Effects of vagus nerve cryoablation on glycemic control and weight loss in obese patients with type 2 diabetes

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I. BACKGROUND/RATIONALE AND PURPOSE:

Obesity is a growing epidemic, currently affecting over 1/3 of the adult US population[1] and is a well-established risk factor for the development of diabetes and cardiovascular disease.[2] Given that the majority of patients with type 2 diabetes (T2D) are obese, weight loss is the cornerstone of treatment, and has been shown to decrease risk of long term complications[3], lead to improvements in A1c and lipid levels[4,5], as well as decreased need for medications and improvements in quality of life[6]. Unfortunately, lifestyle intervention is often ineffective at achieving long-term sustainable, clinically significant weight loss[7]. Bariatric surgery is a successful intervention, leading to 20-30% weight loss with remission of diabetes in 30-65% of patients 1-5 years post surgery[8,9]. However, this invasive procedure is associated with high rates of short- and long-term complications, including need for reoperations, vitamin/mineral deficiencies, anemia, and osteoporosis[10-12]. It is clear that the current management options for obese patients, including lifestyle changes, medications and surgery, are suboptimal and innovative strategies are necessary to optimize diabetes control and weight management.

Energy balance and glycemic control are mediated largely by the gut-brain axis, specifically the vagus nerve. The vagus nerve can stimulate or inhibit food intake depending on nutritional status. Vagal nerve signaling is disrupted in the setting of obesity and thought to contribute to overeating behaviors[13]. Vagus nerve blockade has the potential to be a highly efficacious, minimally invasive intervention to address current obesity treatment limitations. Clinical studies evaluating the efficacy of an implantable electric vagus nerve blockade device found that subjects lost on average 8.8% of total body weight at 1 year; patients with T2D experienced improved glycemic control, with an average A1c improvement of 1.0% at 12 months[14]. Unfortunately, nearly 40% of subjects experienced side effects related to the device[15]. A recent pilot study from our group at Emory University (see preliminary results) reported weight loss efficacy of a minimally invasive CT guided cryoablation of the vagus nerve in obese, non-diabetic subjects. Patients lost 5.6% of total body weight and 22.7% excess body weight at 6 months with no significant side effects[16]. We propose to evaluate the feasibility and efficacy of this procedure through a randomized control trial in obese patients with T2D. We hypothesize that those patients undergoing the cryoablation procedure will experience improvement in glycemic control and enhanced weight loss at 6 months follow-up compared to the control group.

Impact of weight loss on diabetes control and complications: Over 12% of adults in the United States are affected by type 2 diabetes (T2D), the majority (>90%) of whom are overweight or obese. Weight loss, through lifestyle intervention, medications or bariatric surgery, is recommended for all overweight/obese individuals with T2D. Patients who are able to achieve >5% weight loss at 12 months experience improvement in HbA1c, total cholesterol, LDL, HDL, triglycerides, systolic blood pressure and diastolic blood pressure[7]. Intensive lifestyle interventions, glycemic control and weight loss have also been shown to decrease the risk of development of chronic kidney disease[17] and other microvascular diseases[18]. Unfortunately, many studies have shown that long-term maintenance of weight loss is tremendously difficult[19,20].

Current weight management options: medication and bariatric surgery: Weight loss medication and bariatric surgery are approved when adequate weight loss is not achieved with lifestyle interventions alone. Medications lead to clinically significant weight loss of >5% in approximately 50% of patients for whom they are prescribed, while the other half have suboptimal weight response[21]. Furthermore, weight loss effects are durable only while patients take the medications, with regain after cessation of drug therapy[22]. Bariatric surgery has proven superior efficacy over lifestyle interventions with regards to weight management, diabetes remission and reduction of comorbidities[8,23]. However, due to the invasive nature of surgery, concerns about long-term complications, and limited patient access to accredited centers, bariatric surgery is underutilized. Up to 5% of patients experience a surgical complication following the procedure[24], and rates of vitamin and mineral deficiency can reach >60%[25]. As such, options for long-term effective weight loss are limited and alternative strategies are needed to improve outcomes for obese patients.

Gut-brain axis is an important regulator of diet induced obesity: In a lean, healthy milieu, intake of food triggers vagal nerve afferent neurons to relay information about gastric distension[26] and satiety hormones to the hindbrain[27], which responds appropriately to decrease food intake and stimulate the hedonic reward system[28]. In the setting of chronic overeating and obesity**,** the release of satiety-inducing neuropeptides is decreased, while orexigenic signaling (hunger promoting) is preserved[29], which may contribute to further hyperphagia. This data has been replicated in several animal models[30-32] and provides a compelling argument that aberrant vagal nerve signaling promotes weight gain. Neuromodulation of the vagus nerve, therefore, is an attractive therapeutic intervention for obesity management.

Historical utilization of vagotomy: The rationale behind the procedure is rooted in historical surgical treatments of duodenal ulcer disease, namely the evolution of selective and highly selective surgical vagotomies[33-35]. Although these procedures have been largely supplanted by the medical management of Helicobacter Pylori, their safety and ancillary value for the management of obesity – and even subsequent heart disease and diabetes – have long been investigated.[36-41] of particular relevance to this proposal is the development and study of an implanted vagal nerve stimulator for purposes of managing obesity, the Vbloc® device. Investigators have shown that by modifying the afferent and efferent signaling pathways of the distal vagal fibers, significant positive effects are manifested via weight loss, anthropometric variables, cholesterol levels, blood glucose levels, quality of life, and blood pressure values.[42] Said another way, subdiaphragmatic vagotomies have a long history in humans without associated cardiac or sympathetic complications.

Vagus nerve blockade using an implantable device leads to weight loss and improvement in glycemic control and blood pressure: A small, prospective, open label trial evaluated the efficacy of an implantable electric vagus blocking device (VBLOC) on glycemic control and blood pressure in obese subjects with T2D. Patients were implanted with VBLOC and followed prospectively for 12 months. Excess weight loss at 12 months was 25± 4%, with improvement in HbA1c from 7.8% ±0.2% at baseline to 6.8%. Decreases were also seen in fasting plasma glucose values and blood pressure[14]. Other studies using the same device for weight management have reported pain at the VBLOC site in nearly 40% of subjects [15] which may limit the widespread applicability of this device despite promising efficacy data, and supports the notion of cryovagotomy as an alternative approach.

Efficacy of CT guided cryoablation of the vagus nerve for weight loss: Pilot data from investigators at Emory University has demonstrated the safety and feasibility of percutaneous CT guided cryoablation of the posterior vagal trunk in patients with mild to moderate obesity (BMI 30-37 kg/m2). This small and uncontrolled study enrolled twenty subjects for a cryoablation of the vagus nerve along the distal esophagus. This rapid, minimally invasive procedure was found to be 100% technically successful. There were no procedure related complications or adverse events during a 6 month follow up period. In an extension of this protocol, patients were brought back after the 6 month study to be evaluated for gastroparesis. One subject was found to have delayed gastric emptying on imaging but was asymptomatic clinically. It is unclear if this was related to the study procedure since baseline gastric emptying studies were not performed. Patients lost an average of 5.6% total body weight, with 22.7% excess BMI lost [delta BMI/(initial BMI-25)] over the 6-month monitoring period. Participants reported decreases in appetite following the procedure at all time points, with 15.8% reporting "somewhat less appetite", 68.4% reporting "much less appetite", and 10.5% reporting "very much less appetite."[16]

II. SIGNIFICANCE AND INNOVATION:

Pilot data from investigators at Emory University has demonstrated the safety and feasibility of percutaneous CT guided cryoablation of the posterior vagal trunk in patients with mild to moderate obesity (BMI 30-40 kg/m2). This small and uncontrolled study enrolled ten subjects for a cryoablation of the vagus nerve along the distal esophagus. This rapid, minimally invasive procedure was found to be 100% technically successful. There were no procedure related complications or adverse events during a 6 month follow up period. Patients lost an average of 5.6% total body weight, with 22.7% excess BMI lost [delta BMI/(initial BMI-25)] over the 3-month monitoring period. Participants reported decreases in appetite following the procedure at all time points, with 15.8% reporting "somewhat less appetite", 68.4% reporting "much less appetite", and 10.5% reporting "very much less appetite."[43]

In addition to weight loss, we anticipate that the cryovagotomy procedure will result in significant improvement in glycemic control and cardiovascular risk factors, which may result in long-term benefit is reducing diabetic complications. We propose a prospective, randomized controlled trial to determine if a minimally invasive cryoablation procedure of the vagus nerve will lead to greater weight loss and improvements in glycemic control, metabolic profile, and cardiovascular risk factors compared to lifestyle intervention in obese patients with T2D. Our data will provide preliminary data to support application for an NIH grant to further investigate manipulation of the gut-brain axis for management of type 2 diabetes and obesity.

III. DESCRIPTION OF STUDY PROTOCOL

A. SPECIFIC OBJECTIVES:

Objective 1. To compare glycemic control of patients undergoing vagus nerve cryoablation plus lifestyle intervention at 6 and 12 months compared to lifestyle intervention alone in obese patients with T2D. Patients with T2D, BMI 30-40 kg/m2, A1c 7.5-10.5% on stable doses of oral antidiabetic agents will be randomized to cryoablation plus lifestyle or lifestyle intervention alone and will be followed prospectively for 12 months in a controlled randomized trial. We will compare changes in A1c levels between groups at 3, 6 and 12-months of follow up.

Objective 2. To determine changes in weight and anthropometric metrics among patients receiving cryoablation plus lifestyle intervention versus lifestyle intervention only. Changes in body weight, BMI, waist circumference, and BIA measured at baseline, 3 and 6 months after intervention will be assessed.

Objective 3. To determine safety of the cryoablation of the vagus nerve. We will monitor rates of AEs and SAEs related to the procedure which develop during the duration of the trial.

B. ENDPOINTS:

The primary endpoint of the trial is difference in glycemic control, defined as A1c, fasting glucose and insulin sensitivity (HOMA-IR), at 3, 6 and 12 months between the vagus nerve cryoablation group and the lifestyle intervention monotherapy group.

The primary safety endpoint of the trial is occurrence of death and all procedure related complications, such as bleeding, infection, pneumothorax, hemothorax, pulmonary injury, complications of sedation, pain requiring hospital admission or treatment, dysphagia, gastroparesis, nausea and vomiting, and gastrointestinal ulceration for the duration of the study.

Secondary outcomes include differences between treatment groups in any of the following measures:

1. Body mass index (BMI), waist circumference, and waist-to-hip ratio at 3 and 6 months compared to baseline
2. Lipids (total cholesterol, LDL, triglycerides) at 6 months compared to baseline
3. Systolic and diastolic blood pressure at 3 and 6 months compared to baseline
4. Daily caloric intake as measured by 3-day food recall compared to baseline at 3 and 6 months.
5. Changes in antihyperglycemic medication regimen compared to baseline at 3 and 6 months.
6. Appetite, hunger and satiety scoring by visual analog scale at baseline, 1 week, 1 month, 3 months and 6 months
7. Physical activity questionnaire (IPAQ) at baseline, 3 and 6 months
8. Fasting glucose and insulin levels at 3 and 6 months compared to baseline

C. STUDY DESIGN:

This is a randomized, controlled, unblinded clinical study in obese adult patients with T2D, HbA1c 7.5-10.5%, BMI 30-40 kg/m2 treated with non-insulin antidiabetic medications with stable doses for at least 3 months.

Subjects will be pre-screened with the relevant questions from the Three Factor Food Questionnaire by phone or in person to determine eligibility prior to consent. Following consent and screening for trial eligibility, subjects will be randomized to treatment group. The primary endpoint, glycemic control, will be assessed at 6 months post-procedure. Patients will be recruited from the diabetes clinic at Grady Memorial Hospital and Emory University Clinics.

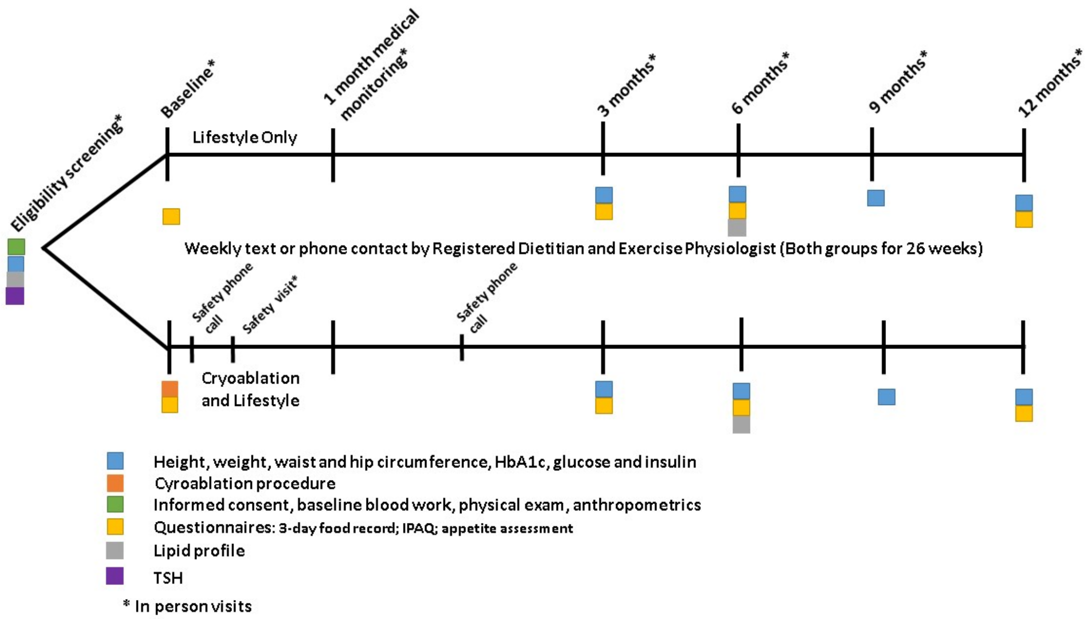
We will be screen up to 40 participants to be able to randomized 30 patients, they will be enrolled in this pilot exploratory study. Patients will be randomly allocated to undergo either CT guided cryoablation of the vagus nerve plus lifestyle intervention or lifestyle intervention alone.

Group 1: CT guided cryoablation of the vagus nerve plus lifestyle intervention (n=15).

Group 2: Lifestyle intervention by trained RD/CDE (n=15).

All subjects will have the procedure performed at Grady Memorial Hospital or Emory University Hospital Midtown or Johns Creek by trained study personnel.

The study schema is shown below. Both groups will undergo screening for eligibility followed by randomization. If the subject is not fasting at time of initial consent and screening, he/she will be brought back for a subsequent visit with fasting blood work. Subjects must be randomized within 4 weeks of the screening visit. If the randomization visit falls outside of the 4 week time frame, the subject must undergo repeat screening procedures. In- person lifestyle counseling will be provided at baseline visit for both groups. Those undergoing cryoablation will receive a phone call 24 hour post-procedure to evaluate for any immediate complications, 1 week in person follow up visit, as well as a safety call at 2 months. Subjects in both groups will have weekly contact with RD and in person follow up visits at 4 weeks, 3 months, and 6 months. Blood work, anthropometric data and questionnaires will be administered at baseline, 3 months, and 6 months. Safety follow up appointments will be scheduled at 9 months and 12 months, though no further lifestyle counseling will be provided after 6 months. Questioning regarding adverse events and side effects will occur at all visits, as well as assessment of glycemic control. Anti-hyperglycemic medications will be adjusted at visits under the direction of the endocrinologist, or as needed for clinically significant hypo- or hyperglycemic events.



Blood work will be as follows: For all lab parameters, subject results must be within the reference range unless otherwise specified by inclusion/exclusion criteria or if assessed by study physician to be not clinically significant.

Lab test	Baseline	3 months	6 months	9 months	12 months
Complete metabolic panel	X	X	X	X	X
Pregnancy test	X	X	X	X	
HbA1c	X	X	X	X	X
Lipid panel	X		X		
Insulin level	X	X	X		X
TSH	X				

D. STUDY PROCEDURE:

Cryoablation procedure (to be performed by Dr. Prologo or Dr. Dariushnia): Subjects will be NPO for 12 hours prior to the ablation procedure. Metformin and sulfonylureas will be held the evening prior to the procedure. Subjects will present to the Interventional Radiology pre-procedure holding area at 8:00 AM on the morning of the procedure and will have a peripheral IV placed by nursing staff. Point of care blood glucose level will be checked; the procedure will be deferred for BG >250 mg/dl until diabetes control can be better optimized. Low doses of sedation will be used with IV versed and fentanyl. An Interventional Radiology nurse will monitor the subject while sedation is being administered. Skin will be numbed using lidocaine. The procedure will be done under CT guidance and involves a 4-5 mm scalpel incision followed by percutaneous probe placement about the posterior gastroesophageal junction (the location of the posterior vagal trunk). The probe will create a zone of decreased temperature (-20 to -40ºC) involving the posterior vagal nerve fibers/plexus. The cryoablation process will include a 3-

minute freeze, followed by a 1-minute thaw, and a second 3-minute freeze and 1 minute thaw. After the procedure, a sterile dressing will be applied, and subjects will be monitored for 12 hours.

Lifestyle Intervention: All subjects will receive standardized dietary and exercise counseling from a registered dietitian and exercise physiologist (Dr. Frediani). Participants will be counseled to follow a low carbohydrate diet providing a moderate amount of carbohydrates per day (~100 g). Focus will be on increasing fruits and vegetables and decreasing refined sugars and processed foods. Dietary counseling will include motivational interviewing, goal setting and nutrition education.[44] Subjects will also be encouraged to slowly increase physical activity to at least 150 minutes weekly. The lifestyle intervention structure will include detailed counseling sessions at baseline, 3 and 6 months. These sessions ideally will occur face-to-face, although telemedicine visit (via zoom) will be permitted on case-by-case basis due to the COVID-19 pandemic. In addition, there will be weekly phone calls or texts (participants' choice) providing a total of 26 points of contact recommended by the USPSTF (United States Preventive Services Task Force).[45]

Surveys: Subjects will complete a number of surveys as part of participation in the trial. at baseline, 3 months, 6 months and 12 months. Three-day food records are a validated method of assess food intake[46] and will be administered at baseline, 3 months, 6 months and 12 months.Subjects will also complete visual analogue scale ratings of appetite at baseline, 1 week, 1 month, 3 month, 6 month and 12 month.[47] The International Physical Activity Questionnaires (IPAQ) is to provide a set of well-developed instruments that can be used internationally to obtain comparable estimates of physical activity.[48] Subjects will also complete the relevant questions from the Three Factor Eating questionnaire during pre-screening and must have an average score ≥3 on questions 4, 8, 9, 13, and 14 to be eligible. The entire questionnaire will be administered after subjects have been consented. The Three Factor Eating Questionnaire is a self-assessment scale used in studies of eating behavior in overweight and normal individuals, designed to assess cognitive restraint, disinhibition, and hunger.[49] Preliminary investigation of this cryovagotomy procedure has identified subjects who score ≥3 on the aforementioned questions to be those who respond best to the intervention.[16]

Blinding. The trial design is an unblinded, randomized control trial. By nature of the study design, participants and study personnel must be aware of which arm participants are enrolled.

E. POTENTIAL RISKS AND BENEFITS:

Risk to Human Subjects: Specific to this procedure, a 20 subject pilot was recently completed that demonstrated no procedure related complications or adverse events during 6 months of follow up. During the 12 month extension, 1/20 patients was found to have a prolonged gastric emptying time, though it is unclear if this was related to the study procedures as no baseline measurements were performed and the subject was asymptomatic. The Visual–Ice Cryoablation System is intended for cryoablative tissue destruction using a minimally invasive procedure. As described in the Icesphere 1.5 Needle user manual on page 14, there are no known adverse events related to the specific use of the cryoablation needles[50]. The procedure is CT guided which allows for real-time visualization of the process to ensure efficacy and avoid damage to any adjacent tissue or structures. Percutaneous CT-guided cryoneurolysis is well established and routinely performed clinically. Specifically, Dr. Prologo's group has conducted three other independent studies of peripheral nerve cryoablation, with procedural methods and outcome measures that parallel the methods described herein[51-53]. **Perhaps more importantly though, the device is routinely used in clinical practice for the ablation of nerves as part of percutaneous procedures that are very similar to the percutaneous cryovagotomy proposed for this study,** including cryoablation for treatment of trigeminal neuralgia in the setting of cancer[54], celiac plexus cryoablation,[55] as well as obturator nerve cryoablation, genitofemoral nerve cryoablation, cryoablation of medial branch nerves in the setting of facetogenic lumbar spine pain, and cryoablation of the inferior alveolar nerve.

Regarding the mechanism of cryoneurolysis, the premise upon which nerve cryoablation procedures have been founded is the induction of a specific, reversible nerve injury.[56-58] Nerve injury classifications are classically described and correlated with clinical course following trauma (crush, stretch, laceration, etc.), the most widely cited of which are the Seddon and Sunderland classifications.[59,60] it has been shown that temperatures induced by cryoablation devices correspond with Sunderland 2 injuries in peripheral nerves.[56,57] This precise neural injury results in several well described events that lead to favorable clinical outcomes – cessation of conduction, induced Wallerian degeneration, and *predictable regeneration* of axons upon an intact connective tissue scaffold. [57,58,61] the translation of these events (beyond conduction cessation) has been documented as nerve function recovery in animal studies and in humans[62-65]. [62-66]

Please see below with more details on the identified potential risks of procedures performed percutaneously in interventional radiology:

1. *Bleeding*: The risk of bleeding is estimated to be <2%, and is specifically localized to the site of the skin incision (4-5 mm). The risk of any internal bleeding is negligible since it is a CT guided procedure and direct visualization of the probe during the procedure limits any inadvertent involvement of vascular structures. After the procedure, patients will have a sterile bandage placed on the incision and will be monitored for 12 hours.

2. *Pneumothorax*: Estimated risk is <1%. We feel that the risk of pneumothorax is non-significant given that this is a CT guided procedure, which will minimize any off target risk. Should any complications arise, this will be visualized in real time on the CT scan and immediate treatment will be provided.

3. *Sedation associated risks*: <0.5% risk. Conscious sedation using fentanyl and versed will be used at standard procedural doses. Should any excess sedation occur, this will be reversed immediately in the procedural suite.

4. *Off target ablation*: This refers to any inadvertent ablation of other nerves, estimated to be <1.0% risk. This would be seen in real-time on CT guidance, and ablation could be halted immediately to prevent complete nerve resection.

Protection against risks: Our strict inclusion and exclusion criteria for entry will help to minimize risks. In addition, we will carefully monitor patients with a phone call 24 hours, and 2 months after the procedure, and a clinic visit at 1 week, 1 month, 3 months, 6 and 12 months. Subjects will be monitored for specific procedure related complications or adverse events at each visit. Subjects will also be provided with contact information for study personnel should any events occur in between visits. Unscheduled events can be arranged to assess any urgent matters. All AEs, regardless of whether or not they are related to the procedure and use of the device, will be documented and reported to the IRB, DSMB, and FDA in a timeline as specified by the FDA Code of Federal Regulations Title 21, section 812.150 reporting (21CFR812.150(b)).Outcomes regarding hypo- and hyper- glycemia will also be collected and reported for safety monitoring.

Subjects with poorly controlled diabetes (A1c >10.5%) or a history of DKA will be excluded from enrollment. Subjects will be educated on the potential for development of hypoglycemia. Diabetic medications will be adjusted in event of hypoglycemia/hyperglycemia under the direction of Dr. Alexandra Migdal (Endocrinologist). Self-monitoring of blood glucose (BG) levels will be recommended twice daily and any time symptoms of hypo/hyperglycemia occur. In the setting of hyperglycemia (average BG >250 mg/dl x 1 week), medication doses will be adjusted. Subjects on metformin will have the dose titrated to a maximum of 2000 mg/d if tolerated. Sulfonylureas can be titrated to maximal doses per manufacturer instruction. Subjects may be prescribed rescue therapy with insulin in the event of significant hyperglycemia unresponsive to titration of oral agents. In the setting of BG <100 mg/dl, sulfonylurea doses will be decreased by 50% and discontinued if necessary. If BG <55 mg/dl, sulfonylureas will be stopped. Metformin will be stopped if hypoglycemia persists.

Technical success rate of the procedure and procedure related complications: Discontinuation of the trial will occur if 3 participants within the first 8 of 30 planned experience significant adverse events (AEs) (Grade 3 procedure-related AE or procedure-related serious AE) at any point during follow-up and if 4 participants experience significant AEs (Grade 3 procedure-related serious AE) at any time. The trial will be stopped at any point if a Grade 4 or Grade 5 AE occurs until determination can be made regarding its potential relationship to study involvement.

Grading of AEs:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization of prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE[67]

Specific clinical signs or symptoms that will qualify for the above criterial include (amongst other potential Grade 3-5 AEs not listed here): constitutional symptoms (severe fatigue interfering with ADLs, fever > 40°C, prolonged and/or severe rigors), endocrine (uncontrolled hyperglycemia, ketoacidosis), gastrointestinal (inadequate caloric intake requiring TPN or IV fluids, diarrhea requiring IV fluids and/or manifesting as >7 stools/day, symptomatic abdominal distention or bloating, severe abdominal pain requiring narcotics, ileus, severe nausea requiring hospitalization, bowel obstruction or perforation), hemorrhage requiring intervention, infection requiring antibiotics, or pain interfering with ADLs.

Withdrawal Criteria: The subject may withdraw at any time during the study by the primary care provider or his/her own decision.

The subject may be withdrawn at the investigator's discretion due to a safety concern or for contravention to the inclusion and/or exclusion criteria. Any subjects experiencing a Grade 3-5 AE as described will be withdrawn from the study. Reasons for study withdrawal will be tracked and documented.

If a subject is withdrawn prior to completion of the 12 month study period, the subject will be encouraged to keep follow up appointments with the study team for monitoring of adverse events or until resolution of any adverse events related to the procedure.

Data Safety Monitoring: In addition, an independent data safety monitoring committee (DSMC) will be established to serve as the primary data and safety monitoring group for the trial. The DSMC will review unblinded interim safety data, evaluate whether the study should be stopped or amended for safety or other reasons, and make such recommendations to the investigators. In addition, the DSMC will provide input to the investigators concerning the study protocol, statistical analysis plan, administrative conduct of the trial, and interpretation of the final safety and efficacy data. The DSMC will meet every 6 months, and as needed in the event of an unanticipated adverse device effect. At each meeting, the DSMC will review the incidence of adverse events, severity of each, statistical considerations, and safety concerns (including information on hypo- or hyper-glycemia)– as well as conduct of the trial and accrual goals.

f. Potential benefits to the subject. We believe that subjects receiving the interventional treatment will benefit from modest weight loss and improvement in glycemic control. Subjects who receive the lifestyle counseling are expected to achieve modest weight loss as well. Furthermore, enrollment in clinical research studies and enhanced focus on glucose monitoring has been shown to reduce complications associated with hyperglycemia.

F. STUDY SUBJECT SELECTION:

Inclusion criteria:

1. Males and females between the ages of 22-65
2. Diagnosis of T2DM for <10 years
3. HbA1c between ≥7.5% and ≤10.5%
4. Treatment with non-insulin antidiabetic medications with stable doses for at least 3 months, with failed prior attempts at dietary interventions to optimize diabetes control
5. BMI 30-40 kg/m2

6. Willing to comply with study requirements
7. Documented negative pregnancy test in women of child bearing potential and use of an effective birth control method
8. Average score of ≥3 on questions 4, 8, 9, 13, and14 from the Three Factor Eating Questionnaire, to be assess prior to consent via phone screen or in person.

Exclusion criteria:

1. Diagnosis of type 1 diabetes or history of diabetic ketoacidosis
2. Use of insulin therapy
3. Significant kidney disease (eGFR < 60 ml/min/1.73m^2)
4. Current drug or alcohol addiction
5. Thyroid disease unless underlying diagnosis is primary hypothyroidism on stable medications for >3 months with TSH in reference range at time of screening visit
6. Systemic steroid use within 30 days prior to randomization
7. Use of prescription or over the counter weight loss medications within 6 months prior to randomization
8. Weight gain/loss >5% over the past 6 months
9. Previous GI surgery or abnormal GI anatomy which may limit technical feasibility of the procedure
10. Recent diagnosis of cardiovascular disease requiring PCI or CABG within the past 6 months
11. Abnormal pathologies or conditions of the GI tract, including peptic ulcers, hiatal hernia, active gallbladder disease, pancreatitis, cirrhosis, inflammatory bowel disease, upper GI bleed within 6 months of randomization
12. Any condition or major illness that places the subject at undue risk by participating in the study
13. Psychiatric condition rendering the subject unable to understand the possible consequences of the study
14. Inability to provide informed consent
15. Female subjects who have been pregnant within 6 months or breast-feeding at time of enrollment into the study, or women who plan to become pregnant within the next 12 months
16. Diagnosis of anemia, RBC transfusion in the preceding 3 months or expectation to receive transfusion within the next 12 months, or hemaglobinopathies that would affect HbA1c reliability
17. Active or recent infection
18. Immunosupression
19. History of coagulopathy or high risk for development of deep vein thrombosis (including congestive heart failure, those who are non-ambulatory, active leukemia/lymphoma, prior thrombotic events, family history of thrombosis)
20. History of blood pressure instability (systolic BP ≤100 or ≥160 mmHg)
21. History of autonomic dysfunction, including amyloidosis, Parkinson’s disease, autoimmune disease, spinal cord injury

G. STATISTICAL CONSIDERATIONS:

The primary outcome is the difference in glycemic control (as measured by HbA1c) at 6 and 12 months between the vagus nerve cryoablation group and the lifestyle intervention group. Summary statistics including mean, median, and standard deviations for the changes in HbA1c at 3, 6, 9 and 12 months will be computed. We will then compare the changes at 6 months between the two treatment groups by a nonparametric Wilcoxon test or a two-sample t-tests (with appropriate data transformation if needed). We will conduct one-way ANOVA to estimate the mean difference in glycemic parameters at 6 and 12 months month between the two treatment groups. We may further adjust for some important confounders by using linear regression models. We will also assess the glycemic control outcomes simultaneously across different follow-up visits (i.e. 12, 24 weeks) through repeated measures ANOVA models, which appropriately account for within-subject correlations in the measurements. In addition, we will consider repeated measures linear regression model with visits incorporated as a continuous time variable. We may include other covariates in the model when feasible.

The primary safety endpoint of the trial is the occurrence of death and all procedure related complications, such as bleeding, infection, pneumothorax, hemothorax, pulmonary injury, complications of sedation, pain requiring hospital admission or treatment, dysphagia, gastroparesis, nausea and vomiting, and gastrointestinal ulceration for the duration of the study. We will first use the Chi-square test (or Fisher's exact test) to compare the occurrence of this primary safety endpoint between the two treatment groups. We will perform logistic regression to evaluate the group difference while adjusting for other potential confounders such as age, gender, and BMI. In addition, we will compare the number of procedure related complications by using Poisson regression or Negative Binomial regression between the two treatment groups. Standard model selection (e.g. forward, backward variable selection) and model checking procedures (e.g. deviance residual plot and Hosmer- Lemeshow test) will be performed to ensure the adequacy of the final models.

Secondary outcomes will be compared between the two treatment groups. For continuous secondary outcomes, we will follow the plan proposed for primary outcome. For discrete secondary outcomes, we will first conduct cross-sectional comparisons based on Chi-squared tests or Fisher's exact test. If the discrete outcome is measured at multiple visits, we will fit repeated measures generalized linear models to simultaneously assess the difference in the longitudinal discrete outcome between the two treatment groups. Other covariates may be included in the models if feasible.

Sample Size Calculation and Power Analysis:

This study is generating pilot data for utilization of this procedure in a novel patient population. Given the 15 patients per group, taking into account 20% attrition rate, we would have 12 patients per group. In this case, we would have 80% power to detect a difference in glycemic control outcome change that equals 1.2 times the standard deviation of the glycemic control outcome change. The data generated from this study will provide useful relevant preliminary data for planning larger randomized studies.

IV. DATA HANDLING AND RECORD KEEPING:

Data collection records with personal identifiers will be stored in locked file cabinets. Blood samples drawn in conjunction with this study will not be labeled with information that could directly identify study subjects. De-identified serum samples will be stored. We may use the samples collected and stored in this study for future studies without a separate IRB consent for the subjects. This will be explained to the study subjects at the time of consent. If we use the samples in future studies, coded identifiers will be used. The informed consent will make it clear that subjects can request their samples to be destroyed at any time. Presentation of the study results at regional or scientific meetings or in publications will not identify subjects. Access to research and confidential records will be limited to clinical investigators, research coordinators, and the IRB at Emory University.

Study coordinators and/or investigators will collect baseline and follow up data, complete the CRF (case report form) and enter data into RedCap (electronic database provided by the Emory Research Information Technology Department). Baseline data will include demographics (gender, age, ethnicity), duration of diabetes, comorbid conditions, medications, BMI, screening labs, QOL assessment scores, appetite score, three-day food records analyzed using Nutrition Database System for Research (NDSR) and physical activity questionnaire (IPAQ).[48] Follow up data will include medications, BMI, body measurements, follow-up labs, QOL assessment scores, appetite score, three-day food record, IPAQ, and adverse events.

V. ETHICS:

A. INFORMED CONSENT

After identification of eligible patients these individuals will be provided basic information regarding the study and, if interested, a member of the research staff using inclusion/exclusion criteria delineated elsewhere in the protocol will then screen patients. Informed consent will be obtained before any trial related procedures including screening procedures. The consent form, potential risks and benefits, and the rights of research participants will be explained to the participant by the investigators or research coordinator. Individuals will be asked if they have questions, and a member of the research staff will answer questions. The principal investigator (PI) will also be available at all times to answer questions that participants may have during the consent procedure or during the time a participant is enrolled in the study. The consent form will be completed only by trained research personnel familiar with the study protocol procedures, informed consent process, who have undergone CITI training in accordance with the IRB guidelines of Emory University. A signed copy of the consent form will be provided to the participant and a copy will be placed in the file that is maintained for each participant in the study office. Adults who speak any of the following languages (English, Spanish) will be approached for participation in the study.

B. RECRUITMENT AND RANDOMIZATION

Subjects will be recruited from the Diabetes Clinic at Grady Memorial Hospital and Emory Healthcare clinics. Patients with diabetes will be identified electronically. Once a potential candidate is identified, we will approach the primary clinician as well as the patient for consent.

Patients will be randomized consecutively using a computer-generated randomization table provided by Dr. Limin Peng at the Emory School of Public Health.

VI. LIABILITY AND SUBJECT INSURANCE:

A. FINANCIAL OBLIGATION

No additional cost to patients or to the institution will be incurred for research purposes. Patients will not be billed for the laboratory work or any test that is being done only for study purposes. Patients will be responsible for the cost of their usual ongoing medical care, including procedures and/or non-study medications that their doctor requires as part of their usual medical care.

B. PAYMENT FOR PARTICIPATION

Participation in this study is voluntary. Patients will receive $25 for the screening visit, $75 for the enrollment visit, $30 for the 1 month, 3 month, 6 month, 9 month and 12 month visit to compensate for time and effort. Total compensation will be two hundred and fifty dollars ($250.00).

C. RESEARCH INJURIES

If a patient is injured because of taking part in this study, Dr. Migdal and investigators at each institution, along with the medical facilities will make medical care available. Emory University, however, has not set aside any money to pay participants or to pay for their medical treatment. The only exception is if it is proved that the injury or illness is directly caused by the negligence of an Emory/Grady employee. "Negligence" is the failure to follow a standard duty of care. Financial compensation for such things as lost wages, disability or discomfort due to an injury related to the study is not available.

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