Chronic Venous Insufficiency (CVI) results from the disruption of normal blood transportation, whether the disruption occurs in the superficial or deep venous system, the perforating veins or any combination of these[1]. When the perforator valves become compromised, pressure in the calf muscle contraction increases and blood begins to flow through the compromised perforator veins into the superficial venous system resulting in venous hypertension or varicose veins[1]. Varicose veins are known as common venous incompetence in the lower extremities and appear as dilated, elongated, or winding superficial veins[2]. Venous pressure in the lower legs results from damaged deep, superficial and or perforating veins and over time this can lead to changes in the skin such as hyperpigmentation, edema, and can lead to ulceration[2]. It is essential for individuals to have regular contraction of the calf musculature as it controls lower extremity venous return[2]. The calf muscle pump function is known as the "peripheral heart" for its crucial role in an individual's calf muscle pump function[4]. Once there is long-term weakness in the calf musculature the blood flow to the lower extremity slows down and increases the risk for a deep venous thrombosis[2]. With many theories leading to the valve reflux being the main cause of varicose veins there has been no evidence to show that if the compromised primary valve initiates the process of varicose veins or if the dilatation or weakening of the vein walls and collagen composition is the cause.

CVI is a highly reported chronic medical condition in the United States and the Western world[1]. In the United States alone over 2.5 million individuals are affected by chronic venous disease with prevalence ranging in geographical locations[1,3]. Beebe-Dimmer et al (2005) reported that over a wide variety of countries from 1942-2003 the prevalence of varicose veins varied from 2% to 56% in men and from <1% to 73% in women. However, in 2017 a decrease was reported that prevalence of CVI varied from <1% to 40% in women and from <1% to 17% in men[3]. CVI impacts countries financial status as wound care alone in the United States allots for 3 billion dollars annually[3].

There are many factors that put individuals at risk for the development of chronic venous insufficiency, such as, advancing age, family history of venous disease, ligament laxity, prolonged standing, increased BMI, smoking, sedentary life style, lower-extremity trauma, prior venous thrombosis, the presence of an arteriovenous shunt, some hereditary conditions, high levels of estrogen and pregnancy[1,5,6,7-20].

6.1 Statement of Design

A feasibility study on the effect of a 12-week at home structured resistance and aerobic exercise programme in individuals with chronic venous insufficiency.

6.2 Study Procedure

There will be a total of sixty participants recruited for the study, with an anticipation of 40 to complete the study. Participants will complete the Physical Activity Readiness Questionnaire (PAR-Q) to ensure that they are able to participate in the structured exercise programme. If the participants' answers "yes" to any question on the Physical Activity Readiness Questionnaire (PAR-Q), he/she is ineligible to participate. Participants will also read a participant information leaflet and sign an informed consent before participating in the study. Baseline demographic will be collected at the start of the study. Participants will complete the SF-36 Health Survey at session one and session 2 (week 12). Baseline testing will be conducted. The following measures will be employed in the study through a baseline testing and repeated at the end of the study period (week 12): Functional ambulatory measurements, physical activity measurements, isokinetic testing, duplex ultrasound screening.

Upon completing baseline testing participants will have the warm-up, cool-down, stretches, all exercise demonstrated and explained to them. Participants will go through each exercise with the principal investigator to ensure understanding. The principal investigator will then describe each section of the "Strength From Within" Booklet. At the end of the first session the participants will be administered their at home structured exercise booklet, recording booklet, resistance band, warm-up and cool-down information sheet and their ankle range of motion information sheet.

The baseline meeting and the week 12 meeting will take roughly 90 minutes to complete all baseline measurements, questionnaires, isokinetic testing and demonstrations. Isokinetic testing will take a total of 32 minutes with resting periods included in the time, baseline measurements including the muscle strength and functional ambulatory measurements will take a duration of 10.5 minutes, demonstration of the home structured exercise programme will take up to 20 minutes, both questionnaires will take 5-minutes total and time left for any other

All patients will complete a Physical Activity Readiness Questionnaire (PAR-Q) prior to participating in the trial. The PAR-Q is designed to determine if physical activity is safe for individuals or if they may need medical clearance from a physician. If a patient fails to complete or pass the PAR-Q they will be ineligible for participation in the trial.

6.11 SF-36 Short Form Health Survey

All patients will complete the SF-36 Short Form Health Survey at baseline and at the completion of the 12-week exercise programme. The SF-36 Short Form Health Survey is utilized to evaluate an individual's quality of life.

6.12 Venous Clinical Severity Score

All patients will complete the Venous Clinical Severity Score at baseline and upon completion of the 12-week study. The Venous Clinical Severity Score will be used to characterized the severity of the patients' chronic venous insufficiency and to monitor any progression made.

6.13 Calf Muscle Pump Function: Duplex Ultrasound Scanning

All patients will undergo a comprehensive duplex ultrasound scanning to determine the nature and extent of venous reflux. The duplex ultrasound will be conducted by Professor Sherif Sultan during a clinical appointment. A repeat of objective measures will be repeated at the completion of their 12-week.

6.14 Biodex Measurements-Isokinetic Testing

All patients will undergo lower limb isokinetic (concentric/concentric) testing using a using a Biodex Multi-joint System[33,34]. All Biodex testing will be conducted based of evidence based clinical protocols provided by Biodex. Biodex measurements will consist of knee flexion/extension and ankle plantar flexion and dorsiflexion. For knee flexion/extension patients will undergo a bilateral isokinetic 3 speed evaluation to establish goals and monitor progress[33]. Patients will move through full range of motion with a percent range of 100 and will be evaluated at three speeds and three repetitions[33]. At 60°/second the patient will complete 5 repetitions, at 180°/ seconds the patient will complete 10 repetitions and at 300°/second the patient will complete

15 repetitions[33]. Ankle plantar flexion and dorsiflexion will be measured with a bilateral isokinetic 2 speed evaluation at 5 repetitions at 60°/second and 10 at 120°/second[34]. Testing will be administered at baseline and at the completion of the 12-week exercise programme; data will be collected and recorded on calf torque, calf work, calf power, plantarflexion range of motion and dorsiflexion range of motion.

6.15 Functional Ambulatory Measurements:

6-minute walk test: All patients will complete a 6-minute walk test on an even/flat 25m ground supervised by a trained exercise technician. Participants will be instructed to walk for 6 minutes at a moderate comfortable rate.

6.16 Physical Activity Measurements

Muscle Endurance Testing

All patients will complete muscular endurance for all major muscles. Patients will be asked to complete a series of upper and lower body exercises testing their muscular endurance within 30 seconds. All patients will complete as many repetitions as they can in 30 seconds at a speed they are comfortable preforming at. Muscular endurance testing will be conducted at baseline and upon the completion of the 12-week structured exercise programme. The muscular endurance testing consists of single leg balance on each leg, step overs, sit to stand, push press, single arm right bicep curl, single arm left bicep curl, and single arm right triceps extension and single arm left triceps extension at a moderate rate or intensity.

6.17 Strength From Within Exercise Programme

- All patients will receive the structured exercise programme, and the "Strength From Within Booklet", a resistance band, a recording booklet, a walking information leaflet, ankle range of motion exercises, a warm-up and a cool-down. The Strength From Within booklet provides a descriptive linguistic and visual demonstration of proper technique and safety for all exercises. The at home resistance exercise programme consists of a total of twenty standing and sitting exercises divided into upper and lower body. Patients will participate in the Strength

From Within structured exercise programme for 12-weeks by choosing their own 5 upper body exercise and 5 lower body exercise per week from the Strength From Within booklet. Patients are able to have a combination of standing and sitting exercises to accommodate their ambulatory needs. Patients will complete lower body exercises on Monday, Wednesday and Friday and complete upper body exercises Tuesday, Thursday and Saturday; Sunday is a rest and recovery day. To further the individualistic aspect of the programme patients will be deciding their own repetitions from a range of eight to twelve, however, the exercise technician will be contacting the patients each week to monitor and implement repetition progression. Progression will be implemented if the patient is able to complete two full weeks of the same repetition count. Built into the exercise programme there will be a dynamic warm-up and static-stretching cooldown, both lasting for five minutes. Ankle range of motion exercises using the resistance band will be included in the exercise programme to be completed on Monday, Wednesday and Friday. Patients will be completing three sets of ten ankle dorsiflexion and plantarflexion with a resistance band. All exercise will be demonstrated and practiced with participants to ensure proper technique and safety. In combination with the Strength From Within programme, patients will participate in a 12-week walking protocol. Each walking protocol will be individualized at the first meeting following the 6-minue walk test. Patients' walking progression will be determined biweekly based on the patients' experience and response to the protocol. Patients will receive a walking protocol recording sheet to fill in the minutes walked each day and the total duration each week. The exercise technician will be referring to the Mayo Clinic 12-week walking protocol for guidance.

Participants will be contacted each week by telephone or personal interaction. Regular weekly check in will be done to know the improvement and status of the participant and to possibly adjust the repetitions and sets to be completed that week accordingly. Upon completion of the study participants will be contacted 3-months after their completion date. Participants will be contacted be telephone and be asked to participate in a short questionnaire on their adherence to the exercise programme after their 12-weeks finished. At the 12-week meeting the study researcher will collect the participants recording booklet in order to evaluate and measure adherence/compliance to the structured exercise programme. Participants have the

The following endpoints will be measured:

1. Ankle Joint Range of Motion
2. Overall physical strength
3. Exercise Capacity
4. Quality of life

8 TRIAL OUTCOME ASSESSMENT

Trial outcomes will be recorded on a baseline measurement form developed by the supervising exercise technician.

8.1 Evaluation of Other Primary and Secondary Outcomes

Remaining primary and secondary outcomes will be determined by the blinded trail assessor through data collected.

10 STATISTICAL APPROACH

Graphical and numerical summaries will be provided for all response variables of interest. For categorical variables, test of association will be performed to test for any associated between factors of interests. Chi squared test (using a significance level of 0.05) will be used if the underlying assumption relating to the expected values are deemed appropriate, otherwise Fisher Exact Test will be employed. For binary variables, comparisons of proportion based on the Normal approximation of the Binomial distribution will be used as necessary. P-values will be reported for those comparisons of specific interest as opposed to comparing all levels of all variables. And post intervention scores will be compared. Baseline characteristics of the participants and physical activity levels will be compared from week one of the study, to week 12 the completion of the study. Duration of the obtaining baseline data and final data will be measured. An ANVOA will be performed to analyse change over time. The outcomes will be found by using a paired t test. Mean baseline values will be computed from both duplex ultrasound screening and Biodex. Treatment effects will be estimated by an analysis variance (ANOVA).

11 SAMPLE SIZE

The primary outcome for this trial is the effect a 12-week at home structured resistance and aerobic exercise programme has on muscle pump function, venous clinical severity score and calf muscle strength in an individuals with chronic venous insufficiency. Research suggest that participation in a structured exercise programme has the ability to improve calf muscle pump function and dynamic calf strength[23,29]. As a pilot study 60 participants will be recruited; with intention of 30 participants completing the trial; previous pilot studies conducted similar to this trial have used similar sample size.

References

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Once diagnosed, treatment for CVI is a conservative management by reducing symptoms and preventing progress of the disease and secondary complications[21]. Initial conservative treatments consist of leg elevation, exercise therapy and compression to improve oxygen transport to the skin and subcutaneous tissues, decrease edema, reduce inflammation, and compress any dilated veins[22]. It is recommended that individuals with CVI maintain an ideal body weight or reduce their weight, if overweight, and maintain an overall healthy lifestyle[19]. Exercise is a recommended form of therapy for individuals with CVI as it can help improved calf muscle pump function[23].

In a clinical setting CVI is diagnosed through the use of the CEAP classification. The CEAP scoring is made up of four clinical components, (C)clinical signs, (E)Etiology, (A) Anatomy and (P)Pathophysiology. Each component of the CEAP classification have numerical subcomponents of their own. Within the clinical settings there are eight subcomponents, (C0) no visible or palpable signs of venous disease, (C1) telangiectasia/reticular veins, (C2) varicose veins, (C3) edema, (C4) Pigmentation or eczema, (C5) healed venous ulcer, (C6) active venous ulcer[24]. In the etiology there are four subcomponents, (Ec) congenital, (Es) secondary, (En) etiology not specified[24]. The anatomy component of the CEAP classification is broken down into four subcomponents, superficial venous system (As), perforating veins (Ap), deep venous system (Ad) and anatomy not specified (An) [24]. The pathophysiology component is made up of four subcomponents, venous reflux (Pr), venous obstruction (Po), venous reflux and obstruction (Pr,o) and reflux not specified (Pn) [24].

In regards to this study a CEAP score of C2, C3 and C4 will be included within the inclusion criteria. The C2 clinical classification is identified as varicose veins which are subcutaneous dilated veins 3mm or more. Edema or C3 is common among individuals with chronic venous insufficiency due to the increased volume of fluid in the skin and subcutaneous tissues, venous edema is commonly found in the ankle[24]. C4 is divided into two categories, C4a is known as pigmentation or eczema where the skin will have a brown/darkening pigmentation due to the hemosiderin deposition a result from the discharge of red blood cells typically occurring in the ankle region[24]. Eczema is typically located near the varicose veins and begins as an erythematous dermatitis and has the potential to progress as blisters[24]. C4b or

questions or concerns. Extra time will be given at any point during both meetings if needed by the participant.

6.3 Selection of Participants

Participants will be screened by Professor Sherif Sultan at his vascular clinic using the inclusion/exclusion criteria.

6.4 Participant Recruitment

Through the vascular clinic of Professor Sherif Sultan at Galway Clinic Hospital. Professor Sherif Sultan will screen the patients with the inclusion and exclusion criteria. Once patients are screened and eligible for recruitment and expressed interest in being contacted by study researcher, with their permission Professor Sherif Sultan will provide their contact information to the study researcher, who will then contact the patient to arrange meet at a time convenient to the patient. At that meeting, the patient will receive the PIL to read. Any questions will be answered by the study researcher. If the patient wishes to participant he/she will sign 2 copies of the consent form, which will also be signed by the study researcher. A signed copy of the consent form will be given to the participant along with the PIL.

6.5Inclusion Criteria

Adult patients with chronic venous insufficiency and a CEAP Score of 2,3,4.

6.6 Exclusion Criteria

i. Younger than 18 years
ii. Painful Ulceration
iii. Severe Cardiac Condition
iv. Cardiorespiratory Disease
v. Failure of Physical Activity Readiness form
vi. ACSM Risk Classification: Class C or above
vii. CEAP classification of 5 or 6
viii. Severe mobility impairment
ix. Severe imbalance
x. Women who are pregnant

right to deny participation in the follow-up questionnaire, if they wish to do so appropriate documentation will be completed to ensure missing data is accounted for. If the study researcher cannot get in touch with the participant on the first attempt to contact the study researcher will call once more a week later. If the study researcher cannot get in contact with the participant after the second attempt the study researcher will not contact that participant again

7. TRIAL OUTCOMES MEASURES

7.1 Primary Outcome Measures

This trial was to determine the effect of a 12-week at home structured exercise and aerobic programme in patients with chronic venous insufficiency. The primary outcome measures is the effect a 12-week at home structured exercise and aerobic programme has on muscle pump function, venous clinical severity score and calf muscle strength in an individuals with chronic venous insufficiency.

7.2 Secondary Endpoints

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