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Proposal for Research

Investigators

Enoch Huang, MD; Davut Savaser, MD; Chae Bliss, CHT, Jessica Castle, MD; Shaban Demirel, PhD

Title

Effects of hyperbaric oxygen therapy on glucose homeostasis in patients living with diabetes mellitus (Protocol HB-002)

Background

Diabetes mellitus (DM) is an epidemic of global proportion with a steadily rising prevalence of disease. It is believed at least 15% of people living with diabetes will develop a lower extremity foot ulcer during their lifetime.[1,2] The annual incidence of foot ulcer development is 5-6% among patients living with diabetes.[1-3] Patients with diabetes mellitus often require hyperbaric oxygen (HBO_2) for treatment of diabetic foot ulcers (DFU)[4]. Hyperbaric oxygen is thought to affect blood glucose (BG) levels,[5-7] leading to treatment protocols that rely on pre-HBO_2 BG to determine whether patients can be safely treated that day or not.[8]

Mechanisms to explain the drop in BG associated with HBO_2 include a rise in serum insulin levels, increased sensitivity to insulin, and inhibition of anti-insulin hormones such as glucagon.[9] An alternative theory as to why patients with DM have lowered blood glucose after HBO_2 is the fact that they may have a decreasing trend in their BG prior to starting HBO_2 that is then exacerbated by the fact that they are sequestered for up to 120 minutes in the hyperbaric chamber without easy access to additional carbohydrate sources.[5,9] A single fingerstick BG prior to HBO_2 is insufficient to determine whether a patient's BG is stable, trending up, trending down, or changing rapidly. Continuous

glucose monitoring (CGM) offers a unique opportunity to monitor BG before, during, and after HBO_2.

We previously studied the reliability of a commercially available Dexcom G6 CGM (Dexcom, Inc., San Diego, CA) under hyperbaric oxygen conditions in healthy volunteers who did not have diabetes. This showed an increase of 3.76 mg/dL (3.72%, $p<0.001$) while patients were breathing HBO_2 at 2.4 atmospheres absolute (ATA) and an increase of 4.12 mg/dL (4.13%, $p=0.015$) when comparing pre-HBO_2 and post-HBO_2 values. The increase in EGV may have been related to increases in interstitial fluid temperature related to the HBO_2, but that was not measured. While this was statistically significant, it was not felt to be clinically relevant. The Dexcom G6 CGM was felt to be accurate and reliable for use with patients without DM receiving HBO_2. The goal for this proposed study is to look at multiple CGMs in patients with DM receiving HBO_2.

Research Goals

Specific Aim 1 – Determine whether the Dexcom G6 CGM accurately estimates blood glucose under hyperbaric oxygen conditions

Specific Aim 2 – Determine whether a single HBO_2 treatment affects blood glucose in patients with diabetes mellitus

Specific Aim 3 – Determine whether glucagon varies in relationship with HBO_2

Materials and Methods

Study Design and Timeline

This will be a prospective, controlled trial comparing a standard HBO_2 treatment vs. a control period. Each patient will serve as their own control.

Recruitment

We will recruit individuals who are living with type 1 or type 2 diabetes and are willing to undergo a single hyperbaric exposure to 2.4 ATA while breathing 100% oxygen. Participants will provide their informed consent after the risks of the study have been explained to them (*e.g.,* HBO_2 possibly decreasing BG) and the risks of HBO_2 (*e.g.,* barotrauma, confinement anxiety, oxygen toxicity, and fire). Upon enrollment in to the study, participants will have a commercial G6 CGM inserted in the subcutaneous tissue of their abdomen and a research G6 data logger inserted in the subcutaneous tissue on the back of the arm. Participants will return >36 hours after insertion for their study exposures.

Compensation up to $400 will be pro-rated to encourage completion of all study sessions (Figure 1):

- Implantation of CGM loggers - $50
- Completion of control study session - $50
- Completion of HBO_2 study sessions- $100
- Completion of follow-up data collection - $200

Figure 1. Study Timeline and Compensation Schedule

Day		Day 1	36 hour interval	Day 3	Day 4	Day 5-9	Day 10
Payment		$50		$50	$100		$250
Event	Consent	Placement of CGM		Control Exposure - 3 hours	HBO_2 Treatment - 3 hours		Return for CGM Removal
Event Log			Meals and Medication Times	Meals and Medication Times	Meals and Medication Times	Meals and Medication Times	
Home Testing			4 capillary measurements per day at home	4 capillary measurements per day at home	4 capillary measurements per day at home	4 capillary measurements per day at home	
Study Testing	UCG			Fingerstick measurement - POC x 12	Fingerstick measurement - POC x 12		
				Venous glucose - laboratory x 12	Venous glucose x 12		
				Glucagon x 3	Glucagon x 3		
				Hba1c x 1			
G6 CGM			Estimated Glucose Value				
G6 CG Logger			Interstitial Temperature				

Commercial CGMs have a 10-day lifespan and data loggers have a 14-day lifespan, but all study sessions should be completed within 10 days of insertion (Figure 2). The color coding represents whether or not participants and staff will have to come in over the weekend for a control or HBO_2 session (red), to insert CGMs or remove CGMs (yellow), or if they won't have to come in over the weekend at all (green).

Figure 2. Weekly schedule of events

Day	Description	Projected weekly schedule for 0730 am insertion						
1	**Insertion of CGM**	Monday	Tuesday	Wednesday	Thursday	Friday	**Saturday**	**Sunday**
2	**36h Observation**	Tuesday	Wednesday	Thursday	Friday	**Saturday**	**Sunday**	Monday
3	***Control***	*Wednesday*	*Thursday*	*Friday*	***Saturday***	***Sunday***	*Monday*	*Tuesday*
4	***HBO_2***	*Thursday*	*Friday*	***Saturday***	***Sunday***	*Monday*	*Tuesday*	*Wednesday*
5	**Observation**	Friday	**Saturday**	**Sunday**	Monday	Tuesday	Wednesday	Thursday
6	**Observation**	**Saturday**	**Sunday**	Monday	Tuesday	Wednesday	Thursday	Friday
7	**Observation**	**Sunday**	Monday	Tuesday	Wednesday	Thursday	Friday	**Saturday**
8	**Observation**	Monday	Tuesday	Wednesday	Thursday	Friday	**Saturday**	**Sunday**
9	**Observation**	Tuesday	Wednesday	Thursday	Friday	**Saturday**	**Sunday**	Monday
10	**Return CGM**	Wednesday	Thursday	Friday	**Saturday**	**Sunday**	Monday	Tuesday

We will plan for recruitment of 24 individuals. Half will be patients living with type 1 diabetes and half will be patients living with type 2 diabetes.

Inclusion Criteria

- Diagnosis of type 1 or type 2 diabetes
- Willing to have 2 subcutaneous glucose monitors for 10 days
- Willing to be NPO after midnight on the day of the study session
- Willing to come to the hyperbaric facility on successive days (one control session and one hyperbaric treatment), spending approximately 3 hours in the facility on each day of testing
- Willing to undergo multiple fingersticks on the days of testing
- Willing to have a peripheral intravenous catheter placed for blood sampling
- Willing to perform four daily fingerstick blood glucose checks throughout the study period

Exclusion Criteria

- Contraindication to HBO_2 as determined by the study investigator (*e.g.,* pregnancy)
- Previous treatment with HBO_2 within 30 days of enrollment

- Current use of CGM is not an exclusion, but participants must use study equipment during the study
- Current use of an insulin pump
- Known allergy to medical-grade adhesives
- Extensive skin changes/disease that preclude wearing the sensor on normal skin (e.g. extensive psoriasis, recent burns or severe sunburn, extensive eczema, extensive scarring, extensive tattoos, dermatitis herpetiformis)

Control Protocol (Figure 3)

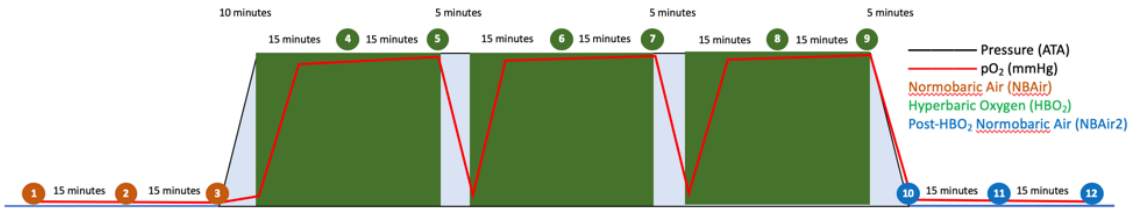
Because the effects of HBO_2 may extend longer than one day, participants will first be exposed to a 2-hour control period where they will simulate an HBO_2 exposure. Patients must be NPO after midnight of the day prior to the control study period. Participants in a control session will sit quietly (as they would in the hyperbaric chamber) and will not be allowed to consume carbohydrates unless directed to by the hyperbaric department hypoglycemia protocol. The timing of the blood draws (Figure 5) will be parallel to that of the HBO_2 exposure.

Figure 3. Control Testing Protocol

Hyperbaric Oxygen Therapy (Figure 4)

The day after the control study period, participants will undergo a standard HBO_2 treatment breathing 100% oxygen at 2.4 ATA with 3 x 30 min O_2 periods and 5 min air-breaks between O_2 periods. Patients must be NPO after midnight of the day prior to the HBO_2 period. Participants will not be allowed to consume carbohydrates during the treatment unless directed to by the hyperbaric department hypoglycemia protocol.

Figure 4. HBO_2 Testing Protocol



Modification of hypoglycemia medication regimen

Because participants are being asked to remain NPO after midnight, they will be asked to modify their normal hypoglycemic medications as follows:

- Oral hypoglycemic medications should be held until after they eat their first meal of the day
- Patients with meal-time doses of insulin should hold their meal-time boluses until they eat their first meal of the day
- Patients who require a correction dose of insulin the morning of study session (control of HBO_2) because of a blood glucose >250 mg/dL should take their normal dose of insulin and document it in their medication log
- Patients who use long-acting insulin should modify their doses as follows
    - Patients who are on BID long-acting insulin to take their normal dose in the morning, but 2/3 of their dose the night before
    - Patients who are on night-time long-acting insulin to take 2/3 their normal dose the night before
    - Patients who are on morning long-acting insulin to take 2/3 of their normal dose in the morning

Study investigators will review insulin doses and provide additional instructions for adjustment if needed for safety.

Modification of the Hyperbaric Department Glucose Protocol

The hyperbaric department currently follows a protocol to provide supplemental carbohydrates to patients with a pre-HBO_2 BG <100 mg/dL whether they are

symptomatic or not. We will be following the hyperbaric department protocol and obtaining pre-HBO_2 fingerstick blood sugars, but we will not provide mandatory supplemental carbohydrate for BG <100 mg/dL unless participants complain of symptoms they associate with hypoglycemia. If participants are documented to have hypoglycemia – defined by the American Diabetes Association (ADA) as a BG ≤ 70 mg/dL[10] – before or during study periods, we will institute the hyperbaric department's hypoglycemia protocol and provide 15 grams of supplemental carbohydrate. Hypoglycemia risk to the patient is mitigated because we will be able to monitor blood sugar in real time using CGM, however clinical decisions will be made using the fingerstick GDH-based POC glucometer.

Transcutaneous Oxygen Monitoring during HBO_2 exposures

We will obtain concurrent transcutaneous oximetry measurements (TCOM) using a Clarke electrode (Radiometer America, Brea, CA) attached no farther than 3 cm from the commercial CGM on the abdomen to measure tissue oxygenation in the region of the CGM only during HBO_2 exposure. The TCOM value closest to the time of each blood draw will be used for analysis. The average pre-HBO_2 TCOM measurements will be used as a surrogate for the control day TCOM.

Hemoglobin A1c

We will obtain a single Hba1c measurement using the central laboratory chemistry analyzer (AU680 Chemical Chemistry Analyzer, Beckman Coulter, Inc., Brea, CA) at the first blood draw to establish baseline control of their DM.

Blood glucose (central laboratory)

We will use the central laboratory chemistry analyzer (AU680 Chemical Chemistry Analyzer, Beckman Coulter, Inc., Brea, CA) to measure blood glucose at each of the time points (Figure 4). This analyzer uses a hexokinase reaction that is insensitive to blood oxygen levels and will serve as the reference for CGM and POC glucometers.

Glucagon (send-out to OHSU)

We will draw blood glucagon before (Timepoint 1), during (Timepoint 9), and after (Timepoint 12) actual or simulated HBO_2 (Figures 2-4) in order to determine whether there are any effects of HBO_2 on glucagon. The protocol for the glucagon handling is described below.

Blood sampling schedule (Figure 4)

We will obtain a venous blood glucose sample on all participants at the following time points during the study (±2 min):

1. 30 minutes prior to starting (NBAir)
2. 15 minutes prior to starting (NBAir)
3. Immediately prior to study session (NBAir)

   10-minute compression
4. 15 minutes into O_2 period 1 (HBO_2)
5. 30 minutes into O_2 period 1 (HBO_2)
6. 15 minutes into O_2 period 2 (HBO_2)
7. 30 minutes into O_2 period 2 (HBO_2)
8. 15 minutes into O_2 period 3 (HBO_2)
9. 30 minutes into O_2 period 3 (HBO_2)

   5-minute decompression
10. Immediately after reaching 1 ATA (NBAir Post-HBO_2)
11. 15 minutes after reaching 1 ATA (NBAir Post-HBO_2)
12. 30 minutes after reaching 1 ATA (NBAir Post-HBO_2)

Figure 4. Timeline of testing

	Pre-HBO_2			HBO_2						Post-HBO_2		
Control/HBO_2	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Time ± 2min	T-30	T-15	T0	T+25	T+40	T+60	T+75	T+95	T+110	T+115	T+130	T+145
CGM EGV	•	•	•	•	•	•	•	•	•	•	•	•
CGL EGV	•	•	•	•	•	•	•	•	•	•	•	•
Interstitial T°	•	•	•	•	•	•	•	•	•	•	•	•
Lab Glucose	•	•	•	•	•	•	•	•	•	•	•	•
NovaStat	•	•	•	•	•	•	•	•	•	•	•	•
AccuChek	•	•	•	•	•	•	•	•	•	•	•	•
TCOM	•	•	•	•	•	•	•	•	•	•	•	•
Glucagon	•							•				•

Because we are using a saline-locked peripheral IV with a 4-way stopcock for blood sampling, our protocol for each blood draw will be as follows:

- Draw approximately 4 ml of venous blood from distal port of the IV catheter, leaving the syringe in place;
- Withdraw 2 ml of venous blood and place in purple top for measurement of glucagon;
- Return the 4 ml of venous blood through proximal port and flush with 10-20 ml of normal saline until line is clear of blood;
- Cap the port with a clean 1 ml syringe;

For glucagon processing

- Prechill a lavender top (EDTA) with aprotonin tube at 4°C before drawing the specimen
- Draw the prechilled lavender (EDTA) top tube and process 2.0 mL of EDTA plasma as follows:
    - Sample should be mixed by inverting gently 6-7 times;
    - Chill lavender (EDTA) top tube in wet ice for 10 minutes;
    - Centrifuge in a refrigerated centrifuge (4 °C) or in chilled centrifuge cups;
    - Spin at ≈2600 RPM in the centrifuge with samples balanced;
    - Aliquot plasma into appropriate number cryo-tubes using a separate transfer pipette for each tube;
    - Freeze samples ASAP in freezer

A runner will process each glucagon sample immediately after removal from the hyperbaric chamber. Frozen glucagon samples will be batched and transported to the OHSU laboratory on dry ice for processing.

Fingerstick point-of-care glucose testing

Because we have not established that CGMs are reliable under HBO_2 conditions, we will collect POC glucose measurements using the hospital's standard GOx-based NovaStat POC glucometer (Nova Biomedical, Waltham, MA) and a GDH-based AccuChek Inform II POC glucometer (Roche Diagnostics, Indianapolis, IN) at each testing point. We will compare the POC glucometer readings against the laboratory readings to generate a mean absolute relative difference (MARD) for each glucometer. Because GOx-based POC glucometers are known to underestimate BG while GDH-based POC glucometers do not, we will primarily use the AccuChek GDH-based POC glucometer for clinical decision making.

Fingerstick protocol

1. Clean the subject's fingertip with soap and water and allow to dry.
2. Puncture the skin with one quick stroke with the lancet to achieve a good flow of blood.
3. Wipe away the first drop of blood as it may be contaminated with plasma or debris.
4. Blood collection - Avoid squeezing the finger too tightly as this will dilute the specimen with plasma and increase the probability of hemolysis.
    a. At 1 ATA - gently squeeze the finger and apply blood to the test strip.
    b. At 2.4 ATA - gently squeeze the finger and collect blood in micro-pipette.
5. When the blood collection procedure is complete, apply firm pressure to the site to stop the bleeding.

Continuous glucose monitor

We will use both a commercial Dexcom G6™ (Dexcom, Inc., San Diego, CA) CGM and a CGM logger for continuous glucose monitoring. A CGM logger differs from a commercially available CGM in that it does not provide feedback to the patient, but it records data that a commercially available CGM does not (*e.g.,* interstitial fluid temperature). Data can be retrieved from the logger at the end of the study period for

analysis. The G6 CGM will be inserted in the subcutaneous tissue of the abdomen according to the manufacturer's directions. The G6 CGM logger will be inserted in the subcutaneous tissue on the back of the arm according to the manufacturer's directions. We will allow at least 48 hours of runtime before hyperbaric exposure in order to allow equilibration of CGM readings. The CGM will be considered the primary data source for EGV, with the CGM logger providing a backup in case of data loss.

Home glucose monitoring

In order to verify that the CGM is working before and after HBO_2 exposure, we will have participants obtain fingerstick BG using a POC Contour One glucometer and test strips (Ascensia Diabetes Care, Parsipanny, NJ) that will be provided to them. This will be done a minimum of 4 times a day throughout the study period. Data from the POC glucometer will be downloaded at the end of the study period for comparison with the CGM data.

Ancillary Data collection

We will provide all participants a log to document the time of their meals and the time of any medications taken throughout the study period.

Risks of hyperbaric oxygen (HBO_2) therapy

HBO_2 is an FDA approved treatment modality for many different conditions. It is administered in a rigid-hulled hyperbaric chamber that either accommodates a single patient (monoplace chamber) or multiple patients (multiplace chamber). Monoplace chambers are compressed with 100% oxygen while patients breathe the ambient atmosphere. Multiplace chambers are compressed with air (21% oxygen) while patients breathe 100% oxygen from a face mask or an oxygen hood. Treatment pressures range from 2.0 atmospheres absolute (ATA) to 2.5 ATA and include at least 90 minutes of oxygen breathing. Treatment protocols include periods of air breathing (air breaks) of 5-10 minutes duration interspersed between 30-minute oxygen breathing periods. The treatments start by increasing pressure during the compression phase of the treatment,

which lasts between 5-10 minutes. Once reaching the prescribed treatment pressure, patients will be maintained at the prescribed treatment pressure for three 30-minute oxygen breathing periods and two 5-minute air breaks. At the completion of the final oxygen breathing period, the decompression phase of the treatment will reduce the ambient pressure until reaching sea level pressure. Treatment protocols for HBO_2 typically range between 30 sessions to 60 sessions offered daily on a Monday-Friday basis.

In this study, participants will be treated in our multiplace hyperbaric chamber for a single HBO_2 session between Monday-Friday. Participants will be pressurized to 2.4 ATA for three 30-minute oxygen breathing periods separated by two 5-minute air breaks. Patients will breathe oxygen from clear plastic hoods fitted over a neck ring with a rubber gasket. Study treatments will occur concurrently with non-study patients during daily hyperbaric operations.

The primary risks to participants from treatment in a hyperbaric chamber are related to the increased partial pressure of gasses in the chamber. The most common risk is middle-ear and sinus barotrauma and confinement anxiety (incidence included in Table 1). Very rare risks include oxygen related seizures, pneumothorax, arterial gas emboli, and decompression sickness.

Ear and sinus barotrauma: Some individuals may have difficulty equalizing the pressures within the middle ears or sinuses which may cause ear or sinus discomfort. Participants will be screened for ear problems, and an ear exam, using an otoscope, will be done before any hyperbaric exposure. Participants will be given a thorough orientation at the time of their consent and instructed on ear clearing maneuvers. If a participant is unable to equalize their ears, the exposure will be discontinued, and they may be referred for myringotomy before continuing in the study. If the participant has any significant otoscopic findings in the eardrum after the study exposure to hyperbaric

treatment, appropriate follow up will be arranged if needed. Follow up will be covered by participant's insurance if necessary.

Confinement anxiety: Some individuals can experience confinement anxiety due to being in the chamber or wearing the oxygen hood or mask. To minimize this risk, we will screen potential participants for a history of confinement anxiety or other psychiatric disorders. Participants will always be accompanied in the chamber and will be reassured by highly trained staff. The chamber is very large (23 feet long and 7 feet in diameter) and is similar in size to a small aircraft cabin. Participants can terminate the exposure at any time and be removed from the chamber with a simple request. Participants can terminate the exposure and be removed from the chamber even there are non-study patients in the chamber at the same time.

Hypoglycemia: HBO_2 has been reported to decrease blood glucose in patients with DM. The hyperbaric department will follow their hypoglycemia protocol and provide supplemental carbohydrates if blood glucose is low either before or during HBO_2

Oxygen related seizure: Seizures occurring while someone is in a hyperbaric chamber are extremely uncommon and range from 0.02% - 0.04% in patients undergoing hyperbaric oxygen treatments at 2.0 to 2.5 ATA (Camporesi, E.M., 2014; Jokinen-Gordon, et al., 2017). The risk of seizures is increased with baseline neurologic disease and prior history of seizures. Screening will be done to determine if there is any increased risk by way of history taking and physical exam. A spontaneous oxygen seizure, should it occur, is self-limited and does not result in any long-term neurologic sequelae. The risk of seizure is only while someone is in the chamber and breathing oxygen. There is no risk after the hyperbaric exposure.

Oxygen related visual acuity changes: Hyperoxic myopia is a phenomenon that occurs after repeated hyperbaric exposures to 100% oxygen and is not a risk for study

participants as it does not typically present until individuals have had several weeks of HBO_2.

Pneumothorax: Pneumothorax, or collapsed lung, occurs in the extremely rare instances when individuals who have air-filled cysts in the lungs are exposed to rapidly changing pressures. Potential participants will be screened to make sure they have no history of lung disease. Pneumothorax is an extremely rare situation that requires medical and/or surgical treatment, such as inserting a tube through the skin into the chest to re-expand the collapsed lung.

Arterial gas emboli: Arterial gas emboli can form if an individual holds their breath while the pressure in the chamber is reduced, causing lung air sacs to rupture, releasing gas bubbles into the chest, neck, and blood. The gas bubbles may travel through the arteries and cause a blockage of blood-flow to the heart, brain, or other organs, and a heart attack or stroke may occur. Arterial gas emboli are extremely rare in the hyperbaric chamber because of the control and monitoring of change of depth and can be successfully treated by prompt recompression with hyperbaric oxygen.

Fire hazard: A risk unique to the hyperbaric chamber is the risk of injury due to fire as a result of elevated oxygen levels. Because of this, there are limits around what electronic devices are allowed in the hyperbaric chamber. Due to this inherent risk, our research team has taken measures to minimize risk of fire. Participants will not be allowed to take any electronic device (phone, computer, pager, etc.) into the chamber. The hyperbaric chamber has fire suppression equipment and the staff is trained how to respond in the event of this extremely rare event.

There has never been a fire in a clinical multiplace chamber in the United States.

Table 1: Outline of documented risks of clinical hyperbaric therapy with associated incidence:

Incidence of side effects during hyperbaric oxygen therapy							
Study	# of sessions	Patients	Hyperbaric profile	Middle ear barotrauma	Sinus barotrauma	Seizure	Confinement anxiety
Beard et al. 2011	463,293	17267	2 - 2.4 atm	1870 events (0.4%)	66 events (0.01%)	88 events (0.02%)	407 events (0.09%)
Sheffield & Sheffield 2003	170,096	8226	2 - 2.4 atm	759 events (0.4%)	130 events (0.08%)	29 events (0.02%)	113 events (0.07%)
Plafki et al. 2000	11376	782	2.4 - 2.5 atm	33 events (0.3%)	9 events (0.08%)	4 events (0.04%)	34 events (0.03%)

Risks of Continuous Glucose Monitoring

The Dexcom Continuous Glucose Monitoring System described in this protocol is considered by the Sponsor to be of non-significant risk as it does not meet the definition of a significant risk device per 21 CFR 812.3(m), in that:

- It is not an implant nor presents a potential for serious risk to the health, safety or welfare of a subject;
- CGM devices are not purported or represented to be for use in supporting or sustaining human life and thus do not present a potential for serious risk to the health, safety, or welfare of a subject; or
- Use of CGM devices does not present a potential for serious risk to the health, safety or welfare of a subject.

There is a very low risk of developing a local skin infection at the site of the sensor placement and a very low risk of sensor breakage. The participant will be instructed to notify study staff if they develop swelling, redness, or pain at the sensor insertion site.

Adverse Events

We will catalog adverse events associated with HBO_2 (*e.g.,* otic/sinus barotrauma, O_2 toxicity, confinement anxiety) or severe hypoglycemia (BG < 70 mg/dL) associated with HBO_2. We will report any complications related to the insertion of the CGM or fingersticks related to home glucose testing. Asymptomatic patients with a BG <100

mg/dL will not be considered an adverse outcome associated with HBO_2 but will be counted for analysis.

Analysis

Endpoint 1

In order to determine the accuracy of the G6 CGM in patients with diabetes who are receiving HBO_2, we will compare CGM values to laboratory results in the pre-HBO_2 NBAir (1-3), HBO_2 (4-9), and post-HBO_2 NBAir (10-12) phases. We will compare the mean absolute relative difference (MARD), which is listed at 9.9% in the Dexcom G6 user guide and has a standard deviation of 7.99 mg/dL. If we are trying to detect a difference of 5 percentage points in MARD (9.9% in room air up to 14.9% in HBO_2) with a standard deviation of 8 mg/dL, alpha level ($p<0.05$), and a power of 0.80, we will require a minimum sample size of 18 patients.

Endpoint 2

We will compare CGM and venous blood glucose readings before (1-3), and after (10-12) each study session and use this to determine if there is any effect of session type (HBO_2 vs control) on BG. Each individual will serve as their own control, which will improve the study's power. We will determine if the BG changes observed during HBO_2 sessions are greater than those observed when the participants are sitting quietly outside the chamber during the control sessions. Linear mixed effects regression (LMER) analyses will be used to account for the clustering of data within an individual while also allowing for the main effect (difference in pre- vs. post- by session type) to be determined.

Endpoint 3

We will evaluate whether a single HBO_2 treatment affects glucagon levels by comparing control glucagon levels with the pre-, intra-, and post-HBO_2 glucagon levels.

Estimated time to conduct study

- Once approved, we will begin recruiting participants and anticipate 2 weeks before the first individual is enrolled.
- We will be able to accommodate up to 2-4 participants per week, which should allow us to complete testing in 12-24 weeks.
- We estimate a total time to complete the study of approximately 30 weeks.

Budget

Description	Unit Price	Quantity	Total
Equipment			
Dexcom G6 CGM Sensors and CGM		24	$ -
Dexcom G6 Data Sensors and Logger		24	$ -
Oxygen Hoods and Neck Rings (1 per subject)	$ 125.00	24	$ 3,000.00
Laboratory Glucose Testing (24 per subject)	$ 5.11	576	$ 2,943.36
Laboratory Glucagon Testing (6 per subject)	$ 20.00	144	$ 2,880.00
Laboratory Hba1c (1x per subject)	$ 15.00	24	$ 360.00
		Subtotal	**$ 8,823.36**
Administrative Fees			
IRB Initial Application Fee	$ 2,500.00	1	$ 2,500.00
IRB Preparation Fee	$ 750.00	1	$ 750.00
IRB Closure Fee	$ 750.00	1	$ 750.00
Stipend for research subjects	$ 400.00	24	$ 9,600.00
		Subtotal	**$ 13,600.00**
Salary Support			
Research Coordinator subject recruitment (20 hours)	$ 45.00	20	$ 900.00
Research Coordinator (Informed consent - 1 hr, data collection 6 hrs, data entry 1 hr) = 8 hrs/subject x 24	$ 45.00	192	$ 8,640.00
Research Coordinator (IRB and Consent Preparation - 10 hrs)	$ 45.00	10	$ 450.00
Laboratory Runner for Glucagon Samples ($25/specimen x 3)	$ 75.00	24	$ 1,800.00
Biostatistician support (Demirel) and manuscript writing	$ 86.32	64	$ 5,524.48
Legacy Research Institute Overhead (35% of salary support)	$ 6,060.07	1	$ 6,060.07
Hyperbaric Chamber Operator - 3 hours per subject per exposures x 24	$ 30.00	72	$ 2,160.00
Hyperbaric Outside Observer - 4 hours per subject x 24	$ 30.00	72	$ 2,160.00
Hyperbaric Inside Observer (RN) for phlebotomy - 3 hours per subject x 24	$ 60.00	72	$ 4,320.00
Research Coordinator (RN) for phlebotomy during control period - 3 hours per subject x 24	$ 60.00	72	$ 4,320.00
Investigator Support (Huang) @ $150/hour (Supervision of hyperbaric exposure x 3 hours per subject [24] x 1 HBOT or control sessions, plus primary manuscript writing - 20 hrs)	$ 150.00	92	$ 13,800.00
Investigator Support (Savaser) @ $150/hour (Supervision of hyperbaric treatment x 3 hours per subject [24] x 1 HBOT or control sessions, plus manuscript writing)	$ 150.00	72	$ 10,800.00
Investigator Support (Castle) @ $150/hour (Consultation, manuscript writing)	$ 150.00	20	$ 3,000.00
		Subtotal	**$ 63,934.55**
		Total	**$ 86,357.91**

References

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