HUMAN MOVEMENT
2014, vol. 15 (3), 171–176

AN ASSESSMENT OF EXERCISE TOLERANCE IN NORMOBARIC HYPOXIA
OF PATIENTS WITH DIABETES MELLITUS TYPE 1

doi: 10.1515/humo-2015-0008

BARBARA GŁUCHOWSKA, ALEKSANDRA ŻEBROWSKA*, TOMASZ KAMIŃSKI
Department of Physiological-Medical Sciences, the Jerzy Kukuczka University of Physical Education, Katowice, Poland

ABSTRACT
Purpose. Physical activity is an integral part of the treatment of diabetes. The aim of the study was to assess aerobic capacity and cardiovascular-respiratory reactions to a single physical exercise with gradually increasing intensity in normobaric hypoxia in patients with Type 1 diabetes. Methods. The study was conducted on a sample of adults with Type 1 diabetes (GT1D, n = 13) and a randomly chosen healthy control (GK, n = 15). The study participants performed a progressive exercise test to exhaustion in normoxia (FiO₂ ~ 20.90%) and 7 days later in normobaric hypoxia (FiO₂ ~ 15.14%). At rest, during exercise, and after completion of the test blood was drawn and physiological indicators were monitored. Results. Two-way ANOVA revealed a significant effect of hypoxia and physical exercise on blood glucose concentrations (F = 6.1 p < 0.01). In GT1D, lower glucose levels were observed in normobaric hypoxia compared with baseline and post-exercise levels in normoxia (p < 0.05). A tendency to increased maximal oxygen uptake and significantly higher minute pulmonary ventilation was observed in both groups in response to exercise and hypoxia. Conclusions. Physical activity and hypoxia may effectively control glucose homeostasis and increase cardiorespiratory adaptation to exercise in Type 1 diabetics.

Key words: Type 1 diabetes, hypoxia, exercise tolerance

Introduction

Diabetes mellitus type 1 (T1D) is a chronic metabolic disorder characterized by hyperglycemia resulting from abnormalities in insulin secretion [1–3]. The underlying disease is the autoimmune destruction of pancreatic β cells in the islets of Langerhans, often completely halting the production of insulin [1, 4]. An integral part of the treatment of diabetes is physical activity [5, 6]. Regular exercise is known to improve carbohydrate metabolism, increase adiponectin levels, increase the concentration of high-density lipoproteins (HDL), as well as initiate a decrease in the concentration of proinflammatory cytokines, including C-reactive protein (CRP) and interleukin 6 (IL-6) [7–11]. Such favorable metabolic effects may reduce the risk of cardiovascular events and the need for exogenous insulin [12]. Although the literature generally indicates that the beneficial effects of physical activity, there is evidence that it may increase the risk of glycemic disorders and health complications in some patients [13]. Moreover, some studies have indicated decreased hemodynamic response to physical exertion compared with healthy controls. Impaired hemodynamic response limits blood flow to muscle, reducing oxygen and nutrient supply and slowing the removal of excretes, which leads to decreased exercise capacity in diabetics. As a result, diabetic patients find it difficult to engage in regular physical activity [14].

As a way to improve the exercise capacity of healthy individuals as well as increase the therapeutic value of physical activity, studies have been performed on the impact of breathing air with reduced oxygen content. This had led to the development of training methods for healthy subjects in an environment with either reduced oxygen concentration (normobaric hypoxia) or at lower partial pressure of oxygen (hypobaric hypoxia) [15, 16]. The positive metabolic effects of physical activity performed in hypoxic conditions (oxygen deficiency in tissue) have also been analyzed in populations with diabetes mellitus type 2 (T2D) [17–19]. In the studies mentioned above, it was demonstrated that hypoxia and contraction of skeletal muscles stimulates glucose uptake, which may indicate an additive effect of both factors. The improvement in exercise tolerance in healthy individuals and the beneficial effects in patients with T2D as a result of hypoxic conditions encouraged the present authors to further study the impact of exercise and hypoxic conditions on various physiological responses in patients with T1D.

Therefore, the aim of this study was to assess aerobic capacity, cardiopulmonary function, and blood glucose levels as a response to exercise to hypoxic and normoxic conditions in an individuals with T1D and a healthy control.

Material and methods

The study recruited adult male and female with diabetes mellitus type 1 for approximately 12 years (GT1D). A control group consisted of 15 randomly chosen healthy
individuals with normal blood glucose levels (CG). Inclusion criteria for the GT1D group included a physical examination, a glycated hemoglobin value below 8% (HbA1c < 8%), and good exercise tolerance. Throughout the study the participants received continuous medical supervision. The study design was approved by the Bioethics Committee for Scientific Research of the Jerzy Kukuczka University of Physical Education in Katowice, Poland.

Body composition was assessed by bioelectrical impedance using an InBody 220 analyzer (Biospace, Korea). The anthropometric characteristics and HbA1c of both groups are presented in Table 1.

All participants performed two exercise tests where intensity was gradually increased. The order of testing was randomized. The second exercise test was performed no sooner than 7 days after the first test. Prior to testing, heart rate (HR), predicted maximum heart rate (HRmax = 220 – age), and arterial blood pressure (BP) were measured. The progressive exercise test was performed on a Sport Excalibur ergometer (Lode, Netherlands) in normoxia (ExNo) with a fractional concentration of inspired oxygen of 20.9% at a partial pressure of 990 hPa and in normobaric hypoxia (ExHy; FiO2 ~ 15.1%, p ~ 990 hPa, respectively). Hypoxic conditions were produced in a hypobaric chamber (Lowoxygen System, Poland) simulating an altitude of 2500 m.a.s.l. Test measures in normoxia and hypoxia included BP, HR in order to determine HRmax during the exercise test, and spirometric and gasometric indicators using a Metalyzer 3B-2R metabolic gas analysis system (Cortex, Germany).

The test began after a 3 min warm-up, after which the load was increased by 30 W every 3 min until reaching maximal oxygen uptake (VO2max) and the respiratory quotient (RER) exceeded 1.1.

Venous and capillary blood was drawn before (at rest), during, and 5 min after (post-exercise) each test in normoxia and hypoxia to measure blood cell counts, blood lactate (Biosen C-Line, EKF Diagnostics, Germany), blood gas tension, and acid–base balance (RapidLab 348, Bayer Diagnostics, Germany). Glucose concentrations were also measured using capillary blood (Glucose 201+, HemoCue, Denmark). The D-max method was used to predict the anaerobic threshold based on the recorded blood lactate levels [20].

The obtained data were statistically analyzed using Statistic ver. 10.0 (Statsoft Polska, Poland). Basic descriptive statistics were calculated and repeated measures analysis of variance (rANOVA) was performed. The significance of the differences between group means was assessed with the post hoc Bonferroni correction. All results are presented as mean (M) ± standard error (SE); statistical significance was set at p < 0.05.

Results

The participants with type 1 diabetes (GT1D) were similar to the controls (CG) for body mass and composition. All were found with normal BMI and percentage body fat (Table 1). Both the prolonged period (12.2 ± 2.3 years) and glycated hemoglobin levels indicate the diabetic status of the participants. It should be noted that 71% were found with HbA1c levels above the established range as recommended by the American Diabetes Association (HbA1c < 7.0%).

Tolerance to maximal exercise in different oxygen concentrations (ExNo vs. ExHy) was performed by analyzing the recorded blood counts and biochemical and physiological (cardiopulmonary) measures. The results are presented in Tables 2 and 3.

ANOVA did not reveal any significant effects of hypoxia on rest and post-exercise red blood cell (RBC), hemoglobin (HGB), and hematocrit (HCT) levels. A significant effect of hypoxia was observed on white blood cell (WBC) (F = 80.2, p < 0.0001), showing a tendency for higher values after exercise in normobaric hypoxia. Repeated measures ANOVA identified significant interaction effects for test condition (ExNo and ExHy) and measurement phase (at rest, exercise, post-exercise recovery) on blood oxygen tension (pO2; F = 27.8, p < 0.0001) and carbon dioxide tension (pCO2; F = 7.5, p < 0.01). Lower capillary pO2 and pCO2 levels were noted in post-exercise hypoxia measures compared with peri-exercise levels measured in normoxia for both GT1D (p < 0.001) and CG (p < 0.001). Glucose concentrations measured before the exercise test (at rest) were higher in GT1D (p < 0.001) as were the concentrations measured during exercise at maximum intensity and post-exercise recovery when compared with the CG (Table 2). ANOVA indicated significant interaction effects for group (GT1D vs. CG) and test condition (ExNo vs. ExHy) on glucose concentration (F = 6.1; p < 0.01).

| Variable          | GT1D | CG |
|-------------------|------|----|
| **M ± SE**        |      |    |
| Age (years)       | 30.1 ± 2.8 | 24.0 ± 1.5 |
| Body mass (kg)    | 74.8 ± 3.5 | 70.7 ± 2.3 |
| Body height (m)   | 1.8 ± 0.0  | 1.7 ± 0.0  |
| BMI (kg/m²)       | 24.0 ± 0.9 | 23.1 ± 0.6 |
| PBF (%)           | 18.9 ± 2.3 | 16.9 ± 1.5 |
| BFMI (kg)         | 14.2 ± 2.0 | 11.9 ± 1.1 |
| FFM (kg)          | 60.5 ± 3.2 | 58.8 ± 2.1 |
| HbA1c (%)         | 7.2 ± 0.2  | n.a. n.a.  |
| Duration of T1D (years) | 12.2 ± 2.3 | n.a. n.a.  |

BMI – body mass index, PBF – percentage body fat, BFMI – body fat mass, FFM – fat-free body mass, HbA1c – glycated hemoglobin, n.a. – not applicable.
Table 2. Biochemical indicators in normoxia and normobaric hypoxia for GT1D and CG

| Indicator          | GT1D            | CG              | GT1D            | CG              |
|--------------------|-----------------|-----------------|-----------------|-----------------|
|                    | Normoxia (M ± SE) | Hypoxia (M ± SE) | Normoxia (M ± SE) | Hypoxia (M ± SE) |
| RBCmax (10^6/mm³)  | 5.4 ± 0.3       | 5.3 ± 0.2       | 6.0 ± 0.2       | 5.5 ± 0.1       |
| HGBmax (g/dl)      | 16.0 ± 0.8      | 15.9 ± 0.5      | 17.9 ± 0.5      | 16.4 ± 0.3      |
| HCTmax (%)         | 48.7 ± 2.9      | 46.8 ± 1.7      | 53.5 ± 1.8      | 48.3 ± 1.1      |
| WBCmax (10³/mm³)   | 7.1 ± 1.1       | 8.7 ± 0.9       | 9.2 ± 0.7       | 9.8 ± 0.5       |
| pO2max (mmHg)      | 86.5 ± 1.6      | 62.8 ± 1.8**    | 87.3 ± 1.5      | 60.2 ± 2.0**    |
| pCO2max (mmHg)     | 33.4 ± 1.2      | 29.0 ± 1.0**    | 33.1 ± 1.1      | 29.1 ± 0.9**    |
| pHmax              | 7.3 ± 0.0       | 7.3 ± 0.0       | 7.3 ± 0.0       | 7.3 ± 0.0       |
| GLUpre (mg/dl)     | 189.0 ± 16.8    | 162.4 ± 12.8**  | 92.9 ± 15.6     | 92.5 ± 12.0     |
| GLUmax (mg/dl)     | 167.8 ± 16.9    | 141.4 ± 11.3*   | 91.1 ± 15.7     | 92.4 ± 10.6     |
| GLUpost (mg/dl)    | 155.8 ± 16.0    | 141.4 ± 11.2    | 96.9 ± 14.9     | 87.3 ± 10.4     |

RBC – red blood cell count, HGB – hemoglobin count, HCT – hematocrit level, WBC – white blood cell count, pO2 – partial pressure of oxygen in blood, pCO2 – partial pressure of carbon dioxide in blood; pre – measured at rest before exercise, max – measured immediately after exercise, post – measured 5 min after exercise; *p < 0.05 and **p < 0.001 indicate statistically significant differences between normoxic and hypoxic conditions.

Table 3. Cardiopulmonary indicators in normoxia and normobaric hypoxia for GT1D and CG

| Indicator          | GT1D            | CG              | GT1D            | CG              |
|--------------------|-----------------|-----------------|-----------------|-----------------|
|                    | Normoxia (M ± SE) | Hypoxia (M ± SE) | Normoxia (M ± SE) | Hypoxia (M ± SE) |
| VO2max (ml/kg/min) | 40.3 ± 2.8      | 43.9 ± 2.4      | 45.4 ± 2.3      | 46.4 ± 2.1      |
| VO2res (ml/kg/min) | 18.6 ± 1.4      | 23.5 ± 1.7**    | 20.5 ± 1.2      | 21.1 ± 1.4      |
| Pmax (W)           | 216.9 ± 12.0    | 207.7 ± 9.2     | 230.0 ± 11.1    | 218.0 ± 8.6     |
| LAmmax (mmol/l)    | 9.2 ± 0.8       | 9.4 ± 0.8       | 9.4 ± 0.5       | 9.3 ± 0.5       |
| LAprompt (mmol/l)  | 8.8 ± 1.0       | 10.3 ± 0.8      | 8.9 ± 0.6       | 10.1 ± 0.5      |
| LAT (W)            | 153.7 ± 10.6    | 145.9 ± 8.2     | 156.0 ± 9.9     | 140.3 ± 7.6     |
| VEmax (l/min)      | 101.6 ± 7.2     | 120.8 ± 7.0**   | 102.3 ± 6.2     | 121.9 ± 6.0**   |
| VPost (l/min)      | 54.8 ± 3.7      | 64.4 ± 3.8      | 50.6 ± 3.2      | 61.1 ± 3.3*     |
| VE/VO2max          | 33.6 ± 1.8      | 35.7 ± 1.6      | 31.8 ± 1.6      | 36.5 ± 1.3      |
| VE/VO2res          | 36.7 ± 2.2      | 38.4 ± 3.1      | 34.2 ± 1.8      | 40.1 ± 2.6*     |
| HRpre (1/min)      | 88.0 ± 4.2      | 81.4 ± 4.0      | 86.3 ± 3.9      | 81.8 ± 3.8      |
| HRmax (1/min)      | 177.8 ± 3.2     | 177.5 ± 3.1     | 183.0 ± 3.0     | 180.6 ± 2.9     |
| HRPost (1/min)     | 143.8 ± 3.1     | 143.8 ± 3.7     | 136.9 ± 2.9     | 140.5 ± 3.4     |
| VO2/HRmax (ml)     | 16.3 ± 1.2      | 18.1 ± 1.3      | 17.0 ± 1.0      | 17.9 ± 1.1      |
| VO2/HRPost (ml)    | 9.5 ± 0.8       | 12.0 ± 1.0**    | 10.4 ± 0.6      | 10.6 ± 0.8      |
| RERmax             | 1.2 ± 0.0       | 1.1 ± 0.0       | 1.1 ± 0.0       | 1.0 ± 0.0       |

VO2 – oxygen consumption, P – power, LA – blood lactate concentration, LAT – lactate threshold, VE – minute ventilation, VE/VO2 – ratio of maximum minute ventilation to oxygen uptake, HR – heart rate, VO2/HR – ratio of oxygen uptake to heart rate (oxygen pulse), RER – respiratory quotient; pre – measured at rest before exercise, max – measured in the last minute of the exercise test, post – measured 5 min after exercise; *p < 0.05 and **p < 0.001 indicate statistically significant differences between normoxic and hypoxic conditions.

showed a significant reduction in post-exercise blood glucose levels in ExHy (p < 0.05) (Table 2). No statistically significant effect was found for hypoxia on maximal oxygen uptake. Instead, GT1D was found with increased oxygen uptake 5 min after the exercise test was finished in ExHy compared with ExNo (p < 0.01). The participants in both groups showed a tendency for lower lactate threshold (LAT) and maximal power (Pmax) values in ExHy compared with ExNo, although the differences were not statistically significant. ANOVA also showed significant interaction effects with test condition (ExNo vs. ExHy) and group (GT1D vs. CG) on maximum minute ventilation (VEmax; F = 21.1, p < 0.0001), heart rate (HRmax; F = 4.1; p < 0.05), blood lactate concentration...
Disclosure of Cardiopulmonary Variables

Post-hoc analysis on the analyzed respiratory and cardiopulmonary variables confirmed the higher values of VEmax during maximal exercise in ExHy than ExNo for both GT1D and CG (p < 0.001). In GT1D, a significantly greater post-exercise oxygen pulse (VO2/Hr; p < 0.01) was noted in ExHy compared with ExNo (Table 3).

**Discussion**

Physical activity is an essential component of diabetes management. According to the latest recommendations, diabetics without vascular complications should participate in regular physical activity [21]. The primary goals are effective control of blood glucose (glucoregulatory control), lipids, and blood pressure as well as increasing exercise tolerance. Despite the well-documented health benefits of physical activity and being aware of the risks of hypo- or hyperglycemia, it is possible that lowered exercise capacity may be one of the factors reducing the motivation of diabetics to perform regular exercise [14].

The aim of the present study was to assess the therapeutic value of physical activity performed in an environment with reduced oxygen content by assessing cardiopulmonary response and glycemic levels in T1D patients. The findings showed a significant reduction in the blood glucose concentrations of the T1D group as a result of hypoxia. Noteworthy is the impact of reduced oxygen content of inspired air, inducing hypoxia (or a shortage of oxygen in tissue) on lower blood glucose levels during exercise with gradually increasing intensity. However, during exercise in hypoxic conditions (ExHy) a tendency of increased oxygen consumption was noted, although paired with statistically significant increases in maximum minute ventilation, heart rate, and high values of maximal power in this group of T1D patients.

There exists plenty of evidence confirming the beneficial effects of hypoxia on the physical performance of healthy individuals [16]. The positive responses of hypoxia-inducible factor-1 (HIF-1) include increased blood oxygen capacity, improved buffering capacity of blood and pulmonary ventilation, and a reduction in the sympathetic response to stress associated with physical effort and/or increased parasympathetic activity [22, 23]. Attention needs to be paid to the fact that the beneficial effects observed in healthy individuals have been found to depend on proper training, i.e., the intensity, volume, and type of physical activity and, above all, the intensity of duration of the hypoxic intervention [16].

Disorders of the mechanisms of adaptation to hypoxia may lead to adverse changes in respiratory, cardiovascular, or nervous system function [24]. Hypoxia may also increase the risk of myocardial ischemia, endothelial dysfunction as a result of the modulation of growth factors, proinflammatory cytokine production, or oxidative stress. The literature does have reports that nonetheless suggest short-term hypoxia and/or moderate exercise may prevent the negative effects mentioned above of hypoxia [25].

The benefits of exercise in simulated high-altitude conditions in the case of patients requires further study on the influence of additional factors determining cardio-vascular function, the risk of anemic hypoxia, or within the general concept of glycemic control. Glycated hemoglobin is known to provide a retrospective overview of blood glucose levels while also serving as a risk marker of the long-term complications of diabetes. Mean HbA1c for the group of T1D patients was above the levels outlined by the American Diabetes Association (HbA1c < 7.0%) [21]. However, most showed on-target glycemic control and only a small percentage of the participants had HbA1c values above 7.5%. Of note is the lack of improvement in red blood cell count in response to the progressive exercise test in hypoxia, indicating that this factor was not responsible for increasing blood oxygen capacity. O2 content in a hypobaric chamber simulating 2500 m.a.s.l. appears to provide a sufficient stimulus to increase muscle aerobic capacity [26]. The literature suggests that the lack of an effect on the number of red blood cells and hemoglobin levels may stem from relatively short exposure to hypoxic conditions. It cannot be excluded that such changes may in fact occur only in the post-exercise recovery period.

Physical exertion is known to induce inflammatory changes in the body and may increase proinflammatory cytokine and leukocyte levels [27]. In the present study, it was observed that the increase in white blood cells during exercise was induced in hypoxic rather than normoxic conditions and may have been the result of the additive effects of both factors and/or what is known as cellular metabolic stress. It may be that the observed stimulation of a post-exercise immune response could be the result of the body adapting to exercise in the more demanding conditions of hypoxia.

Exercise tolerance in the present study was also measured by the use of other indicators, including maximal power in the progressive test and anaerobic threshold. Although the tendency of the response to exercising in hypoxia indicated lower values, these differences were not statistically significant. Both GT1D and CG produced less maximal power (Pmax) in hypoxia than in normoxia (GT1D: 207.7 ± 9.2 vs. 216.9 ± 12.0 W, respectively; CG: 218.0 ± 8.6 vs. 230.0 ± 11.1 W, respectively). In addition, the lactate threshold was lower in both groups in hypoxic conditions. Based on previous results, this suggests that limiting the amount of exercise performed in hypoxic conditions may be associated with nervous system response. The occurrence of hypoxemia, confirmed in the present study by significantly lower partial pressure of oxygen in capillary blood when compared with normoxic conditions, causes a decrease in the supply of oxygen to neurons. These changes during aerobic exercise are known to reduce motor unit recruit-
ment and may be responsible for the reduction in muscle power [28]. Vogiatzis et al. confirmed in a study on athletes that a reduction in cerebral oxygen delivery during hypoxia or intense physical exercise may accelerate central nervous system fatigue and lead to decreased exercise tolerance [29]. Earlier studies on energy production in hypoxic conditions concluded that hypoxia may increase the dominance of the anaerobic system to meet the body’s energy demands. Changes in acid–base balance and an increase in the partial pressure of CO2 in the blood stimulate blood chemoreceptors and consequently lead to an increase in minute ventilation. The present study recorded an increase in lactate concentrations at a lower load in hypoxia compared with normoxia. It also demonstrated a significant effect of exercise performed in different oxygen concentrations on the respiratory quotient (RERmax). These observations appear to confirm the studies mentioned above on the significant role anaerobic metabolism in adapting to normobaric hypoxia and possible use of glycolytic processes to adapt to exercise-induced hypoxia in individuals with T1D. One important result was the reduction in post-exercise glucose concentrations in ExHy with no hypoglycemic events reported. These results correspond to those published by Mackenzie et al., who point to the greater role of endocrine and paracrine events on metabolic performance during exercise in hypoxia [17–19].

Conclusions

In conclusion, it should be noted that the patients with type 1 diabetes were found with satisfactory levels of exercise tolerance and good cardiovascular responses to hypoxia. Physical exercise lowered blood glucose concentrations, where the most beneficial effect on glycemic control was by exercise in hypoxic conditions. This was theorized to be the dominance of anaerobic processes and increased transport of glucose to muscle cells stimulated by reduced oxygen supply. The present findings appear to confirm the applicability of normobaric hypoxia in the management of type 1 diabetes. However, caution is urged as administering hypoxia therapy during physical exercise may also trigger certain side effects.

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