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Two weeks of moderate hypoxia improves glucose tolerance in individuals with type 2 diabetes

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Abstract

We previously showed that nightly exposure to moderate hypoxia reduces fasting glucose levels and improves both whole-body skeletal muscle and hepatic insulin sensitivity in individuals with obesity. The goal of this study was to extend this observation in an “at home” setting and determine if nightly exposure to moderate hypoxia improves glucose tolerance in individuals with type 2 diabetes. Eight adults, ages 20–65 years with type 2 diabetes enrolled in our study and slept for 14 consecutive nights at home in a hypoxic tent maintained at 15% O₂ (~2400 m). The primary endpoint was insulin sensitivity (Matsuda Index) calculated from a 75-g oral glucose tolerance test. Secondary endpoints included calculations of insulin secretion and beta-cell function, including the area-under-the-curve (AUC) for glucose and insulin, the Insulinogenic Index, and the Disposition Index. We observed the Matsuda Index trended towards a 29% increase following 14 nights of moderate hypoxia (from 1.7 ± 0.7 to 2.2 ± 1.7 ; $p = 0.06$). Two-hour glucose AUC was significantly reduced from 501 ± 99 to 439 ± 65 mg/dL $\times$ h ($p = 0.01$). We conclude that 14 nights of moderate hypoxia improves glucose tolerance in individuals with type 2 diabetes. Future studies should confirm whether exposure to moderate hypoxia consistently improves glucose homeostasis in larger sample sizes.

Introduction

Adipose tissue hypoxia in obesity results when blood flow to adipocytes does not increase in proportion to adipose tissue expansion thus leading to dysfunction at the cellular level [1]. The production of several adipokines and glucose transporters are altered under cellular hypoxia and results in the development of insulin resistance. Conversely, short-term exposure to moderate altitude hypoxia improves transient insulin sensitivity in individuals

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Author contributions KLM conducted research, interpreted data, and drafted most of the manuscript; FLG provided medical oversight for data collection, interpreted data, and edited the manuscript; JKS conducted research, interpreted data, and edited the manuscript; ER designed study, conducted research, interpreted data, edited the manuscript, and has primary responsibility for final content. All authors approved the final manuscript before submission.

Data availability

The dataset pertaining to the current study is available from the corresponding authors in accordance with appropriate data use agreements and IRB approvals for secondary analyses.

Conflict of interest ER is the inventor of the used technology and is seeking patent protection. FLG has a patent application that is pending for an insulin sensitizer. The remaining authors declare that they have no conflict of interest.

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with type 2 diabetes [2], while more prolonged exposure increases whole-body glucose turnover and utilization in healthy adults [3]. The ability of hypoxia to promote glucose uptake in skeletal muscle via distinct signaling pathways, and independent of insulin action, is similar to how exercise promotes glucose disposal by contraction-stimulated mechanisms [4, 5]. We were the first to report that nightly (continuous) exposure to moderate hypoxia (~2400 m altitude) for 10 consecutive nights in a clinical unit reduced fasting glucose levels and improved both whole-body skeletal muscle (>20% at both low- and high-dose insulin) and hepatic insulin sensitivity in individuals with obesity [6]. Whether continuous exposure to nighttime hypoxia improves glucose metabolism in individuals with type 2 diabetes is unknown. Our objective was to determine if nightly exposure to moderate hypoxia in an “at home” setting improves glucose tolerance in individuals with type 2 diabetes. We hypothesized that individuals with type 2 diabetes would have improved glucose tolerance following 14 nights of exposure to moderate hypoxia.

Materials and methods

Individuals aged 20–65 years with confirmed type 2 diabetes were eligible to participate in the SleepDiabetes study [1] at the Pennington Biomedical Research Center (PBRC). Participants were required to sleep for 14 consecutive nights (7–12 h per night) at home in a hypoxic tent (Hypoxico Inc., New York, NY, USA) maintained at ~15% O₂ (range 14.5–15.5% O₂; ~2400 meters above sea level) by nitrogen dilution. We implemented a multi-stage screening visit paradigm to identify eligible participants with confirmed type 2 diabetes from 2015 through 2018. Type 2 diabetes was confirmed by either having a fasting glucose between 125 and 200 mg/dL or elevated hemoglobin A1c ≥ 48 mmol/mol (or 6.5%). Absence of obstructive sleep apnea was confirmed by a negative outpatient home sleep test, as well as an inpatient sleep monitoring assessment by the Louisiana Sleep Foundation in Baton Rouge, LA. An individual with confirmed sleep apnea was eligible as long as a continuous positive airway pressure (CPAP) device was worn while sleeping. Participants were further excluded if they: (1) had type 2 diabetes < 15 years; (2) had body mass index (BMI) ≥ 55 kg/m²; (3) were taking insulin, sulfonylureas, meglitinides, or glucagon-like peptide-1 (GLP-1) agonists; (4) had previously diagnosed chronic obstructive pulmonary disease or cardiovascular disease; and (5) had a history of altitude sickness. All participants provided written informed consent before participating. The PBRC Institutional Review Board approved the study.

Participants completed inpatient visits at day 0 (baseline, pre-intervention) and day 14 (end of intervention) at PBRC. Body composition was measured on day 0 by dual-energy X-ray absorptiometry (Lunar iDXA, GE Healthcare, Madison, WI, USA), while a 75-g oral glucose tolerance test (OGTT) was conducted on days 0 and 14. Blood samples were collected at –5, 30, 60, 90, and 120 min during the OGTT for measurements of plasma glucose and insulin concentration. Insulin sensitivity was estimated using the whole-body insulin sensitivity index (WBISI), also known as the Matsuda Index [7]: $WBISI = 10,000 / \text{square root of } (Glu_0 \times Ins_0) \times (\text{mean glucose} \times \text{mean insulin during OGTT})$, where Glu₀ and Ins₀ denote baseline glucose and insulin concentrations. Insulin secretion was estimated by the Insulinogenic Index (IGI) calculated from the ratio of increments of serum insulin to glucose measured at 30 min: $I30 / G30 = (Ins_{30} - Ins_0) / (Glu_{30} - Glu_0)$ [8]. Beta-cell function

was also estimated by the Disposition Index (DI) as the product of insulin sensitivity and insulin secretion: Matsuda Index $\times$ IGI. Additional OGTT measures of 2-h glucose area-under-the-curve (AUC) and 2-h insulin AUC were calculated.

Statistical analyses

All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) with a significance level set at $\alpha = 0.05$. Differences between day 0 and day 14 were made using a two-sample paired *t*-test and expressed as raw (unadjusted) mean $\pm$ standard deviation (SD) within the text. We report mean $\pm$ standard error of the mean (SEM) only in Fig. 1.

Results

Eight adults (5 males, 3 females) mean age 49 ± 10 years, weight 117.8 ± 18.6 kg, and BMI 39.6 ± 5.8 kg/m² were enrolled. Mean systolic and diastolic blood pressures were 121 ± 13 mmHg and 74 ± 10 mmHg at baseline, respectively. Mean lipid levels were considered normal at screening, including total cholesterol (<200 mg/dL), LDL (<100 mg/dL), HDL (>50 mg/dL) and triglycerides (<150 mg/dL) [9]. Participants had $43 \pm 8\%$ body fat resulting in 50.5 ± 12.2 kg of fat mass and 67.3 ± 14.0 kg of fat-free mass. As expected, females had significantly higher percent body fat and trunk fat, as well as lower fat-free mass and triglycerides (all $p < 0.05$) compared to males.

Following 14 nights of exposure to moderate hypoxia, 2-h glucose AUC was significantly reduced from 501 ± 99 to 439 ± 65 mg/dL $\times$ h ($p = 0.01$) and a trend towards a significant increase (29%) in Matsuda Index from 1.7 ± 0.7 to 2.2 ± 1.7 ($p = 0.06$) was observed (Fig. 1). A trend towards a significant increase (55%) in Disposition Index from 0.9 ± 1.0 to 1.4 ± 1.7 ($p = 0.09$) was also observed. No differences in hemoglobin A1c, fasting glucose, insulin, or free-fatty acids, as well as 2-h insulin AUC were observed following the intervention. Similar findings were observed following adjustment for sex.

There were two adverse events reported that were not related to the intervention. Specifically, one subject who was taking medication for depression reported feelings of depression (non-serious) prior to baseline assessment. Another subject reported experiencing cold symptoms (non-serious) during the 2-week intervention.

Discussion

Our study shows for the first time that 14 nights of moderate hypoxia improves glucose tolerance in individuals with type 2 diabetes. These findings were expected based on our previous study conducted in an inpatient setting, which demonstrated that only 10 nights of moderate hypoxia was sufficient to significantly improve whole-body insulin sensitivity ($>20\%$) in 10 individuals with obesity (but no diabetes) and especially among those individuals with marked insulin resistance [6]. Collectively, our results provided a strong basis to propose that nightly exposure to moderate hypoxia may provide a new therapeutic avenue to improve carbohydrate metabolism in individuals with prediabetes and type 2 diabetes.

Similar to exercise and skeletal muscle contraction, hypoxia exposure stimulates glucose transport into muscle cells and thus improves insulin sensitivity. Short-term (1-h and 4-h) exposure to moderate hypoxia improves transient insulin sensitivity, as well as reduces glucose concentrations without altering insulin concentrations in individuals with type 2 diabetes. Prolonged exposure to hypoxia (3 weeks at 4300 m) increases whole-body glucose turnover and utilization in healthy individuals [3]. Using isolated, insulin-resistant skeletal muscle of lean and obese females, Azevedo et al. reported two- to three-fold increases in whole-body glucose transport rates when the tissue was exposed to hypoxia for 60 min [5]. We also reported a 62% increase in basal glucose uptake following in vitro muscle tissue exposure to hypoxia (15% O₂ for 4 h) in individuals with obesity [6]. A much lower prevalence of impaired fasting glucose and type 2 diabetes has also been reported at high altitudes in Northern Chile despite relatively high levels of obesity (especially in women) and dyslipidemia [10]. Our findings add to this growing body of evidence, and expand our knowledge to individuals with type 2 diabetes.

Our study had a few limitations. First, our study included a small sample size, which yielded several non-significant, albeit noteworthy improvements in several markers of glucose tolerance with large effect sizes. Second, administration of moderate hypoxia using a hypoxic tent (with a portable generator) is neither convenient nor realistic for large-scale dissemination. Future model designs could include a programmable hypoxic bedroom via modification of heating and cooling units, the installation of a portable temperature-controlled system with hypoxic capabilities, or offering a nitrogen dilution function on a CPAP device. While the administration of hypoxia remains a challenge, our combined studies support the development of a larger scale randomized controlled trial assessing whether hypoxia can be developed into a safe therapeutic tool.

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Fig. 1.

Plasma glucose and insulin across the 2-h OGTT are reported as mean $\pm$ SEM at baseline (day 0) and post-intervention (day 14). Additionally, 2-h glucose AUC (in mg/dL $\times$ h) and 2-h insulin AUC (in μ U/mL $\times$ h) are reported within the *inset*. Insulin sensitivity estimated by Matsuda Index is also reported (unitless)