetic ulcers [56]. This phenomenon is defined as the “angiogenic paradox”. Long-term T1DM is associated with reduced skeletal muscle capillarity and deregulation of complex angiogenesis pathways, which can be abnormally enhanced or insufficient in different organs of the same individual [57].

With the decrease in oxygen concentration in the body, the concentration of nitric oxide (NO) increases, and activation of nitric oxide synthase occurs, which results in vasodilation. When another stimulus in the form of physical exercise is added, a synergistic effect known as compensatory vasodilation is observed. The resulting reduction in blood pressure and vascular stiffness as well as vasodilation are more strongly expressed compared to training in normoxia [58]. Exercise in hypoxia can also decrease serum levels of pro-inflammatory cytokines, including tumour necrosis factor alpha (TNF- $\alpha$ ), thus contributing to a reduced risk of cardiovascular complications in patients with T1DM [59, 60].

## Benefits of exercise in hypoxia in healthy individuals and patients with T1DM

### *Impact of hypoxia on glycaemia*

The percentage of patients with type 2 diabetes and obesity is lower in high-altitude populations. Long-term exposure to high altitude may decrease glucose levels in people living in low-altitude areas. In turn, it may increase in people from high altitudes when they start living in low-altitude areas [61]. The impact of exposure to high altitude on glycaemia in healthy individuals and patients with diabetes depends primarily on the degree of hypoxia and its duration. Severe hypoxia associated with high altitude leads to increased insulin resistance, while moderate hypoxia improves insulin sensitivity. Among individuals living 1500 m above sea level (moderate altitude meeting the criteria

for moderate hypoxia), lower fasting glucose and better glucose tolerance were reported compared to people living in low-altitude areas. These individuals also presented with the co-occurrence of higher glucagon levels and low blood glucose levels, which may indicate lower hepatic glucagon sensitivity, resulting in decreased glycogenolysis, thus affecting glycaemic control [62]. Because blood glucose concentration is tightly regulated by insulin, lower glycaemia in high-altitude residents can be due to higher plasma insulin concentrations. In addition, higher insulin sensitivity was reported, which may be partly explained by increased adiponectin levels under conditions of moderate hypoxia [63].

HIF-1 $\alpha$ , activated under hypoxic conditions, is responsible for activating GLUT4 translocation to muscle cell membranes independently of muscle activity. It allows more efficient glucose uptake from the blood and improves impaired glucose metabolism [64]. HIF-1 $\alpha$  also stimulates glycolysis through an activating effect on glycolytic enzymes (hexokinase, phosphofructokinase, and pyruvate kinase) [65]. In the cytoplasm, glucose is converted to pyruvate by glycolysis. It is catabolised in the mitochondria by the tricarboxylic acid (TCA) cycle and oxygen-dependent mitochondrial oxidative phosphorylation (OXPHOS). Unlike oxidative phosphorylation, oxygen-deprived cells convert pyruvate to lactic acid, which is a less energy-efficient metabolism. In response to hypoxia, HIF-1 $\alpha$  also induces the expression of pyruvate dehydrogenase kinase (PDK), which is an important mitochondrial enzyme. By inhibiting pyruvate dehydrogenase, which is a key regulator of oxidative phosphorylation, PDK blocks the conversion of pyruvate to acetyl coenzyme A (acetyl-CoA), thus preventing its entry into the TCA cycle, which reduces oxygen consumption by the mitochondria. HIF-1 $\alpha$  modulates key metabolic pathways to optimise glucose and oxygen utilisation under hypoxic conditions [66].

Regular high-intensity interval training (HIIT) has been shown to increase the levels of glycolysis, glycogenesis, and lactate transport proteins in skeletal muscle [67]. As a result, the body is adapted to anaerobic conditions, stable peri-training glycaemic control, and a more rapid metabolism of lactic acid [10]. The exact cause of the metabolic changes occurring during HIIT is not fully understood. However, it is associated with HIF-1 $\alpha$  activated by tissue hypoxia during vigorous-intensity exercise [66].

### *Impact of exercise under hypoxia on glycaemia*

There are few studies on training under hypoxia in patients with T1DM. In one study on this group of patients, a single 40-min moderate-intensity exercise session (RPE range: 4–7) under hypoxia was associated with more stable glycaemic control immediately and up

to 24 h after training compared to the same exercise under normoxia [68].

The beneficial effect on glycaemia under hypoxia is due to the activating effect of HIF-1 on glycolysis and glucose transporters. In addition, the increased production of NO during exercise in hypoxia may be important, which may enhance insulin uptake from the injection site through more dilated blood vessels, and it can result in increased blood flow through contracting muscles due to compensation for reduced oxygen concentration in the blood [15].

Another study analysed the effects of 2 types of exercise in patients with T1DM performed once only in hypoxia and normoxia. The training included 40-min aerobic exercise of moderate intensity (RPE range: 4–7) and intermittent high-intensity interval training (I-HIIT) (RPE range: 8–10). Exercise of moderate intensity led to a post-exercise safe decrease in glucose levels irrespective of the oxygen level in the room. In the high-intensity exercise group, a significant post-exercise decrease in glucose level was obtained only under hypoxia, which suggests a beneficial effect of hypoxia on glycaemia related to resistance training, which is associated with a tendency towards hyperglycaemia [59]. A lowering effect on blood glucose level was also found in a 6-week study in which patients with T1DM with low baseline physical activity underwent mixed aerobic and resistance training sessions under hypoxic or normoxic conditions conducted twice a week for 60 min. Training under hypoxia (2500 m above sea level) resulted in more stable glycaemia during and after training, a lower need for insulin reduction before training, and a lower tendency to hypoglycaemia compared to training under normoxia. In addition, training under such conditions was safe and did not lead to right ventricular dysfunction, as confirmed by echocardiography [14].

Hypoxia in combination with physical training seems to be good and safe for patients with T1DM, especially due to more stable glycaemia during and after exercise.

### ***Impact of exercise under hypoxia on hypertrophy, muscle strength, and $VO_2$ max***

Due to years of exposure to hyperglycaemia, patients with T1DM are at increased risk of developing complications. Apart from typical locations, such as the kidneys, retina, peripheral nerves, heart, and great vessels, complications can also be related to muscle tissue, which leads to muscle atrophy and reduced muscle strength. Muscles are the largest reservoir of protein in the body, which can be used as a source of energy in catabolic states. Maintaining proper muscle function and regeneration is crucial for preventing metabolic

disorders and providing energy to vital organs under stress [69].

Many factors play a role in the development of diabetic myopathy. These include hyperglycaemia and excessive activation of the polyol pathway, protein glycation, decreased insulin expression, impaired GH/insulin-like growth factor (IGF-1) axis, as well as increased glucocorticoid and IL-6 levels [70]. IGF-1 is the main factor controlling muscle growth and efficient functioning of the neuromuscular system. With age and in patients with T1DM, a reduced expression of IGF-1 is found. Additionally, an impaired IGF-1/IGF binding protein (IGF BP) ratio is reported, which translates into reduced levels of free, bioavailable IGF-1 and the loss of muscle mass and strength [71]. IGF-1 activated by HIF-1 $\alpha$  is responsible for controlling muscle growth and plays a vital role in maintaining the normal function of the neuromuscular system [72].

In patients with T1DM, reduced expression and levels of IGF-1, which is an essential autocrine and paracrine factor, are associated with progressive neuropathy and muscle atrophy [73].

Training under hypoxia contributes more significantly to an increase in IGF-1 expression compared to training under normoxia, which leads to a more efficient myocyte formation [74].

Exercise in moderate hypoxia additionally induces adaptive and regenerative mechanisms occurring in muscles. Studies have confirmed the increase in the activity of oxidative enzymes (e.g. citrate synthase), mitochondrial density, the ratio of capillaries to muscle fibres, and the cross-sectional area of fibres [75]. Therefore, training under hypoxia increases the level of performance ( $VO_{2max}$ ). In addition, under hypoxia, the number of insulin receptors in skeletal muscle increases, the function of these receptors improves, and the number of cellular glucose transporters also increases, thus contributing to increased glucose uptake from the blood [76].

### ***Impact of exercise in hypoxia on lipid and endocrine metabolism and bone turnover***

Exercise in hypoxia performed by obese individuals allows for effective fat reduction, and it significantly improves the lipid profile [77]. Improvement in the lipid profile was found in participants of high-altitude mountaineering expeditions, which showed that even short stays at high altitudes (> 4000 m) can lead to beneficial health effects [78]. Blood concentrations of total cholesterol (TC), LDL-C, and TG decrease after prolonged exposure to high altitude, while high-density lipoprotein (HDL-C) levels increase [79].

In people living in low-altitude areas, appetite and food intake decrease after exposure to high altitude,

while basal metabolism increases. This phenomenon, known as “high-altitude anorexia”, results from the effect of hypoxaemia on the concentrations of hormones that regulate feelings of hunger and satiety. Reduced oxygen concentration results in increased leptin, glucagon-like peptide 1 (GLP-1), peptide YY, and pancreatic polypeptide (PP) and decreased ghrelin levels [80].

Exercise under hypoxia improves the blood’s ability to transport oxygen by increasing the plasma volume and red blood cell production induced by an increase in erythropoietin (EPO) concentration. After exposure to hypoxia, EPO concentration increases within 1.5–2 h, reaching maximum values within 48 h, and then decreases despite the sustained hypoxic stimulus. In spite of the rapid decrease in EPO concentration, erythropoiesis is not inhibited, which indicates that a slight increase in EPO is sufficient for effective erythropoiesis under chronic hypoxia [81].

In T1DM patients, osteoporosis and osteopaenia occur significantly more frequently than in the healthy population. Bone remodeling occurs mainly with the involvement of osteoblasts and osteoclasts. Osteoporosis develops when bone resorption induced by osteoclasts is greater than its formation by osteoblasts.

Studies found a correlation between reduced IGF-1 levels and reduced bone density on densitometry in patients with T1DM. The most important factors contributing to osteoporosis include insulin and IGF-1 deficiency, hyperglycaemia, frequent episodes of metabolic acidosis, and dyslipidaemia [82]. Insulin and IGF-1 produced in the liver under the influence of GH show anabolic effects in the bone. They contribute to the proliferation of osteoblast precursors, chondrocytes, and other components of the bone matrix [83, 84]. During training under hypoxia, IGF-1 concentrations increase significantly, which may help improve bone mineral density and prevent bone resorption [85, 86].

## Conclusions

Regular physical activity in patients with T1DM shows some benefits, including better glycaemic control and a reduced risk of late complications of diabetes and comorbidities. It also improves fitness and physical performance.

In terms of glycaemic control with a low risk of hypoglycaemia, resistance exercise or high-intensity aerobic exercise is a good alternative for patients with T1DM. Combining conditions of controlled hypoxia with adequate physical training seems to be a good and safe solution for patients with T1DM, mainly due to more stable glycaemia during and after training sessions and a lower risk of hypoglycaemia.

HIF-1, produced under hypoxia, has beneficial effects not only on glycaemic control but also on lipid parameters, vascular endothelium, and muscle structure and function. It improves physical performance as measured by  $VO_{2max}$  and reduces the risk of osteoporosis.

Of note, during training, regardless of oxygen concentration in the room, peri-training glycaemia and the risk of hypoglycaemia depend on many factors, including pre-exercise glucose levels, injection site, the amount of insulin administered, the composition and size of the pre-training meal, and the duration and intensity of exercise in patients with T1DM. Therefore, reliable patient education is crucial for training to be effective and safe.

Evaluation of the impact of the type of training, its intensity, and the conditions under which it should be conducted (hypoxia/normoxia) on glucose requirements during and after exercise, the risk of exercise-induced hypoglycaemia, and the development of late complications in patients with T1DM are important directions for future research.

## Author contributions

P.N. — preparation of the manuscript; D.R. — critical reading, preparation of the manuscript; M.W. — critical reading, preparation of the manuscript, systematic review, revision of the manuscript; A.G. — revision of the manuscript; S.R. — analysis of current knowledge about the main topic; D.S. — was involved in revising the manuscript critically for important intellectual content; D.K. — analysis of current knowledge about the main topic; B.M. — revising the manuscript critically for important intellectual content; K.S. — systematic review, revision of the manuscript

## Conflict of interest

The authors declare no conflict of interests.

## Funding

None.

## Acknowledgments

The authors wish to thank Arkadiusz Badziński, DHSc, authorised medical interpreter and translator, for translating this paper.

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