Accelerated Sarcopenia
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1. Introduction and Purpose:

Accelerated Sarcopenia. Sarcopenia is a complex geriatric syndrome characterized by the loss of skeletal muscle mass, strength and function with aging[15]. It is a major contributor to the cycle of frailty [38] and increases the risk of falls, physical dependence, disability and mortality in older adults[15,68,82]. While the loss of muscle mass and function occurs gradually with healthy aging, diseases or other insults and injuries can accelerate sarcopenia and lead to catastrophic declines in mobility and independence[74].

Type 2 Diabetes Chronically Accelerates Sarcopenia. Chronic diseases are associated with acceleration of sarcopenia. Among these, Type 2 Diabetes Mellitus (T2DM) has been reported in longitudinal studies to hasten the loss of muscle mass and strength in older persons, even after adjustment for comorbidities, glucose control, disease length and other factors[58,72-74]. Insulin resistance may play a role in this process[62]. However, *we do not know which specific mechanisms are involved in the acceleration of sarcopenia by T2DM*.

Knowledge Gap. Conditions that accelerate sarcopenia, such as T2DM, increase the risk of disability and dependency in older adults. However, the fundamental mechanisms by which sarcopenia accelerators induce loss of muscle mass and function are unknown. As a consequence of this knowledge gap, and in the absence of specific therapeutic targets, it is not possible to develop innovative and effective strategies for prevention and treatment of accelerated sarcopenia in older patients.

Significance. The proposed research is expected to spur a vertical advancement in our knowledge of the mechanisms that underlie accelerated sarcopenia in older adults. *This work is significant because it will lead to the identification of novel, specific targets for the development of evidence-based interventions to prevent and treat accelerated sarcopenia and maintain independence in older adults at high risk of physical dependence.*

Benefit. Mobility disability and physical dependence are major concerns for older adults, and important contributors to rising healthcare costs in the geriatric population[53]. In the year 2010, 26.9% of the U.S. adults 65 and older had diabetes[11]. A decline in muscle mass and muscle quality in this patient population is associated with reduced mobility[90] and increased risk of functional disability[91]. Hospitalization and bed rest for any cause are major events that interact with chronic conditions, further reducing function and independence in older adults[14,47]. By identifying the fundamental mechanisms that accelerate sarcopenia in these disabling conditions, we will be able to develop novel treatments for maintenance of independence. Thus, our research has the potential to positively impact not only healthcare outcomes but also costs over the long term.

2. Background:

Low muscle mass is a basic component of sarcopenia[15]. The association between muscle mass and function is not linear in healthy older adults[35]. However, conditions that accelerate sarcopenia decrease muscle mass at the same rate as strength, or faster[3]. A major determinant of skeletal muscle mass is contractile protein content, which is regulated by the balance between protein synthesis and proteolysis[99]. Incorporation of dietary amino acids into newly synthesized proteins is a fundamental process for maintenance and growth of skeletal muscle, because it allows for replacement of the essential amino acids released by proteolysis and lost with oxidation or transport to other tissues[92]. The stimulatory effect of an amino acid/protein meal on skeletal muscle protein synthesis is large and rapid[48,84], and driven by essential amino acids, particularly leucine, which directly stimulate muscle protein synthesis by activating translation initiation via the mTORC1 pathway[18,5]. To activate mTORC1 signaling and protein synthesis, amino acids must first enter the muscle cell via amino acid transport. Amino acid transport is an active process that is emerging as a key regulator of skeletal muscle protein homeostasis and anabolism[55]. Amino acid transport is controlled by several factors [1,55]. We have reported that dietary amino acid intake[27,96], insulin [86] and resistance exercise[26] can independently activate amino acid transporter expression and function in humans, and this effect is associated with increased muscle protein synthesis [19].

There is growing evidence from our group[43,75,87] and others[80] that healthy aging *per se* induces a mild but significant reduction in the response of muscle proteins to anabolic stimulation. This phenomenon has been termed "anabolic resistance" and may account for the slow loss of muscle mass with advancing age. It is characterized by a reduced anabolic response to low amino acid doses[17,56,57,84,94] and insulin[43]. This is a true "resistance" because the maximal anabolic response to high doses of amino acids[83,93,96] or insulin[43] is preserved in healthy older adults and comparable to that observed in younger individuals.

Our preliminary data suggest that a global, underlying mechanism of accelerated sarcopenia is an increase in anabolic resistance associated with a reduction in amino acid transport. With this application we will examine how amino acid transport is impacted by conditions accelerating sarcopenia and identify factors that control it.

We propose that resistance exercise will improve the response of muscle protein anabolism to amino acids in T2DM by increasing mTORC1 signaling and amino acid transporter expression. Upstream regulatory pathways will be explored also in this aim to identify promising therapeutic targets for interventions.

Innovation

The research we propose is innovative, in our opinion, for at least three major reasons:

1. Conceptual Innovation. Our proposed studies will explore for the first time the potential global role of amino acid transport in conditions that accelerate sarcopenia chronically and acutely. By using a well described and common model of accelerated sarcopenia, T2DM, this research may also rapidly yield practical innovation that could be rapidly translated in the clinical setting.

2. Methodological Innovation. Innovation also stems from our novel integrative and interdisciplinary translational approach that combines state of the art and novel methodologies to determine amino acid transporter expression and function and their upstream regulation. These methodologies include: a 3-pool model tracer methodology to measure amino acid trafficking across vascular and intracellular compartments[20]; molecular techniques to measure regulation of muscle protein synthesis and amino acid transport[26,27]; and near infrared spectroscopy (NIRS) to determine the role of endothelial function and microvascular muscle perfusion[86,87]. Exercise is a well-established means to induce muscle growth. Resistance exercise also stimulates amino acid transport and transporter expression independent of changes in amino acid availability[26]. In this application, we will *innovatively use exercise as a tool to modify the response of amino acid transport and transporter expression* with the purpose of testing our hypotheses and identifying new therapeutic targets.

3. Discovery of Novel Molecular Targets. Our secondary outcomes will include exploration of the role of novel regulatory proteins in relation to the changes in amino acid transport associated with T2DM. The basic assumption is that chronic and acute sarcopenia accelerators may reduce amino acid transport with different mechanisms. Thus, we will determine the potential role of newly identified amino acid sensing pathways such as the Sestrins-GATOR1/2 and the lysosomal vATPase/SLC38A9/Ragulator complex in the activation, or lack of thereof, of mTORC1 signaling and amino acid transporter expression and function.

Our approach — unique and substantially different from the status quo — is expected to unravel the key underlying mechanisms responsible for accelerated sarcopenia due to T2DM. The knowledge generated by our studies is needed to develop future evidence-based clinical trials of interventions.

3. Concise Summary of Project:

Subjects. We will test our central hypothesis in community dwelling, independent older adults with non-insulin dependent T2DM. To account for screening failures and drop-outs/withdrawals we plan to enroll about 30 subjects in order to have 15 subjects completing the study. Since data previously gathered on healthy subjects will serve as controls for T2DM subjects, who are expected to be overweight or obese, we will limit inclusion to subjects with BMI 23-35 kg/m^2. Those who have a BMI ≥ 35 kg/m^2 will be considered for inclusion on a case-to-case basis, depending on whether or not

thigh adiposity would impair muscle biopsy. Morbidly obese, frail or exercise trained subjects will be excluded, as these conditions can significantly impact muscle protein metabolism[13,79,89], confounding the results. Subjects will be weight stable, as active weight loss in obese older adults can temporarily improve the response of muscle protein synthesis to anabolic stimuli[88]. Subjects will be recruited from the UTMB Pepper Center Volunteer Registry, the Diabetes Clinic for Seniors directed by Dr. Volpi, and the UTMB Stark Diabetes Clinic.

Screening: After carefully explaining procedures and risks, informed consent will be obtained from all subjects. Eligibility will be assessed with clinical history, physical exam, questionnaires, functional testing, and a number of laboratory tests including blood count, metabolic panel, hemoglobin A1c, uric acid levels, lipid profile, thyroid function, coagulation panel, urinalysis, urine toxicology drug screening, hepatitis B and C screening, HIV test, DEXA scan, and a stress test. An OGTT will also be performed, and may involve the use of tracer methodology (U-C^{13} glucose) to better describe glucose kinetics. Habitual physical activity will be measured using both StepWatch Activity Monitors (SAM) and pedometers for approximately 1 week during the screening process.

4. Study Design. Subjects will undergo a two acute experiments, one prior to and one immediately following the completion of 13 weeks' (1 run-in week and 12 weeks progressive resistance exercise) training, in which we will test the effects of 7 g of EAA in older T2DM patients.

1) Run-In: The day prior to the experiment we will:

- Admit subjects to the ITS-CRC.
- Draw safety labs (blood count, metabolic panel, coagulation panel, urinalysis) and other individualized clinical labs necessary to follow up on safety parameters.
- Provide standardized meals
- Hold vasodilators, monitor blood pressure, and manage hypertension with other medications if necessary [43,75,87].

2) Metabolic Experiment. The experimental procedure is designed to measure skeletal muscle amino acid transporter expression and function, whole body and muscle amino acid kinetics, muscle protein synthesis and proteolysis. The subjects will be studied in the post-absorptive state, after an overnight stay in the ITS-CRC. After admission, subjects will be given dinner at approximately18:00 and a snack at approximately 21:00, after which they will be allowed only water ad libitum. At approximately 05:00 we will insert: an antecubital forearm venous catheter for systemic infusions; at approximately 07:00 we will insert a retrograde venous catheter in the opposite hand placed in a heating pad for arterialized blood draws; at approximately 09:00 we will attempt to place a pediatric central catheter in the femoral vein for blood draws. Subsequently, we will start a primed-continuous infusion of L-[ring-$^{13}C_6$]-phenylalanine, L-[5,5,5-$^{2}H_3$]-leucine, and [1-^{13}C]-glycine to measure muscle protein turnover as well as the amino acid transport rates through LAT1 (Phe, Leu), SNAT2 (Gly), and PAT1 (Gly)[55,93]. To reduce risks we will use arterialized blood samples, rather than arterial blood, to measure arterial amino acid concentrations and enrichments. This method has been previously validated for amino acid and other metabolite concentrations[8], and we have preliminary data indicating that it is also valid for amino acid enrichments. After an approximately 4-hr baseline period, subjects will ingest the amino acid mixture, as a bolus. The mixture will contain EAA in the pattern found in animal protein[22] and will be enriched with L-[ring-$^{13}C_6$]-phenylalanine, L-[5,5,5-$^{2}H_3$]-leucine to maintain the isotopic steady state[22] (labeled glycine will not be added because glycine is not included in the oral mixture). Large vessel blood flow will be measured by Doppler[86,87]. Microvascular nutritive flow is emerging as a potential regulator of muscle amino acid and protein metabolism[85-87]. Thus, whenever possible we will perform a Flow Mediated Dilation (FMD) test to detect endothelial function using Doppler Ultrasound and Near Infrared Spectroscopy. Frequent blood samples will be collected during the last hour of the basal period and the first and third hour of the amino acid period to measure amino acid concentrations and enrichments, glucose, insulin, cytokines and endothelin-1. T2DM is characterized by hyperglycemia, hyperinsulinemia, inflammation and endothelial dysfunction, which may have an impact on muscle protein metabolism [69,86]. Additional serum samples will also be collected and stored for future analyses (e.g. other hormonal assays, proteomics, metabolomics). Up to two muscle biopsies will be taken in each period to measure pertinent parameters including amino

acid and protein kinetic parameters, cross-sectional area, cell signaling, novel regulatory pathways, and gene expression (see Analytical Methods). A portion of the biopsies will be collected for immunohistochemistry. A third incision may be made should the need arise. At the end of the experiment catheters will be removed and subjects will be given a meal.

3) *Resistance Training*: This experiment will involve measurement of the chronic effect of resistance exercise on the response of muscle amino acid transport and protein anabolism to approximately 7 g of EAA in older adults with T2DM. Within one week after the first metabolic experiment, subjects will initiate progressive, supervised resistance exercise training, 3 times per week for 12 wks. Prior to initiating the 12-week program, a run-in week will be completed, for a total of 13 weeks overall (*Table 1*). During the intervention, we will monitor physical activity with SAMs in all subjects to determine if exercise reduces habitual physical activity. If possible, we will also use continuous glucose monitors to assess changes in blood glucose control throughout the intervention. At the end of the 12-week period, and approximately 48 hours after the last bout of exercise, we will repeat oral glucose tolerance testing. The Metabolic Experiment will be repeated the following day, to measure the effect of training on amino acid transport and muscle protein anabolism.

Table 1. Progressive resistance exercise training protocol.

Resistance Exercise Training
• 5 min. warm up • 3 times per week • Weights will be increased as necessary and 1RM will be formally determined every 6 weeks to progressively increase weight lifted. • If subjects are unable to complete the entire training session, leg exercises will be prioritized • Modifications to exercises, including substitution with free weight or band exercises, will be made as necessary to accommodate orthopedic limitations of subjects

	Free Weights	Machine	Run-In Week	Weeks 1-4	Weeks 5-8	Weeks 9-12
Bicep curl	X	X	2 x 15 @ 60% 1-RM	3 x 15 @ 60% 1-RM	3 x 12 @ 65% 1-RM	3 x 10 @ 70% 1-RM
Triceps Extension		X				
Chest press		X				
Lat pulldown		X				
Shoulder press		X				
Leg press		X				
Leg extension		X				
Leg curl		X				
Seated calf raise		X				
crunches	-	-				

5. Sub-Study Procedures:

Specimens obtained during the study will be stored in the principal investigator's laboratory and may be used in future research. For example, from time to time, new laboratory tests and procedures are developed that could be used to better understand the human body during metabolism studies.

The extra muscle tissue/blood left over after the initial research study tests are done will be stored and used in future research. The samples will be used to look at muscle growth related pathways. DNA will not be stored and no genetic testing will be done. Any future research will not involve additional specimens being taken or require any extra involvement from subjects. We will not need to contact the subjects again. The specimens will be labeled with a code number and will not directly identify any of the subjects who partake in the study.

6. Criteria for Inclusion of Subjects:

- Age 60-85 yr
- Body mass index: 23-35 kg/m^2

- Or BMI>35 if thigh adiposity does not impair muscle biopsy
- Stable body weight for at least 3 months
- T2DM
- Able to provide informed consent

7. Criteria for Exclusion of Subjects:

- Insulin therapy that cannot be converted to non-insulin therapies
- Significant diabetes complications
- A1c > 8%. Those excluded based on A1c will be eligible for re-evaluation.
- Impairment in Activities of Daily Living
- Score <25 on the 30-item Mini Mental State Examination
- Severe depression as determined by Geriatric Depression Scale >5
- ≥ 2 falls in the past 12 months
- Weight loss ≥ 10% bodyweight in the past 12 months
- Moderate or High activity level as indicated by the International Physical Activity Questionnaire Short Form
- Significant Cardiac abnormalities considered exclusionary by the study physician (e.g., CHF, CAD)
- Vascular disease
- Use of anticoagulant therapy. (e.g., warfarin, heparin, Pradaxa)
- Uncontrolled blood pressure: systolic >160 mmHg or diastolic > 100 mmHg
- History of stroke with motor disability
- Significant Chronic kidney disease
- Anemia
- Liver disease (AST/ALT 2.5 times above the normal limit)
- Significant Respiratory disease (acute upper respiratory infection, chronic lung disease)
- Active cancer or infection
- Recent (within 3 months), chronic treatment with anabolic steroids, systemic corticosteroids or estrogen.
- HIV or active hepatitis B or C
- Alcohol (CAGE questionnaire) or drug abuse (urine screening)
- Inability to perform OGTT (i.e., bad veins)
- History of mastectomy with axillary lymph node dissection
- Any other condition or event considered exclusionary by the PI and faculty physician

8. Sources of Research Material:

Participants will provide verbal and written data specifically for research purposes. The study physician will have access to UTMB EPIC for subjects Measurement equipment (DEXA, stress test, food diary, timers for functional tests) will capture numerical and qualitative data. The SAM device will collect data on steps. Study data will also be securely stored on REDCAP. Only trained study staff will have access to study data. These data will be confidential.

9. Recruitment Methods and Consenting Process:

Subjects will be recruited through an institutional review-board approved advertisement that will be posted at UTMB, in local newspapers, and at social centers such as the library and recreation centers. We will also utilize university announcements, flyers, patient letters, and word of mouth. After responding to ads, subjects will be pre-screened and asked to come in for a screening visit at the ITS-CRC. If they qualify, they will be offered an opportunity to participate in the study. This will happen on a "first come first served" basis. We will study a normal healthy population between the ages of 60-85 representative of the ethnic makeup of the United States. Prior to screening at the ITS-CRC, subjects will be asked to provide informed consent. During the consenting process, each subject will have a private room. The door will be closed during the consenting process. We will take

all measures to ensure that subject privacy is maintained. The details of the experimental procedures, including risks and benefits, will be explained by a research team member at the time of initial screening at the ITS-CRC. At this time, the subject will be given ample time to read the consent form, ask questions and discuss any concerns. After the subject has been satisfied, the subject will be given an opportunity to sign the consent form. At every study encounter, each subject will be asked if they are still willing to participate in the study. Each subject will be asked if they have any questions, concerns, complaints, or comments. If the subjects have any of those listed, they will be appropriately addressed by the PI.

10. Potential Risks:

Possible risks and discomforts a subject might be exposed to during the course of the study include:

Psychological Stress: Some of the questions asked as part of the study may make the subject feel uncomfortable.

Positive screening tests: One or more of the screening tests might be positive of for a medical condition. This information might be upsetting for the subject. The PI and study physician, Dr. Elena Volpi, will provide counselling to the subject in the event that a screening test is positive for a medical condition or a blood level is abnormal. The likelihood of this is low.

Fasting: Risks of fasting include hypoglycemia, dizziness, nausea, and light headedness. Risk is low.

Blood draws: The subjects will undergo blood draws during the course of the study. The total amount of blood drawn will be approximately 170 ml for each of the two metabolic study days. The risks are pain, bruising and infection. People with borderline anemia might become more anemic with the repeated blood draws. Fainting is also a risk as some people faint at the sight of needles and/or blood. The risk of this event is low.

Anemia: Repeated blood draws or excessive sampling volume increases the risk of anemia. This is unlikely as the blood collected is less than a blood donation.

Muscle biopsies: The risks of this procedure are pain, bleeding, bruising, infection, and a little scar at the site of the incision. The risks are low. The biopsy scar is in the shape and size of this "_" Some people may also faint at the sight of needles and/or blood. Up to 50% of subjects experience some soreness at the site of the biopsy up to 48 hours after it is done.

Stable Isotopes Infusion: The only possible risks are sepsis (blood infection) and fever, but the risk of these is so small that the precise number is unknown. The isotopes are tested in order to assure their sterility (absence of microorganisms, such as bacteria, that may cause infections and fever). Antibiotics can treat these infections should they occur.

DEXA Scan: Each DEXA scan will expose the subject to a small amount of radiation. Exposure to radiation can increase the risk of cancer and birth defects. The amount of radiation that a subject will be exposed to is so small that the exact risk is unknown.

Femoral Venous Catheter: We will insert only a pediatric catheter in the femoral vein. The risks are the following: (A) Trauma to structures adjacent to the targeted vein (hematoma, nerve injury) is the most commonly recognized complication/error during the cannulation process (1.9-3.6% incidence during central venous cannulation are generally reported). Traumas rarely are serious, but the experience of the operator and the use of ultra-sound assistance can bring the risk to virtually 0%. (B) Complications related to the presence of the catheters, i.e., infection, thrombosis and

thromboembolism. For patients with central venous catheters (CVC), an infection rate of 1.4 per 1,000 catheters is reported. However, most patients with CVC are immunosuppressed because of their underlying disease, and therefore have a higher risk of infections than our research volunteers. Infection in the immediate post-insertion period (3-5 days) is commonly due to infection of the subcutaneous track caused by intraoperative contamination and as such are more easily diagnosed and treated than the feared systemic infections more prone to appear later. Catheter-related thrombosis occurs in 3.7-10% of patients. This complication is more likely to occur in patients with specific thromboembolic risk. Factors that contribute to thrombosis in patients are hypercoagulability (malignant tumors), venous irritation caused by chemotherapeutic agents and hyperalimentation fluids. The risk is moderate.

Stress Test/Exercise*:* Risks may include muscle tightness, soreness, fatigue and rarely a muscle strain or tear. In older individuals, there is a small risk of myocardial infarction during maximal exercise tests. This is generally assumed to be approximately 1 in 10,000. Stress testing with ECG monitoring will be done at screening in the older subjects under the supervision of a MD to exclude subjects with asymptomatic heart disease. The exercise training sessions will be performed at the UTMB Center for Recovery, Physical Activity & Nutrition under the supervision of a CPR trained and BCLS licensed physical therapist or certified trainer. The exercise facility is equipped with emergency defibrillators. Muscle soreness or cramps, the most likely side effects of stress and muscle performance testing, can be reduced or avoided with an adequate warm-up and ramped up exercise training, both of which are integrated into our research protocol.

Strength Testing: The subject will experience soreness and tenderness in the muscles for 2 to 3 days following exercise. This is normal and is one of the ways in which the human body responds to exercise in order for the muscle to grow. A cardiovascular event such as a heart attack is a very rare potential risk.

Weight Training: It is rare but also possible that subjects may experience a major injury to their back, ligaments, joints, muscles, or tendons during exercise. This is a potential risk with any physical activity.

Near Infrared Spectrometry (NIRS): No additional protection is necessary. The effect of heat due to near infrared light absorption is low – less than 0.5°C.

Confidentiality: There is a general risk of disclosure of personal sensitive data in a clinical investigation. The risk is minimal.

11. Subject Safety and Data Monitoring:

Data Safety and Monitoring Plan. The ultimate responsibility for data and safety monitoring rests with Dr. Volpi. The risk level associated with this study is estimated to be moderate.

Our data safety and monitoring plan will include:

1. Review during of screening results and any other available data at the weekly investigators' meeting. A signed eligibility form will be kept on file for each subject.
2. A quarterly review of data safety and interim data analysis performed by the PI.
3. An annual review performed by the UTMB IRB.
4. Semi-annual patient safety review by a Medical Monitor, Mukaila Raji, MD, Chief of the Division of Geriatric Medicine, UTMB, will be initiated after completion of the first 10 subjects or after the occurrence of the first SAE whichever comes first. Minutes of the semi-annual Medical Monitor review will be kept on file and submitted to UTMB's IRB in a Miscellaneous form within a two week period.

Careful monitoring of the recruitment, enrollment, retention, adverse events, and study procedures will help protect the safety of study subjects, the quality of data, and the integrity of the study. As part of the safety plan for this study, Dr. Volpi, who is ultimately responsible for the medical

management of the subjects, will review each subject's records to ensure that appropriate mechanisms to protect the safety of study participants are being followed; that protocol requirements are being adhered to; and that data are accurate, complete, and secure. Subject records include consent forms, case report forms, flow of data forms, laboratory specimen records, inclusion/exclusion forms, adverse event logs, and medical charts.

Non-serious, anticipated adverse events (AE) include hematoma, pain, infection, syncope, and loss of subject confidentiality. If an anticipated adverse event occurs, Dr. Volpi will be immediately notified and a note will be entered into the subject's CRC chart. Dr. Volpi will be responsible for evaluating each AE and determining attribution as well as the impact of the AE on the risk/benefit ratio.

All unanticipated, serious, fatal and/or life-threatening adverse events will be reported to the IRB within 24h of occurrence. The IRB and the PI will be responsible for determining whether modifications to the protocol and consent form are required. If a determination is made that participants are found to be exposed to excessive risks in relation to anticipated benefits, the study will be immediately suspended. Studies will not resume until modifications are made that are deemed to result in an acceptable risk/benefit ratio by the PI and the IRB. Aggregate reports of adverse events will be prepared as mandated and forwarded to the IRB and ITS-CRC for review.

Plan for Adverse Event Reporting. The PI will be responsible for evaluating each adverse event and determining attribution as well as the impact on the risk/benefit ratio, using the following Grading and Attribution criteria:

Mild – transient laboratory test alterations that do not suggest injury; discomfort noted but no disruption of daily activities; no therapy, or only symptomatic therapy required.

Moderate – Laboratory test alterations indicating injury without long-term risk, discomfort sufficient to modify normal daily activity, specific therapy required (i.e., more than symptomatic).

Serious – laboratory tests indicating a serious health threat or permanent injury, incapacity, inability to work, or to perform normal daily activity, hospitalization required or prolonged, emergency treatment required, life-threatening events, death.

The attribution scale assesses the relation of the event to the study procedures. Dr. Volpi will judge whether an adverse event is: 1) *not related*; 2) *possibly related*; 3) *probably related*; or 4) *definitely related to the study interventions*.

Data Safety and Monitoring Board. We will consult our IRB at the time of protocol submission to determine if we need to establish a DSMB. Should a DSMB be required, we will establish it including physician-investigators from the Texas Regional CTSA Consortium and other Claude D. Pepper Centers.

12. Procedures to Maintain Confidentiality:

All study data will be collected in REDCap by the research team. Paper data flow sheets or case report forms will be stored in locked file cabinets in a secure area of the PI's recruitment office. Interim data will be reviewed by the PI. Any appearance of a Conflict of Interest by the research team will be avoided by the periodic monitoring by UTMB's Conflict of Interest Committee. The subjects' right to confidentiality will be protected at all times and no subject will be identified by name in any publication that results from this research.

13. Potential Benefits:

The only potential benefits for the participation in this protocol are related to the knowledge of the results of the screening tests that will be released to the volunteer, and the availability of nutritional counseling at the conclusion of the study. T2DM patients who participate in progressive resistance exercise training may experience an improvement in their blood glucose control, strength and endurance with training. No other benefits are expected for the subjects. The knowledge collected from the present studies may be of benefit to society, as these studies will help develop the scientific basis for designing treatments for reducing loss in muscle mass and function in older subjects with T2DM.

Importance of the Knowledge to be Gained. These studies will allow us to identify the biological mechanisms by T2DM accelerate sarcopenia in older individuals. Since T2DM is quite common in older adults and increases the risk of physical dependence, the knowledge to be gained will be very important to develop interventions to maintain independence in older adults.

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