RESEARCH ARTICLE

A double-blind placebo-controlled clinical trial testing the effect of hyperbaric oxygen therapy on brain and cognitive outcomes of mildly cognitively impaired elderly with type 2 diabetes: Study design

Ori BenAri[1,2] | Shai Efrati[2,3] | Mary Sano[4] | Barbara B. Bendlin[5] | HungMo Lin[4] | Xiaoyu Liu[4] | Inbar Sela[1] | Ganit Almog[1] | Abigail Livny[1,2,6] | Israel Sandler[7] | Simona Ben-Haim[8,9] | Roy Sagi[3] | Derek LeRoith[4] | Michal Schnaider Beeri[1,4] | Ramit Ravona-Springer[1,2,10]

[1] The Joseph Sagol Neuroscience Center, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel

[2] Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[3] Sagol center for Hyperbaric Medicine & Research, Shamir (Assaf Harofeh) Medical Center, Be'er Ya'akov, Israel

[4] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[5] Wisconsin Alzheimer's Disease Research Center, University of Wisconsin-Madison School of Medicine and Public Health, Madison, Wisconsin, USA

[6] Division of Diagnostic Imaging, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel

[7] Department of Nuclear Medicine, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel

[8] Department of Biophysics and Nuclear Medicine, Hadassah University Hospital, Ein Kerem, Jerusalem, Israel

[9] Institute of Nuclear Medicine, University College London Hospitals, NHS Trust, London, UK

[10] Department of Psychiatry, Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel

Correspondence
Michal Schnaider Beeri, Department of Psychiatry, One Gustave L. Levy Place, Box 1230, New York, NY 10029-6574, USA.
E-mail: michal.beeri@mssm.edu

Abstract

Introduction: Type 2 diabetes (T2D) is a risk factor for dementia. Ischemia due to vascular pathology is hypothesized to be an underlying mechanism for this association. Hyperbaric oxygen therapy (HBOT) is a treatment in which oxygen-enriched air (up to 100%) is administered to patients in a chamber at a pressure above one atmosphere absolute. HBOT is approved for the treatment of T2D ischemic non-healing wounds. Evidence from animal studies and small clinical trials suggests that HBOT improves hypoxic/ischemic brain injuries, consequently inducing brain angiogensis, leading to cognitive improvement.

Methods: We present the design of the first double-blind, placebo-controlled, clinical trial on brain and cognitive outcomes in elderly (n = 154) with T2D and mild cognitive impairment to compare the effects of HBOT versus sham (normal air with 1.1 ATA pressure in the first and last 5 minutes of the session). Eligible candidates are randomized with equal probability to HBOT and sham. Outcomes are assessed before and after treatment, and at 6- and 12-month follow-up. The primary cognitive outcome is global

cognitive change, indexed by a composite sum of z-scores of four executive functions and four episodic memory tests. The primary neurobiological outcome is cerebral blood flow (CBF; via arterial spin labeling magnetic resonance imaging [ASL-MRI]) and cerebral glucose utilization via fluorodeoxyglucose positron emission tomography (FDG-PET). Secondary outcome measures are specific cognitive domains (executive function and episodic memory) and functional measures (Clinical Dementia Rating sum of boxes, activities of daily living). Efficacy analyses will be performed for the intent-to-treat sample.

Discussion: Recent studies suggest that HBOT induces neuroplasticity and improves cognition in post-stroke and traumatic brain injury patients. However, its effect on cognition, cerebral blood flow, and brain glucose utilization in T2D patients at high dementia risk is yet to be determined. If effective, this study may provide strong evidence for the brain and cognitive benefits of HBOT in this population.

KEYWORDS
dementia, hyperbaric oxygen therapy, mild cognitive impairment, type 2 diabetes

1 | BACKGROUND

The estimated worldwide number of people with dementia is 50 million,[1] projected to triple by 2050.[2] Cumulative evidence shows that about 30% of late life dementia cases may be attributable to modifiable risk factors, among which type 2 diabetes (T2D) contributes 6% to 8%.[3] T2D and pre-diabetic states (impaired fasting glucose, obesity, metabolic syndrome) are associated with increased risk for dementia[4] and mild cognitive impairment (MCI), worse cognitive functioning, and brain hypometabolism.[5] People with T2D (vs without) have 1.5 to 2.8 increased risk for dementia.[6-8] The contribution of diabetes to dementia is expected to grow with the accelerating T2D prevalence,[9] because there is no known treatment to halt T2D-related cognitive decline.

Several mechanisms have been proposed to underlie the detrimental effects of T2D on the brain.[6] Cerebrovascular pathology and related ischemia constitutes a major factor,[10] demonstrated by the high prevalence of stroke,[11] lacunar infarcts,[12] microbleeds,[13] and white matter hyperintensities (WMH)[14] observed in T2D. Likewise, reduced cerebral blood flow (CBF)[14] and impaired cerebrovascular reactivity[15] have also been observed in T2D. Cerebrovascular disease[16] and lower CBF,[5,17] mediate the adverse effects of T2D and metabolic syndrome on cognition, further supporting these pathological processes as underlying mechanisms. Reduced CBF in the absence of brain atrophy has been shown in older adults with T2D,[18] suggesting that CBF alterations occur early before cerebral atrophy and structural changes occur. Lower CBF is found in individuals with metabolic syndrome, a state preceding T2D,[19] and mediates the relationship of metabolic syndrome with poorer memory function further supporting the notion that reduced CBF may be an early, important marker of risk for cognitive decline and dementia in T2D.[5]

In addition to cerebrovascular disease, there is evidence for neurodegeneration in T2D. Brain volume loss in the form of smaller total brain[20] and gray matter,[21] and larger cerebrospinal fluid (CSF)[15] volumes have been demonstrated in elderly patients with T2D. Smaller hippocampi were found in both middle-aged[22-24] and older T2D patients.[25,26] Even pre-diabetic states such as impaired glucose tolerance, insulin resistance,[27] and higher fasting glucose levels[28] have been associated with lower hippocampal volume, and medial temporal lobe volumes.[29] The heterogeneous mechanisms underlying brain atrophy are not necessarily associated with neuronal loss or AD-related mechanisms.[5] Accordingly, people with T2D (vs without) show hypometabolism of glucose in AD-signature brain regions but do not have greater amyloid load as demonstrated by amyloid PET[17] and in postmortem studies.[30,31] Cerebrovascular pathology has been demonstrated by some,[32,33] but not other,[34] previous studies to underlie brain atrophy in T2D. Moreover, cerebrovascular pathology in the form of WMH, rather than brain atrophy, was associated with cognitive outcomes in patients with T2D.[35] Overall, the evidence points toward a major role of cerebrovascular disease (either directly or indirectly) in T2D-related cognitive compromise.

Hyperbaric oxygen therapy (HBOT) is a treatment in which oxygen-enriched air (up to 100%) is administered to patients in a chamber at a pressure above one atmosphere absolute (1 ATA), which is the ambient sea level atmospheric pressure. For peripheral vasculature related disease, a well-accepted clinical indication for HBOT is non-healing ischemic foot ulcers, for which there is broad evidence for significant improvements with HBOT through stimulation of regenerative processes and angiogenesis.[36] Similarly, in the brain, based on previous evidence in animals and relatively new human clinical trials, it was demonstrated that HBOT can induce neuroplasticity and improve CBF in ischemic non-recoverable brain

regions, leading to cognitive improvements even years after the acute insult.[37-39] Angiogenesis is induced by HBOT through upregulation of hypoxia-inducible factor-1α and vascular endothelial growth factor, including in the hippocampus.[40] HBOT also increased vascular density in the hippocampus, improved spatial learning in rodents, reduced cortical infarct area, and improved CBF in adult rats with vascular dementia.[41]

It is well established that glucose utilization is impaired in cortical regions with ischemia.[42,43] Conversely, in animal models, neuronal hypometabolism is improved with HBOT,[44] suggesting that intracellular bioavailability of oxygen attenuates the deleterious effects of ischemia on neuronal glucose utilization. In humans, HBOT has been associated with improvement in neurological and functional outcomes in post-stroke patients,[45] and with cognitive performance[38] even years after the acute stroke. These improvements correlated with brain activity as demonstrated by single-photon emission computed tomography.[38,46] Similarly, HBOT had positive effects compared to hyperbaric air on neurological and cognitive outcomes in a small (n = 26) randomized controlled trial of patients with cerebrovascular disease.[47] HBOT—compared with normobaric oxygen—was associated with increased CBF in frontal and temporal regions in healthy young adults.[48]

Numerous therapies previously developed for the treatment of dementia have failed. Late introduction of treatment, at a phase in which the brain is overwhelmed by pathology, has been proposed as a leading explanation for the failure of clinical trials.[49] The neuropathological process of dementia starts 15 to 35 years before clinically overt symptoms, providing a window of opportunity for prevention. MCI[50] is considered to be a prodromal state preceding dementia and the stage at which interventions aimed at dementia prevention may be effective. People with MCI have 10% to 15% risk for conversion to dementia, ≈10 times the risk for those without MCI.[51] With regard to T2D, individuals with T2D and pre-T2D[52] compared to those without T2D[6,53] previous studies demonstrated up to 1.6 increased risk for MCI, and higher risk of conversion from MCI to dementia. Moreover, WMH, indicative of cerebrovascular pathology, are associated with worse cognitive and brain volume outcomes in people with MCI (comparing to AD and comparing to healthy controls).[54] Altogether, these findings suggest that addressing vascular pathology may have a beneficial impact on cognition among individuals with T2D, and particularly among individuals who are both T2D and MCI.

Given the biological plausibility of HBOT for T2D-related cognitive compromise, our research group is testing the extent to which the cognitive compromise in T2D may be addressed by the improvement in vascular function by HBOT therapy on the brain. This report describes the design of our pilot double-blind, placebo-controlled clinical trial examining the short- and long-term effects of HBOT on cognition, CBF, and cerebral glucose utilization, in T2D patients with MCI.

The specific aims of the trial are to:

Aim 1. Determine the impact of HBOT on cognitive function: The primary outcome is a composite measure of cognitive function balancing tests of both executive and memory function. Domain-specific measures of cognition (executive function and episodic memory) are secondary outcomes.

Aim 2. Determine the impact of HBOT on neuronal function: Fluorodeoxyglucose positron emission tomography ([F18]FDG-PET) measuring cerebral glucose utilization is the outcome.

Aim 3. Determine the mediation effects of CBF and glucose utilization: To examine whether CBF and glucose utilization mediate HBOT effects on cognitive function.

2 | METHODS

2.1 | Participants

This study is a collaboration among the Icahn School of Medicine, New York; the Sheba Medical Center, Israel; and the Shamir (Assaf Harofeh) Medical Center, Israel. Participants are recruited in Israel, primarily from the center of Israel area (see Figure 1). Recruitment, eligibility criteria, and brain and cognitive outcomes are assessed at Sheba. HBOT and sham therapy are performed at the Sagol Center for Hyperbaric Medicine & Research, Shamir (Assaf Harofeh) Medical Center, Israel. Elderly patients (n = 154) with T2D and MCI (amnestic or non-amnestic) will be enrolled; Mini Mental State Examination (MMSE) score > 24 and Clinical Dementia Rating (CDR) = 0.5 are required. An informant must be available to provide supplemental information throughout the trial. Participants are recruited through advertisements, mailing lists of elderly interested in receiving health-related updates, word-of-mouth, and talks in the community. Table 1

RESEARCH IN CONTEXT

1. Systematic review: This trial examines the efficacy of hyperbaric oxygen therapy (HBOT) in improving cognition in mildly cognitively impaired elderly with type 2 diabetes (T2D), who have high dementia risk. T2D is a vascular disease culminating in a deficiency of oxygen in the tissues, and which affects the blood vessels in the brain (increasing risk for cerebrovascular disease, which is an important factor in the risk of developing Alzheimer's disease).

2. Interpretation: The trial will be a randomized controlled trial, in which one group will experience conditions in the hyperbaric chamber where the rate of oxygen is higher than in the normal environment, and the second group will serve as a control, in which the conditions in the hyperbaric chamber will be the condition found in the normal environment.

3. Future directions: If effective, this study may provide strong evidence for the brain and cognitive benefits of HBOT in this population.

FIGURE 1 Central Israel, where most participants live. Arrows mark the approximate location of the Sheba Medical Center and Asaf Harofeh Medical Center

summarizes eligibility criteria. Participants are preferably from central Israel, relatively close to Asaf Harofeh, where HBOT treatment is performed (Figure 1).

2.2 | Randomization and blinding of intervention

Using the SAS PROC Plan v9.4,[55] eligible participants are randomized with equal probability to the HBOT and sham interventions, with a total of 77 for each. When a cluster of three to six participants is filled, with a maximum wait of 3 weeks, the intervention for that cluster will begin. Therefore, the number of clusters may vary. Three study technicians who activate HBOT or sham protocol sessions are the only unblinded staff who have the key for the participants' group assignments. All participants and other clinic staff remain blinded to group assignment.

TABLE 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
1. T2D diagnosis	1. Brain disease that affects cognition (eg, Parkinson's disease, schizophrenia)
2. MCI diagnosis	2. Stroke
3. Age ≥ 65 years	3. Epilepsy
4. Hebrew fluency	4. Chest pathology incompatible with HBOT
5. An informant	5. Inner ear disease
	6. Claustrophobia
	7. Treatment with cholinesterase inhibitors
	8. An indication for HBOT
	9. Previous HBOT treatment
	10. Cancer or other medical illnesses requiring intensive therapy
	11. Proliferative retinopathy

Abbreviations: HBOT, hyperbaric oxygen chamber; MCI, mild cognitive impairment; T2D, type 2 diabetes.

Staff from Sheba, who assesses outcomes, remain blinded and do not meet participants during their intervention.

2.3 | Procedures

Table 2 presents study procedures for each participant. After undergoing an informed consenting process, the eligibility screening includes a medical and neurological clinical evaluation to confirm T2D and MCI diagnoses. Each assessment incudes medication review that may indicate an exclusion (intake of cholinesterase inhibitors). At baseline, eligible patients are tested on outcome measures. Cognitive, affective (by the Beck Depression Inventory; see the supporting information), and functional assessments are repeated after the intervention to test short-term effects, and after 6 and 12 months to test longer-term effects. CBF and cerebral glucose utilization (FDG-PET) are repeated after the intervention and at 12 months to evaluate neuropathological processes relevant to T2D. Physical exams and blood sugar tests for safety monitoring occur before randomization and after the intervention, when a questionnaire examines whether blindness was maintained.

2.4 | HBOT intervention

HBOT is administrated in a multiplace chamber (HAUX 2700). The unit comprises a seating area with comfortable chairs for 12 participants, resembling an airplane (Figure 2), and is staffed by a nurse who stays throughout the session. The HBOT protocol includes 60 daily sessions of 90 minutes of 100% oxygen at 2 ATA with 5-minute air breaks every 20 minutes, 5 days/week. This hyperbaric oxygen treatment protocol is used clinically for treatment of ischemic non-healing wounds (diabetic foot or post radiation injury), and was used in a previous clinical trial

TABLE 2 Summary of study procedures

| | Screening | Baseline | End of intervention[a] | After intervention | |
				6 months	12 months
Informed consent	X				
Medication review	X	X	X	X	X
Eligibility assessment	X				
Cognitive testing		X	X	X	X
Functional assessment (CDR)	X		X	X	X
ADL and IADL		X	X	X	X
Beck depression inventory		X	X	X	X
CBF		X	X		X
Cerebral glucose utilization		X	X		X
Randomization		X			
Physical exam	X		X		
Adverse event monitoring[a]			X		
Blindness testing			X		

[a]The intervention protocol begins within 3 weeks after baseline assessment and ends after 60 HBOT/sham treatments. A physician is always present during the HBOT/sham sessions, and a nurse is in the chamber throughout the whole treatment, so adverse events are closely monitored at each session of the intervention.

Abbreviations: ADL, Activities of Daily Living; CBF, cerebral blood flow; HBOT, hyperbaric oxygen chamber; IADL, Instrumental Activities of Daily Living.

FIGURE 2 Hyperbaric oxygen chamber

in post-stroke patients.[46] Study nurses monitor adverse events (AEs) during all sessions and a physician is present in the hyperbaric center during each session. While in the chamber, participants may drink, read, write, sleep, hear music with headphones, or watch TV. Video games, laptops, phones, or other electronic devices are not allowed in the chamber. Each participant has his/her own mask. The atmospheric pressure increases to 2 ATA during the first 5 minutes of the session, which is accompanied by the sound of circulating air. Participants feel ear pressure; the nurse advises releasing it by pumping the ears—closing the nose with fingers and pushing air. In the last 5 minutes of the session, the pressure is slowly decreased to 1 ATA. Additional procedures performed before entrance to the chamber are described in the supporting information.

2.5 | Sham intervention

The sham control condition replicates all experiential aspects of the HBOT therapy except for the degree of pressure and oxygen levels. The sham condition exposes subjects to 1.1 ATA, which provides a pressure sensation in addition to the noise of air circulation. Pressure then decreases very slowly during the next half hour; in the last 5 minutes of the session, air is circulated again with its related noise. Sham and HBOT sessions are never adjacent, so participants from the two groups cannot meet and compare sessions. This sham model makes the two conditions very comparable.

2.6 | Outcome measures

Primary cognitive outcome: The primary outcome was a composite sum of z-scores of four executive function tests (Trails B, Mazes, Digit-Symbol, and Category Fluency), and four episodic memory tests (immediate and delayed recall of the word list from the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), and immediate and delayed recall of Logical Memory Story I from the Wechsler Memory Scale-III). These functions are affected by T2D[56] and commonly evaluated in other MCI trials.[57,58] Z-scores are reversed if necessary so that a positive value reflects better performance.

Secondary cognitive outcomes: These are domain-specific composites—four tests each for executive function and episodic memory, both affected by T2D,[56,59] and benefitted by HBOT.[38]

Secondary outcomes: The four measures are the CDR scale and an alternative scoring (sum of boxes, described in the supporting

TABLE 3 Two group *t* test of equal means, equal n's[a]

	Outcome		
	Overall cognition z-score	CBF[b]	CGU
Sham mean change, D_1	−0.020	−0.450	−0.08
HBOT mean change, D_2	0.224	2.28	2.065
Difference in means, $D_1 - D_2$	−0.244	−2.73	−2.145
SD (both groups)	0.50	5.60	4.40
Minimum N per group	67	67	67
Enrollment N per group[b]	77	77	77

Abbreviations: CBF, cerebral blood flow; CGU, cerebral glucose utilization.
[a] Test of significance level = 0.05.
[b] Assuming a 13% drop-out rate; two-sided test; power = 80%; effect size = 0.49.

information) based on participant and informant interviews, and the activities of daily living (ADL) and IADL questionnaires.

2.6.1 | Neuroimaging

CBF: Participants undergo a full magnetic resonance imaging (MRI) protocol to acquire CBF and ancillary scans on a 3 Tesla (3T) Philips Ingenia scanner using a 32-channel radio frequency coil. The MRI protocol includes: arterial spin labeling (ASL), T2-weighted fluid-attenuated inversion recovery (T2 FLAIR), resting-state functional MRI (fMRI), and T1-weighted imaging (additional information on procedures and image processing is provided in the supporting information).

Cerebral glucose utilization: Participants undergo an [F18]FDG-PET scan to examine cerebral glucose metabolism on a Philips Vereos scanner using digital photon counting. Procedures are detailed in the supporting information.

2.7 | Statistical analysis plan

Efficacy analyses will be performed for the intent-to-treat (ITT) sample, our primary analysis, and for fully and partially compliant per-protocol (PP) samples. The ITT sample will include all participants in the group to which they were randomized, regardless of any protocol deviation including non-compliance, AEs, or loss of follow-up. The PP samples will include participants in the group according to the intervention actually received, with separate analyses for those who were fully compliant (at least 80% of sessions completed) and for those who were partially compliant (at least one session completed). A complier-average causal effect analysis[60] using a latent class modeling approach will also be performed on both fully and partially compliant samples. Participants missing a baseline value of a continuous efficacy

outcome measure will be excluded from all its analyses; maximum likelihood estimation methods will be used on missing data from an unobserved outcome follow-up visit.

For all outcome measures, baseline will be compared to outcomes at each time after intervention by mixed model analysis of covariance (ANCOVA) with time of assessment (baseline or outcome) as the within-subjects factor, treatment group (HBOT vs sham) as the between-subjects factor, and baseline value of the outcome measure as the covariate. For CBF and cerebral glucose utilization, as exploratory analyses, linear mixed effects models will be used to assess relationships between treatment group (fixed effect) and the longitudinal trend (random intercept and slope for each subject), assessed post-intervention and after 12 months. Because CBF derived from ASL perfusion may represent combined effects of neural metabolism and vascular effects, a secondary ANCOVA of CBF changes from baseline to 12 weeks will adjust for cerebral glucose metabolism. Changes in CBF and cerebral glucose utilization will be further explored as mediators of the relationship between treatment group and the change in cognition.

2.8 | Power analysis and sample size justification

Cognitive outcomes: Power is presented for detecting the difference in mean change (from baseline to 12 weeks) in overall cognition z-scores between the sham and HBOT treatment groups. Power calculations are based on two-sample *t* tests and are conducted with a two-sided 5% significance level (Table 3). The predicted mean change in the sham group from baseline to 12 weeks is −0.02 (based on the Israel Diabetes and Cognitive Decline [IDCD] study). Assuming a standard deviation (SD) of 0.50 in both the sham and HBOT groups, with a minimum sample size of 67 patients per arm, we have 80% power to detect an improvement in the HBOT group of 0.224, a "medium" effect size of 0.49. To account for an anticipated dropout rate of 13%—conservative compared to 5% in our previous stroke study[46]—we plan to enroll 77 patients per group for a total of 154 patients. In a previous trial assessing the efficacy of HBOT years after mild traumatic brain injury,[61] an effect size of 0.47 was detected for information speed processing, which is clinically comparable to our primary outcome measure of overall cognition. An HBOT trial for stroke patients[46] showed an effect size of 0.49 for the National Institutes of Health stroke scale, suggesting our detectable effect size of 0.49 is plausible.

CBF outcomes: Power is presented for detecting the difference in the mean changes in CBF and cerebral glucose utilization between the sham and HBOT groups. Assuming a mean change in CBF of −0.45 in the sham group and an SD of 5.6 in both groups, with a minimum sample size of 67 patients per arm we have 80% power to detect an improvement in the HBOT group of 2.28, an effect size of 0.49. To account for an anticipated dropout rate of 13%, we plan to enroll 77 patients per group for a total of 154 patients.

Cerebral glucose utilization outcomes: Assuming a mean change in the sham group of −0.08 and an SD of 4.40 in both groups, with 67 patients per group we are powered to detect an improvement in the

HBOT group of 2.065, an effect size of 0.49. According to literature sources,[5,62] these are observable effect sizes.

3 | DISCUSSION

This study aims to examine the effect of HBOT versus sham on cognition, CBF, and brain glucose utilization in elderly patients with T2D who are at high dementia risk due to MCI.

Our design has few limitations. Assessment of outcomes and HBOT therapy are performed in two different hospitals imposing some burden on participants but ensuring blindness of the team to the group assignment. Several patient groups who may benefit from the treatment are not included, such as pre-T2D conditions, which already show brain alterations associated with cognitive impairment.

The prevalence of T2D is increasing worldwide and its deleterious role on cognition and dementia is increasingly recognized.[5] Cerebrovascular pathology is hypothesized to be a significant contributor to T2D-related poor cognitive outcomes as demonstrated by the association of brain hypoperfusion, independent of brain atrophy, with worse cognitive performance in patients with T2D.[14] Currently, HBOT's approved U.S. Food and Drug Administration (FDA) indication in the context of T2D includes the treatment of diabetes-related ischemic foot ulcers[63]; preliminary results also point to its efficacy in improving neurological and brain activity outcomes in post stroke,[46] and vascular dementia.[64] While the biological plausibility of HBOT in T2D-related cognitive outcomes is supported, ours is the first study to date to test the impact of HBOT on cognitive function in T2D.

Two 1970s studies evaluated efficacy of HBOT at 2.5 ATA (two daily 90-minute sessions for 15 days) in dementia. No beneficial effects were found for 13 patients with cortical atrophy and eight with evidence of cerebrovascular disease.[65] For 40 older adult participants with cognitive impairment, hyperbaric or normobaric oxygen therapy did not show significant improvement.[66] These studies had a short intervention period, which might have been too short to determine an effect. Moreover, the small sample size in both studies limited the power to detect an effect. More recently, in 64 patients with vascular dementia, randomization to HBOT as an adjuvant to donepezil improved cognition versus donepezil alone. This study had some methodological limitations, including no sham group and no blinding. In addition, the study protocol was not fully revealed,[67] suggesting more work is necessary.

Our protocol design is based on regenerative medicine paradigms, which postulate that changes in oxygen availability, rather than steady state hypoxic or hyperoxic conditions, are required to induce processes required for angiogenesis and neurogenesis.[68] The present study addresses several limitations of previous studies: (1) patients with T2D have compromised cerebral vasculature, leading to chronic mild hypoxia and poorer CBF that HBOT may remedy; (2) patients have MCI, rather than frank dementia, so some brain vasculature changes may be reversible, preventing or delaying dementia; (3) sham therapy is preferable to a crossover control condition; (4) we assess longer-term HBOT effects (12 months); (5) our sample size is larger, and thus, more sufficiently powered to predict HBOT effects; and (6) sham at 1.1 ATA may be preferable to 1.3 ATA, given that the latter has been shown to increase tissue oxygenation by >50% in a mouse model.[69]

Our study focuses on cerebrovascular disease and cerebral glucose uptake as the primary underlying mechanisms; however, HBOT has also been suggested to affect other mechanisms relevant to diabetes-related brain insult, including: improved blood-brain-barrier features,[45] mitochondrial function,[70] cellular metabolism, inflammation, and oxidative stress.[39]

If our results support the hypothesis of beneficial effects of HBOT for individuals with both T2D and MCI, a future randomized controlled trial will have a strong rationale to broaden the eligibility criteria to include cognitively normal pre-T2D older adults. It will also provide crucial information for optimizing design for planning a multi-center large-scale clinical trial to provide definitive evidence for the benefits of HBOT for the brain and cognition in T2D patients at high risk for dementia: effect sizes, subgroups benefitting most, design, biomarkers, cognitive outcomes, recruitment strategies, and attrition. Because HBOT is widely available and well tolerated, the success may suggest testing HBOT efficacy in non-T2D elderly with MCI as well.

REFERENCES

1. Prince M, Wimo A, Guerchet M, Ali G, Wu Y, Prina M. *Alzheimer's Disease International: World Alzheimer Report 2015: The Global Impact of Dementia: An Analysis of Prevalence, Incidence, Cost and Trends. 2015.* London: Alzheimer's Disease International; 2019.
2. Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. *Nat Rev Neurol.* 2018;14(11):653-666.
3. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol.* 2014;13:788-794.
4. Li W, Huang E. An update on type 2 diabetes mellitus as a risk factor for dementia. *J Alzheimers Dis.* 2016;53:393-402.
5. Birdsill AC, Carlsson CM, Willette AA, et al. Low cerebral blood flow is associated with lower memory function in metabolic syndrome. *Obesity.* 2013;21:1313-1320.
6. Biessels GJ, Despa F. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. *Nat Rev Endocrinol.* 2018;14:591.
7. Schneider JA, Aggarwal NT, Barnes L, Boyle P, Bennett DA. The neuropathology of older persons with and without dementia from community versus clinic cohorts. *J Alzheimers Dis.* 2009;18:691-701.
8. Beeri MS, Goldbourt U, Silverman JM, et al. Diabetes mellitus in midlife and the risk of dementia three decades later. *Neurology.* 2004;63:1902-1907.
9. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet.* 2016;387:1513-1530.
10. Zeadin MG, Petlura CI, Werstuck GH. Molecular mechanisms linking diabetes to the accelerated development of atherosclerosis. *Can J Diabetes.* 2013;37:345-350.
11. Tziomalos K, Spanou M, Bouziana SD, et al. Type 2 diabetes is associated with a worse functional outcome of ischemic stroke. *World J Diabetes.* 2014;5:939.

12. van Harten B, Oosterman JM, van Loon B-JP, Scheltens P, Weinstein HC. Brain lesions on MRI in elderly patients with type 2 diabetes mellitus. *Eur Neurol*. 2007;57:70-74.

13. Cordonnier C, Al-Shahi Salman R, Wardlaw J. Spontaneous brain microbleeds: systematic review, subgroup analyses and standards for study design and reporting. *Brain*. 2007;130:1988-2003.

14. De Bresser J, Reijmer YD, Van Den Berg E, et al. Microvascular determinants of cognitive decline and brain volume change in elderly patients with type 2 diabetes. *Dement Geriatr Cogn Disord*. 2010;30:381-386.

15. Last D, Alsop DC, Abduljalil AM, et al. Global and regional effects of type 2 diabetes on brain tissue volumes and cerebral vasoreactivity. *Diabetes Care*. 2007;30:1193-1199.

16. Qiu C, Sigurdsson S, Zhang Q, et al. Diabetes, markers of brain pathology and cognitive function: the Age, Gene/Environment Susceptibility–Reykjavik study. *Ann Neurol*. 2014;75:138-146.

17. Roberts RO, Knopman DS, Cha RH, et al. Diabetes and elevated hemoglobin A1c levels are associated with brain hypometabolism but not amyloid accumulation. *J Nucl Med*. 2014;55:759-764.

18. Bangen KJ, Werhane ML, Weigand AJ, et al. Reduced regional cerebral blood flow relates to poorer cognition in older adults with type 2 diabetes. *Front Aging Neurosci*. 2018;10:270.

19. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. 2005;365:1415-1428.

20. Espeland MA, Bryan RN, Goveas JS, et al. Influence of type 2 diabetes on brain volumes and changes in brain volumes: results from the women's health initiative magnetic resonance imaging studies. *Diabetes Care*. 2013;36:90-97.

21. Saczynski JS, Siggurdsson S, Jonsson PV, et al. Glycemic status and brain injury in older individuals: the Age Gene/Environment Susceptibility–Reykjavik study. *Diabetes Care*. 2009;32:1608-1613.

22. Moran C, Phan TG, Chen J, et al. Brain atrophy in type 2 diabetes: regional distribution and influence on cognition. *Diabetes Care*. 2013;36:4036-4042.

23. Bruehl H, Wolf OT, Convit A. A blunted cortisol awakening response and hippocampal atrophy in type 2 diabetes mellitus. *Psychoneuroendocrinology*. 2009;34:815-821.

24. Gold S, Dziobek I, Sweat V, et al. Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. *Diabetologia*. 2007;50:711-719.

25. Korf ES, White LR, Scheltens P, Launer LJ. Brain aging in very old men with type 2 diabetes: the Honolulu-Asia Aging study. *Diabetes Care*. 2006;29:2268-2274.

26. den Heijer T, Vermeer S, Van Dijk E, et al. Type 2 diabetes and atrophy of medial temporal lobe structures on brain MRI. *Diabetologia*. 2003;46:1604-1610.

27. Convit A, Wolf OT, Tarshish C, De Leon MJ. Reduced glucose tolerance is associated with poor memory performance and hippocampal atrophy among normal elderly. *Proc Natl Acad Sci*. 2003;100:2019-2022.

28. Cherbuin N, Sachdev P, Anstey KJ. Higher normal fasting plasma glucose is associated with hippocampal atrophy: the PATH study. *Neurology*. 2012;79:1019-1026.

29. Willette AA, Xu G, Johnson SC, et al. Insulin resistance, brain atrophy, and cognitive performance in late middle–aged adults. *Diabetes Care*. 2013;36:443-449.

30. Beeri MS, Silverman JM, Davis KL, et al. Type 2 diabetes is negatively associated with Alzheimer's disease neuropathology. *J Gerontol A Biol Sci Med Sci*. 2005;60:471-475.

31. Arvanitakis Z, Schneider J, Wilson R, et al. Diabetes is related to cerebral infarction but not to AD pathology in older persons. *Neurology*. 2006;67:1960-1965.

32. Exalto L, Whitmer R, Kappele L, Biessels G. An update on type 2 diabetes, vascular dementia and Alzheimer's disease. *Exp Gerontol*. 2012;47:858-864.

33. Moran C, Münch G, Forbes JM, et al. Type 2 diabetes, skin autofluorescence, and brain atrophy. *Diabetes*. 2015;64:279-283.

34. Van Harten B, Oosterman J, Muslimovic D, Van Loon B-JP, Scheltens P, Weinstein HC. Cognitive impairment and MRI correlates in the elderly patients with type 2 diabetes mellitus. *Age Ageing*. 2007;36:164-170.

35. Mankovsky B, Zherdova N, van den Berg E, Biessels GJ, de Bresser J. Cognitive functioning and structural brain abnormalities in people with type 2 diabetes mellitus. *Diabet Med*. 2018;35:1663-1670.

36. Mathieu D, Marroni A, Kot J. Tenth European Consensus Conference on Hyperbaric Medicine: recommendations for accepted and non-accepted clinical indications and practice of hyperbaric oxygen treatment. *Diving Hyperb Med*. 2017;47:24-32.

37. Asl MT, Yousefi F, Nemati R, Assadi M. 99mTc-ECD brain perfusion SPECT imaging for the assessment of brain perfusion in cerebral palsy (CP) patients with evaluation of the effect of hyperbaric oxygen therapy. *Int J Clin Exp Med*. 2015;8:1101.

38. Boussi-Gross R, Golan H, Volkov O, et al. Improvement of memory impairments in poststroke patients by hyperbaric oxygen therapy. *Neuropsychology*. 2015;29:610.

39. Efrati S, Ben-Jacob E. Reflections on the neurotherapeutic effects of hyperbaric oxygen. *Expert Rev. Neurother*. 2014;14:233-236.

40. Sunkari VG, Lind F, Botusan IR, et al. Hyperbaric oxygen therapy activates hypoxia-inducible factor 1 (HIF-1), which contributes to improved wound healing in diabetic mice. *Wound Repair Regen*. 2015;23:98-103.

41. Choudhury R. Hypoxia and hyperbaric oxygen therapy: a review. *Int J Gen Med*. 2018;11:431.

42. Saito H, Kuroda S, Hirata K, et al. Validity of dual MRI and 18F-FDG PET imaging in predicting vulnerable and inflamed carotid plaque. *Cerebrovasc Dis*. 2013;35:370-377.

43. Murata T, Omata N, Fujibayashi Y, et al. Neurotoxicity after hypoxia/during ischemia due to glutamate with/without free radicals as revealed by dynamic changes in glucose metabolism. *Brain Res*. 2000;865:259-263.

44. Zhang Y, Yang Y, Tang H, et al. Hyperbaric oxygen therapy ameliorates local brain metabolism, brain edema and inflammatory response in a blast-induced traumatic brain injury model in rabbits. *Neurochem Res*. 2014;39:950-960.

45. Machida T, Takata F, Matsumoto J, et al. Contribution of thrombin-reactive brain pericytes to blood-brain barrier dysfunction in an in vivo mouse model of obesity-associated diabetes and an in vitro rat model. *PLoS One*. 2017;12:e0177447.

46. Efrati S, Fishlev G, Bechor Y, et al. Hyperbaric oxygen induces late neuroplasticity in post stroke patients-randomized, prospective trial. *PLoS One*. 2013;8:e53716.

47. Vila J, Balcarce P, Abiusi G, Dominguez R, Pisarello J. Improvement in motor and cognitive impairment after hyperbaric oxygen therapy in a selected group of patients with cerebrovascular disease: a prospective single-blind controlled trial. *Undersea Hyperb Med*. 2005;32:341.

48. Micarelli A, Jacobsson H, Larsson S, Jonsson C, Pagani M. Neurobiological insight into hyperbaric hyperoxia. *Acta Physiologica*. 2013;209:69-76.

49. Anderson RM, Hadjichrysanthou C, Evans S, Wong MM. Why do so many clinical trials of therapies for Alzheimer's disease fail. *Lancet*. 2017;390:2327-2329.

50. Winblad B, Palmer K, Kivipelto M, et al. Mild cognitive impairment–beyond controversies, towards a consensus: report of the International Working Group on Mild Cognitive Impairment. *J Intern Med*. 2004;256:240-246.

51. Petersen RC, Negash S. Mild cognitive impairment: an overview. *CNS Spectr*. 2008;13:45-53.

52. Cooper C, Sommerlad A, Lyketsos CG, Livingston G. Modifiable predictors of dementia in mild cognitive impairment: a systematic review and meta-analysis. *Am J Psychiatry*. 2015;172:323-334.

53. Luchsinger JA, Reitz C, Patel B, Tang M-X, Manly JJ, Mayeux R. Relation of diabetes to mild cognitive impairment. *Arch Neurol.* 2007;64:570-575.

54. Vipin A, Foo HJL, Lim JKW, et al. Regional white matter hyperintensity influences grey matter atrophy in mild cognitive impairment. *J Alzheimers Dis.* 2018;66:1-17.

55. Inc. SI. The randomization for this paper was generated using SAS software, Version 9.4 of the SAS System. Copyright © 2019 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA. 2019.

56. Wong RHX, Scholey A, Howe PRC. Assessing premorbid cognitive ability in adults with type 2 diabetes mellitus—a review with implications for future intervention studies. *Curr Diab Rep.* 2014;14:547.

57. Marshall GA, Rentz DM, Frey MT, et al. Executive function and instrumental activities of daily living in mild cognitive impairment and Alzheimer's disease. *Alzheimers Dement.* 2011;7:300-308.

58. Salloway S, Ferris S, Kluger A, et al. Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. *Neurology.* 2004;63:651-657.

59. Palta P, Schneider AL, Biessels GJ, Touradji P, Hill-Briggs F. Magnitude of cognitive dysfunction in adults with type 2 diabetes: a meta-analysis of six cognitive domains and the most frequently reported neuropsychological tests within domains. *J Int Neuropsychol Soc.* 2014;20:278-291.

60. Dunn G. Complier-average causal effect (CACE) estimation. In: Lovric M, ed. *International Encyclopedia of Statistical Science.* Berlin, Heidelberg: Springer Berlin Heidelberg; 2011:273-274.

61. Boussi-Gross R, Golan H, Fishlev G, et al. Hyperbaric oxygen therapy can improve post concussion syndrome years after mild traumatic brain injury-randomized prospective trial. *PLoS One.* 2013;8:e79995.

62. Büsing KA, Schönberg SO, Brade J, Wasser K. Impact of blood glucose, diabetes, insulin, and obesity on standardized uptake values in tumors and healthy organs on 18F-FDG PET/CT. *Nucl Med Biol.* 2013;40:206-213.

63. Zhao D, Luo S, Xu W, Hu J, Lin S, Wang N. Efficacy and safety of hyperbaric oxygen therapy used in patients with diabetic foot: a meta-analysis of randomized clinical trials. *Clin Ther.* 2017;39:2088-2094.e2.

64. Xu Y, Wang Q, Qu Z, Yang J, Zhang X, Zhao Y. Protective effect of hyperbaric oxygen therapy on cognitive function in patients with vascular dementia. *Cell Transplant.* 2019;28(8):1071-1075.

65. Thompson LW, Davis GC, Obrist WD, Heyman AH. Effects of hyperbaric oxygen on behavioral and physiological measures in elderly demented patients. *J Gerontol.* 1976;31:23-28.

66. Raskin A, Gershon S, Crook TH, Sathananthan G, Ferris S. The effects of hyperbaric and normobaric oxygen on cognitive impairment in the elderly. *Arch Gen Psychiatry.* 1978;35:50-56.

67. Wang S, Tao Z, Ding S, Cheng J, Bensong Y, Wang Y. Hyperbaric oxygen combined with donepezil in the treatment of vascular dementia. *Chinese J Physical Med Rehabilitat.* 2009;31:478-480.

68. Rocco M, D'Itri L, De Bels D, Corazza F, Balestra C. The "normobaric oxygen paradox": a new tool for the anesthetist. *Minerva Anestesiol.* 2014;80:72.

69. Neuman TS, Thom SR. Physiology and Medicine of Hyperbaric Oxygen Therapy E-Book. NewYork, NY: Elsevier Health Sciences; 2008.

70. Yu Q, Fang D, Swerdlow RH, Yu H, Chen JX, Yan SS. Antioxidants rescue mitochondrial transport in differentiated Alzheimer's disease transmitochondrial cybrid cells. *J Alzheimers Dis.* 2016;54:679-690.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.