Hyperbaric oxygen therapy increases insulin sensitivity in overweight men with and without type 2 diabetes

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The authors have no potential conflicts of interest to declare

Introduction

It has been a long-standing observation in hyperbaric medicine that people with diabetes may experience a fall in their blood glucose levels when they undergo hyperbaric oxygen treatment (HBOT). In a recent pilot study of hospital patients with type 2 diabetes, we showed that insulin sensitivity as measured by the hyperinsulinemic euglycemic clamp was increased during the 3rd and the 30th HBOT sessions[1].

The development of insulin resistance is considered to be one of the best predictors of the future development of type 2 diabetes. Obesity is also associated with insulin resistance[2], and both obesity and type 2 diabetes are increasing in prevalence and have become major health issues globally. Obesity-related insulin resistance is closely associated with a chronic low grade inflammatory response within adipose tissue, characterised by immune cell infiltration, altered cytokine production and activation of inflammatory signalling pathways[3].

This study aims to determine whether the insulin-sensitising effect of HBOT can be demonstrated in a relatively healthy urban population including those with and without type 2 diabetes, whether the effect is still measurable after exit from the hyperbaric chamber and whether HBOT-induced changes in insulin resistance are associated with changes in pro-inflammatory cytokines in serum and adipose tissue.

Methods

Participants

Nineteen male volunteers were recruited, aged 45-70 years old with BMI in the range of 24 to 45 kg/m^2, 11 without and 8 with type 2 diabetes (Table 1). Exclusion criteria included anything that could potentially alter insulin response or the inflammatory pathways being investigated, and any contraindications to HBOT. Body composition was measured by Dual-emission X-ray absorptiometry (DXA) scan to calculate fat free mass. One non-diabetic subject was unable to adequately perform middle ear equalization during the first HBOT and took no further part in the study. Data from SS2 were not available for 2 volunteers.

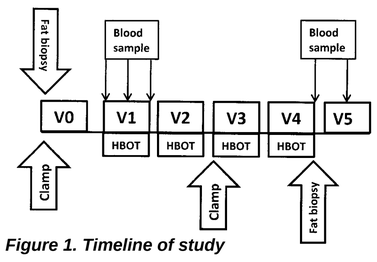

Figure 1. Timeline of study

Study design

Baseline assessments (V0) were performed one week and the following week participants attended the facility for five consecutive days (V1 to V5) after overnight fasting (Figure 1).

HBOT was provided in a multiplace chamber with compression to 2 atmospheres absolute while breathing 100% oxygen via a "hood" for 90-minutes, followed by a linear decompression over 30-minutes.

The 3½-hour hyperinsulinemic euglycemic clamp was performed at baseline visit V0 (80 mU/m^2/min insulin, target BGL 6 mmol/L). The clamp was repeated during visit V3 with the 2-hour HBOT session administered between the 1 and the 3-hour period of the clamp.

Insulin sensitivity was calculated from the glucose infusion rate (GIR) during two separate 30-minute steady state (SS) periods at the end of the 3½-hour clamp. SS1 represented the period 2½ to 3-hours (last 30-minutes of the HBOT) and SS2 with 3 to 3½-hours (first 30-minutes immediately post-HBOT). The GIR was standardized against fat free mass for each volunteer.

Blood samples were taken at 3 time points during the first HBOT at visit V1 - at time zero (pre-HBOT) and at 60 and 120-minutes. Further blood samples were taken at visit V4 (immediately after the 4th HBOT) and visit V5 (24-hours later). Blood samples were analysed for fasting glucose and insulin as well as cytokine markers of inflammation that are known to be associated with insulin resistance.

Abdominal subcutaneous adipose tissue was biopsied at baseline (V0) and visit V4 and analysed for gene expression of inflammatory markers.

Statistics

Differences between groups were analysed using one way ANOVA. Other outcomes were analysed with linear mixed effects models using maximum likelihood estimation. Correlations were analysed by linear regression with coefficient of determination (r^2) and p value. Data were reported as means ± S.D, unless otherwise stated.

Results

Insulin Sensitivity

During SS1, GIR increased by 29±32% in those without (n=10, p=0.01) and by 57±66% in those with type 2 diabetes (n=7, p=0.04, Fig. 2A). The increase in insulin sensitivity was maintained for an additional 30 minutes after exit from the hyperbaric chamber whilst breathing normobaric air in those without diabetes (n=9, p=0.008, Fig. 2B). A trend towards this effect was also seen in the smaller group with type 2 diabetes (n=6, p=0.09, Fig. 2B).

Glucose and Insulin

There were significant reductions in fasting glucose during the first HBOT session at 60 and 120-minutes in those with type 2 diabetes only (Fig. 3A). Serum insulin was reduced during the first HBOT session in both groups (Fig. 3B).

Inflammatory Cytokines

MCP-1 was significantly reduced after HBOT at visits V1 and V4 in those without diabetes (Fig. 3C), but this did not reach statistical significance in those with type 2 diabetes (Fig. 3C). TNF-α was significantly reduced after visit V4 in those without diabetes and this suppression was evident 24-hours later in both groups (Fig. 3D). In contrast, serum IL-6 was elevated in those without diabetes during and after HBOT at visits V1 and V4 (Fig. 3E). The increase in IL-6 from baseline to visit 4 in the group without diabetes correlated with the increase in insulin sensitivity during SS2 (n=9, r^2=.72, p=0.004, Fig. 4).

Adipose tissue was analysed for gene expression of IL-6, MCP-1, TNF-α and IL-1ra, however no significant changes were detected.

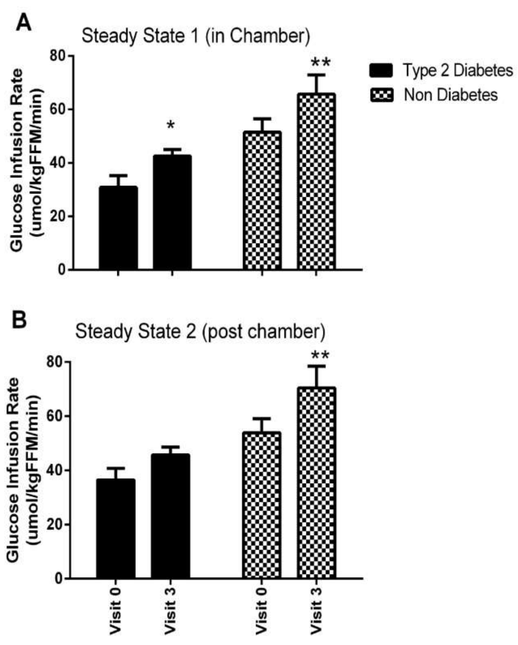

Figure 2: (A) Glucose infusion rate at baseline (V0) vs. HBOT (V3) during Steady State-1 (last 30-min of HBOT) in individuals with and without type 2 diabetes; (B), Glucose infusion rate at baseline vs. HBOT at Steady State-2 (first 30-min after HBOT). (*p<0.05, **p<0.01)

Discussion

HBOT may induce an insulin sensitizing effect by a number of possible mechanisms. Here, we studied circulating concentrations of pro-inflammatory cytokines since these have been observed in obesity and are closely associated with insulin resistance. HBOT has been demonstrated to have anti-inflammatory actions in animal[4] and human[5] studies of disease as well as in the treatment of decompression illness[6].

Other possible mechanisms include adipose tissue hypoxia resulting in adipose tissue dysfunction leading to insulin resistance[7], with HBOT reversing this hypoxia.

Alternatively, the substantial rise in tissue oxygen tensions associated with HBOT will also be accompanied by a transient increase in reactive oxygen species. This warrants further investigation since reactive oxygen species, whilst having the potential to cause cell damage, also act as vital messengers in cell signalling[8], including insulin signalling[9].

Insulin resistance is a pivotal early change in obesity-related type 2 diabetes. The identification of pathways that influence insulin responsiveness may potentially lead to clinical therapies that prevent the development or progression of this disease. This study introduces a pathway that has not previously been exploited. The new findings that HBOT can also increase insulin sensitivity in those without diabetes and also that the effect is sustained for a period after HBOT has implications beyond diabetes involving obesity and glucose metabolism broadly. Further studies are now required to describe the precise mechanisms involved and to define the time course of the insulin sensitising effect – how much HBOT is required to initiate the effect and how long it persists after leaving the hyperbaric chamber.

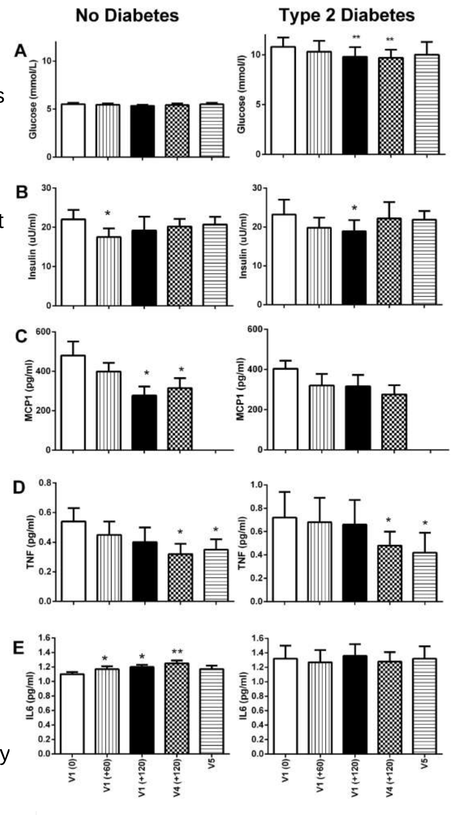

Figure 3: (A) Fasting Glucose; (B) Insulin; (C) MCP-1; (D) TNFα; (E) IL6 concentrations taken prior to and during the first HBOT exposure at 60 and 120 minutes, immediately following the 4th HBOT and 24-hours after the final HBOT (*p<0.05, **p<0.01).

	No Diabetes	Type 2 Diabetes
Number	11	8
Age (years)	59 ± 9	54 ± 6
Weight (kg)	94.4 ± 20.9	99.7 ± 14.1
Body Mass Index (kg/m^2)	31.0 ± 5.3	32.6 ± 3.4
Glucose (mmol/L)	5.4 ± 0.7	10.5 ± 2.9*
HDL (mmol/L)	1.2 ± 0.4	1.1 ± 0.3
LDL (mmol/L)	3.3 ± 0.9	3.2 ± 1.0
Triglycerides (mmol/L)	1.5 ± 0.8	2.9 ± 2.4
Total Cholesterol (mmol/L)	5.2 ± 0.8	5.4 ± 1.2
Body fat percentage (%)	33.7 ± 6.5	35.0 ± 6.3
GIR (umol/kgFFM/min)	53.7 ± 16.6	30.8 ± 11.6*

Table 1: Baseline characteristics of men, stratified by diabetes status (Means ± SD, *p≤0.006).

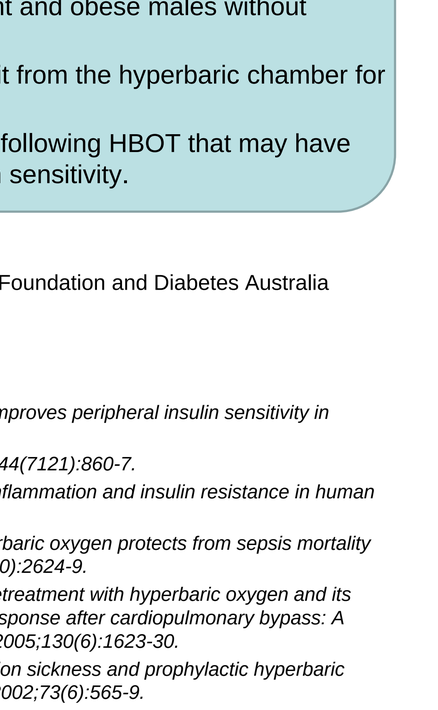

Figure 4: Relationship between the change in insulin sensitivity measured at visit V3 and change in serum IL-6 at visit V4 in non-diabetics (r^2=0.72, p=0.004).

Summary

- Peripheral insulin sensitivity as assessed by hyperinsulinemic euglycemic clamp is increased following HBOT in a relatively healthy urban population sample.
- The increase in insulin sensitivity occurs in overweight and obese males without diabetes as well as those with type 2 diabetes.
- The insulin sensitising effect was maintained after exit from the hyperbaric chamber for at least 30-minutes.
- There were small changes in inflammatory cytokines following HBOT that may have partly contributed to the observed increases in insulin sensitivity.

Funding

This study was funded by grants from the Royal Adelaide Hospital Foundation and Diabetes Australia Research Trust.

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