Multimodal Prehabilitation for Peripheral Arterial Disease

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Neither by nature, then, nor contrary to nature do the virtues arise in us;
rather we are adapted by nature to receive them,
and are made perfect by habit.
Aristotle

TABLE OF CONTENTS

1. ABSTRACT

Despite the well demonstrated benefits of structured exercise on functional capacity in peripheral arterial disease (PAD), there is still a lack of implementation of such interventions in the clinical setting. Other lifestyle modifications, such as nutrition and smoking cessation play a very important role in PAD prevention and progression and need to be optimized prior to considering endovascular revascularization. Nevertheless, evidence on the effects of programs that combine those interventions is scarce, and in most cases lacks supervised structured exercise, the intervention that has shown the most benefit. Moreover, there is a lack of evidence on the impact of multimodal multidisciplinary programs on health-related quality of life in this population.

Multimodal prehabilitation, understood as a multidisciplinary preoperative optimization tool that consists of structured exercise, nutritional counseling, smoking cessation and psychosocial support, has been shown to improve perioperative functional capacity, reduce postoperative complications and increase survival in surgical patients. Prior to this thesis, there was no data regarding the feasibility and effects of multimodal prehabilitation in peripheral arterial disease patients.

In this thesis, a systematic review of the literature on combined exercise and nutrition interventions is presented prior the introduction of the feasibility and efficacy of multimodal prehabilitation in a case series of patients presenting with moderate to severe PAD. The aim is to provide a proof of concept of prehabilitation in PAD patients in order to foster further research on the effectivness of prehabilitation at improving health related quality of life, exercise capacity and emotional status in PAD patients. Multimodal prehabilitation seems to be a promising tool to help optimize PAD patients and could

potentially be implemented as first line treatment for PAD patients with intermittent claudication prior considering endovascular revascularization, although further research is needed.

2. RÉSUMÉ

Malgré les bénéfices bien démontrés des programmes d'exercices structurés sur la capacité fonctionnelle des patients atteints de maladie vasculaire périphérique (MVP), il y a un retard dans l'implantation de telles interventions dans le contexte clinique. D'autres modifications des habitudes de vie, telles que la nutrition et la cessation tabagique, jouent également un rôle très important dans la prévention et la progression de la MVP, et devraient être optimisées avant de considérer la revascularisation endovasculaire. Très peu d'études ont évalué la combinaison de ces différentes interventions. Dans la plupart des cas, l'exercice structuré manque à l'appel malgré le fait qu'il s'agit de l'intervention ayant démontré le plus de bénéfice. De plus, il y a un manque d'évidence concernant l'impact des programmes multimodales et multidisciplinaires spécifiquement sur la qualité de vie dans cette population.

La préhabilitation multimodale, définie comme un outil multidisciplinaire d'optimisation préopératoire, inclut un programme d'exercice structuré, des conseils nutritionnels, de l'aide pour la cessation tabagique, ainsi qu'un support psychosocial. Cette approche multimodale a démontré une amélioration préopératoire de la capacité fonctionnelle, une réduction des complications postopératoire et une augmentation de la survie de différents types de patients chirurgicaux. Avant cette thèse, il n'y avait pas de données permettant d'évaluer la faisabilité et l'effet de la préhabilitation multimodale pour les patients atteints de maladie vasculaire périphérique.

Cette thèse présente une revue systématique de la littérature évaluant la combinaison d'interventions d'exercices et nutritionnelles, pour ensuite introduire une étude de faisabilité et d'efficacité potentielle de la préhabilitation multimodale pour une série de

patients présentant de la claudication intermittente modérée à sévère. Le but est de fournir une preuve de concept pour l'utilité de la préhabilitation dans la MVP et d'inciter la recherche future sur son efficacité à améliorer la qualité de vie, la capacité d'exercice et le status émotionnel de ce type de patients. Bien que plus de recherche soit nécessaire, la préhabilitation multimodale semble être une avenue prometteuse pour l'optimisation des patients atteints de MVP et pourrait potentiellement être implémentée comme traitement de première ligne pour les patients avec claudication intermittente et avant de considérer les thérapie de revascularisation endovasculaire.

3. LIST OF COMMON ABBREVIATIONS

6MWT, 6-Minute Walk Test

12-W, 12-week Assessment

ABI, Ankle-Brachial Index

BL, Baseline Assessment

BMI, Body Mass Index

CI, confidence interval

COT, claudication onset time

DASH, Dietary Approaches to Stop Hypertension

DASI, Duke Activity Status Index

ER, endovascular revascularization

ERAS, Enhanced Recovery After Surgery

HADS, Hospital Anxiety and Depression Scale

HbA1c, glycated hemoglobin

HR, heart rate

HRQoL, Health Related Quality of Life

IC, intermittent claudication

IQR, interquartile range

LBM, Lean Body Mass

METs, metabolic equivalents

MMP, Multimodal Prehabilitation

NO, Nitric oxide

PAD, peripheral arterial disease

PGSGA, Patient Generated Subjective Global Asssessment

PUFA, Polyunsaturated Fatty Acids

QoL, Quality of Life

RCT, Randomized Controlled Trial

SD, standard deviation

SF-36, 36-Item Short Form Health Survery

STS, sit-to-stand test

TUG, Timed Up and Go

VascuQol, Vascular Quality of Life Questionnaire

VO2 AT, anaerobic threshold oxygen consumption

VO2 peak, peak oxygen consumption

WIQ, Walking Impairment Questionnaire

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Lastly, I would like to dedicate this thesis to my beloved parents and my partner, who have given me the courage and strength to pursue this path and who have provided me with endless moral support and love throughout this journey.

5. THESIS FORMAT

This is a manuscript-based thesis composed of two chapters. Each chapter includes the manuscript that has been submitted for publication in peer-reviewed journals.

Chapter one aims to review the current literature with respect to exercise and nutrition optimization in patients with peripheral arterial disease (PAD). A systematic review of programs that include exercise and nutrition for PAD patients was conducted as a prior step to introducing the concept of multimodal prehabilitation for PAD, which includes nutrition and exercise as the two main components of a holistic optimization approach. In chapter two the feasibility, safety and efficacy of multimodal prehabilitation in PAD is assessed in a case series of PAD patients who underwent a 12-week multimodal prehabilitation program. The manuscript in chapter two is therefore used as a proof of concept for the use of multimodal prehabilitation in patients suffering from peripheral arterial disease, yielding the ground for future research to assess effectiveness of prehabilitation in this population. A preface before each manuscript is presented with the aim of facilitating the logical flow of the concepts, from one chapter to the next, thus producing a unified and logically coherent thesis script.

6. LIST OF ORIGINAL MANUSCRIPTS

This thesis includes two original manuscripts that have been submitted for publication:

Coca-Martinez M., Kinio A, Hales L, Carli F, Gill HL. *Combined Exercise and Nutrition Optimization for Peripheral Arterial Disease: A Systematic Review.* Submitted to the European Journal of Vascular & Endovascular Surgery.

Coca-Martinez M., Carli F, Gill HL. *Multimodal Prehabilitation for Peripheral Arterial Disease: A Case Series.* Submitted to the Journal of Vascular Surgery.

7. CONTRIBUTION OF AUTHORS

- **Chapter 1**: **Miquel Coca-Martinez**, Anna Kinio, Lindsay Hales, Francesco Carli, Heather L. Gill. Combined exercise and nutrition optimization for peripheral arterial disease: a systematic review.
    - The author of this thesis wrote the protocol for the systematic review, performed the screening, selection and qualitative analysis of the selected articles, performed the statistical analyses and wrote the manuscript.
    - Anna Kinio performed the screening and selection of articles and was involved in the qualitative analysis of the selected articles. She reviewed contributed to the final manuscript.
    - Lindsay Hales performed the literature search.
    - Francesco Carli co-supervised the data interpretation and contributed to the final version of the manuscript.
    - Heather L. Gill was involved in the conception and the design of the systematic review, supervised data interpretation and contributed to the final version of the manuscript.

- **Chapter 2: Miquel Coca-Martinez**, Francesco Carli, Heather L. Gill Multimodal Prehabilitation for Peripheral Arterial Disease: A case series.
    - The author of this thesis had a primary role in patients' recruitment and assessment, data acquisition and interpretation. The author wrote the manuscript.
    - Francesco Carli co-supervised data acquisition and he contributed to conception and design of the manuscript.

- Heather L. Gill partook in patient recruitment, co-supervised the research project and contributed to conception and design of the manuscript.

8. PREFACE TO CHAPTER 1

It is estimated that peripheral artery disease (PAD) affects up to 10% of the worldwide population and the prevalence increases to as high as 20% among patients 70 years of age and older[1,2]. For patients with mild and moderate levels of PAD, the primary symptom often reported is intermittent claudication (IC), namely significant pain in the calves, thighs and/ or buttocks induced by walking and relieved by rest caused by inadequate blood supply. Thus, individuals with IC are often sedentary, avoid most forms of ambulation, and suffer from decreased functional capacity, severe disability and increased risk of premature mortality[3,4]. Recently, endovascular revascularization (ER) most commonly done via angioplasty and stenting, has become the standard for improving blood flow and resolving symptoms, due to its quick results, and ease and simplicity for the patient[5]. Unfortunately, ER does not have good long-term results, with good results showing patency rates of 80% at 1 year and a drop off to 60% at 2 years[6]. In fact, a small but significant proportion of patients end up worse off than before the initial procedure.

Functional capacity and nutritional status have been shown to be major determinants of disease progression, quality of life and risk of major adverse cardiovascular events in patients suffering from PAD[7-10]. Therefore, lifestyle modifications that aim at optimizing a low functional status and nutrition are crucial to increase this population's walking capacity, delay onset of pain, improve their quality of life and prevent further deterioration prior to considering endovascular revascularization[11].

Exercise training has been shown to improve functional capacity, blood flow in the legs and, is equal to medication and endovascular revascularization with respect to increasing

pain-free walking[12]. Over the past years, international vascular surgery societies have incorporated walking recommendation in their standard of care for patients with IC before considering surgery[13-16]. Current recommendations suggest that patients should be advised to walk at least three times a week by themselves. Nevertheless, growing evidence suggests that the use of structured supervised exercise is superior to unsupervised unstructured exercise (walking advice)[17,18] when it comes to improve claudication time and exercise capacity. Furthermore, evidence on how this increase in pain-free walking or exercise capacity impacts on patient's quality of life is still of very low quality, with small numbers of studies and participants as most of the studies have walking capacity as a primary endpoint and are underpowered to assess the effect of supervised exercise on quality of life[19].

Nutritional interventions, as part of a lifestyle modification, have been less studied than exercise interventions; nevertheless, current evidence shows that they can contribute to improved outcomes in claudicants[20-23]. Yet, the power of nutrition as an optimization and preventive tool is still undervalued and underutilized in the PAD population compared to other cardiovascular disease such as coronary artery disease[24,25].

Nutritional interventions to optimize PAD are also very heterogenous throughout the literature, with different therapeutic goals that range from interventions aimed to lower cholesterol and triglycerides in order to improve or prevent atherosclerosis[26,27], to interventions that seek increasing limb blood flow to allow increased oxygen delivery to the lower extremity muscles to increase exercise capacity and delay onset of pain or nutritional interventions that focus on increasing antioxidants intake. Different types of diets such as the DASH diet or the Mediterranean have been shown to reduce

cardiovascular risk in PAD. Experts recommend that patients affected by PAD follow a diet rich in nutrients with anti-inflammatory and antioxidant properties[28].

Nutrition and exercise interventions should be considered as the two main pillars of a multimodal lifestyle optimization approach for PAD patients suffering from intermittent claudication[29]. In this first chapter a systematic review of the literature to assess the impact of combined exercise and nutrition intervention on quality of life, exercise capacity, limb blood flow and need for surgery in peripheral arterial disease is presented as an introduction to the concept of multimodal prehabilitation.

9. CHAPTER 1

Combined Exercise and Nutrition Optimization for Peripheral Arterial Disease: A Systematic Review

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Key words: nutrition, structured exercise, peripheral arterial disease, intermittent claudication, quality of life, exercise capacity.

WHAT THIS PAPER ADDS

The effects of an exercise and nutrition intervention in peripheral arterial disease patients with intermittent claudication on patient centered outcomes, limb blood flow or need for revascularization are unclear. More good quality data from randomized controlled trials is needed to determine if this population might benefit from such combined interventions.

9.1. ABSTRACT

Background and Objectives:

Patients with Peripheral arterial disease (PAD) who suffer from claudication have a low exercise capacity, poor quality of life and often severe disability. Structured exercise (SE) is more effective at increasing exercise capacity than non-supervised exercise such as instructions to walk. Poor nutrition has also been associated with worse outcomes in patients with PAD. This systematic review aims to assess the published evidence supporting the use of a combined nutrition and structured exercise intervention in patients with intermittent claudication.

Materials and Methods:

Publications that included a combination of SE plus a nutritional and that reported quality of life, exercise capacity, pain-free walking distance, limb blood flow, need for revascularization surgery or surgical outcomes were systematically searched. Publications were screened, selected and reviewed by two independent reviewers.

Results:

Four publications were found reporting the effects of combined SE and nutrition programs. Pooled statistical analysis across trials was not performed due to the heterogeneity of study designs and type of interventions. Only two randomized controlled trials were found, reporting conflicting results with regards to the effects of combined SE and nutrition on exercise capacity. Only one trial reported quality of life measures. Limb blood flow was increased in interventions involving a diet high in inorganic nitrate in addition to exercise.

Conclusions:

There are conflicting results and a lack of quality data proving the benefit of nutrition and SE programs on patient-centered outcomes. Limb blood flow might be increased with the combination of a diet rich in inorganic nitrate plus exercise. There is no data of the effects of combined nutrition and exercise on the need for revascularization surgery or post-revascularization outcomes. More randomized controlled trials, including more subjects, are needed to assess the effects of multimodal interventions on patient centered outcomes and clinical outcomes in the PAD population.

9.2. INTRODUCTION:

Despite the importance of lifestyle modifications such as exercise, healthy diet or smoking cessation for peripheral arterial disease (PAD), there is a lack of consistency in the clinical implementation of these elements (1-7). Supervised structured exercise has been proven to be more effective at increasing walking capacity than simple walking advice alone and it seems that it might be as effective as medication and endovascular revascularization with respect to increasing pain-free walking distance and quality of life (8-13). Healthy nutritional habits and other lifestyle modifications play an essential role in PAD prevention and disease progression and they are often underestimated and underused despite supportive evidence and expert recommendations (14-18). Multimodal multidisciplinary programs that aim to optimize surgical patients preoperatively with bundled therapeutic modalities have been shown to be more beneficial than implementing single therapeutic elements (19). The synergistic effects of nutrition and exercise on performance have long been studied in athletes and healthy populations (20-23). However, the combined effects of exercise and nutrition optimization on quality of life, functional capacity, limb blood flow and need for surgery in patient with PAD have not

been systematically reviewed. This systematic review aims to evaluate the impact of combined nutrition and exercise programs on quality of life, exercise capacity, pain-free walking distance, limb blood flow, and the need for surgery in patients suffering from PAD.

9.3 METHODS:

The present systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses Statement (24). It was conducted following the registered protocol on Prospero (Registration number CRD42019131684).

Search strategy

The following databases were searched for relevant human studies: Medline (via Ovid 1946 to 2019/05/29); Embase Classic + Embase (via Ovid 1947 to 2019/05/29); The Cochrane Central Register of Controlled Trials (via The Cochrane Library, Issue 5 of 12, May 2019); Biosis (via Clarivate Analytics 2019/05/29) and Scopus (via Elsevier 2019/05/29). The search strategies were designed by a librarian who used text words and relevant indexing to identify studies reporting the effects of exercise and nutrition in peripheral artery disease. The full Medline strategy (Appendix 1) was applied to all

databases, with modifications to search terms as necessary. No language limits were applied. Search strategies were peer-reviewed by two librarians. In addition, clinicaltrials.gov was searched for relevant studies. Further studies were identified in Web of Science and Scopus by carrying out citation searches for the reference lists of included studies. The Medline strategy was rerun prior to submission (March 2020) with no relevant studies found.

Study selection

Studies that examined the combined effects of an exercise and nutrition-based intervention on exercise capacity, quality of life, pain-free walking distance, limb blood flow, need for surgery or surgical outcomes were included. Nutrition-based intervention was defined as any nutritional intervention including nutritional supplementation, dietary counseling or modification. Exercise intervention was defined as any structured exercise program either supervised or unsupervised in which time, intensity, type of exercise and frequency was indicated. Inclusion was restricted to adults with intermittent Claudication (IC).

Data extraction and synthesis

One reviewer (LH) performed the searches. The same reviewer exported all references in EndNote X9 (Thomson Reuters, Thomson Corporation, USA) and removed duplicates. Results were then imported to the Rayyan platform (25) (Screening platform) and a PRISMA flow diagram of the selection process was created. Data was extracted and screened blindly by two independent reviewers (MCM and AK) based on the inclusion criteria. Any discrepancies were resolved by a 3rd independent reviewer (HLG). Full-text analyses and data extraction of those deemed eligible were conducted by one reviewer (MCM). Study population, demographics and clinical characteristics of every selected article were extracted, as well as nutritional intervention characteristics and exercise protocol used. The use of any cointerventions such as smoking cessation, psychosocial intervention or medical optimization was also recorded. The quality of included trials was assessed using the RoB 2 tool for assessing risk of bias in randomized trials (26) and the ROBINS-I tool for assessing risk of bias in non- randomized studies (27). Quality assessment was conducted by 2 independent reviewers (MCM and AK), with

disagreements resolved by a third reviewer (HLG.). Given the amount of heterogeneity in study designs and intervention modalities, statistically pooled data across trials was not performed. Statistical analyses were performed using SPSS Statistics (IBM SPSS Statistics for MacOS, Version 23.0. Armonk, NY, USA).

9.4. RESULTS

Search results

The full search done using the Mesh terms described in appendix 1 produced 2983 potentially relevant publications. The full PRISMA flow diagram is displayed in Figure 1. After duplicate removal was performed, 1952 publications underwent title and abstract screening by two reviewers, of which 22 publications of which were found eligible for full-text screening. Following full text analysis, four publications were included in the qualitative analysis.

Study & population characteristics

Population characteristics of the included studies as well as the study design and detailed type of intervention are summarized in Table 1. Two of the four included studies were RCTs and two were non-randomized studies. Woessner et al. (28) performed a prospective double blind randomized controlled trial, while Collins et al. (29) designed a prospective double-blind with a two by two factorial randomized controlled trial. On the other hand, Hall et al. (30, 31) published two non-randomized studies, one of which was an uncontrolled before-and-after study in a sample of 16 subjects, and his second study consisting of a case report with the same type of intervention. Risk of bias for the selected publications is summarized in table 2. The weighted mean age (SD) of participants was 66.65 (3.43) years and there was a clear predominance of male participants in all

publications assessed, with males accounting for 87% (15.06) of the total participants, and male representation in the studies ranging from 62.5% to 100%.

Type of intervention and control

The duration of the intervention as well as the type of control group and both the nutritional and exercise components of the intervention differed significantly between studies (table 1). For instance, a two-factorial RCT was carried out by Collins et al. (29) comparing a 24-week program of either three weekly sessions of polestriding at 70-80% of maximal exercise HR plus 400 UI of vitamin E daily with the two components alone. In contrast, Woessner et al. (28), compared a 12 week-program that consisted of three

weekly sessions of 30-minute supervised treadmill exercise adapted to subject's baseline graded maximal treadmill test (control group) to the same exercise protocol plus 4.2 mmol of beetroot juice extract consumed prior to every exercise session (intervention group). Both of the non-randomized publications included in the review were based on the same intervention, consisting in an intensive 26-day program of daily supervised treadmill walking for one hour, stretching and flexibility plus an exercise prescription to walk for 30-45 minute twice daily, in addition to a high-complex- carbohydrate, high-fiber, low-fat diet(30, 31). Length of the intervention and follow-up period also differed substantially between studies and ranged from 26 days to 24 weeks for intervention period.

Outcomes

Exercise Capacity and Pain-Free Walking

Three out of the four publications included in the systematic review reported an increase in exercise capacity using the combination of both nutrition and exercise interventions (28, 30, 31). On the contrary, Collins et al.(29), in a two-factorial RCT, found a significant polestriding exercise effect ($F=53.9$, $p<0.0001$), but no significant vitamin E size effect ($F=0.7$, $p = 0.42$) or interaction between the two ($F = 1.1$, $p = 0.30$). After six months of training the polestriding groups (polestriding plus vitamin E and polestriding alone) reported increased duration on treadmill test by 57% and 47% respectively, while in the vitamin E alone group exercise time declined by 14% and in the Placebo group without either intervention improved their exercise time by 1%. Similar results are shown in the constant work-rate test where polestriding significantly improved the duration of the test ($F = 29.42$ $p <0.001$) whereas there was no effect of vitamin E ($F = 0.84$, $p= 0.36$). With respect to leg claudication, the exercise intervention, but no vitamin E alone conferred a benefit. Woessner et al.(28), in their RCT comparing exercise plus placebo (control group) with exercise plus beetroot juice extract (intervention group) reported an increase in the 6-minute walk test of 24.6±12.1 meters in the exercise plus placebo group and 53.4±19.6 meters in the exercise plus beetroot juice extract group ($p\leq0.05$), which shows a similar pattern in both groups with a standardized effect size of 0.43 (95% CI, −0.44 to +1.21). Peak walk time also increased significantly for both groups 238.7±207.0 and 269.9±195.3 seconds respectively for the control and intervention groups ($p \leq0.01$). An increase in pain-free walking distance was observed in both groups as well, with an increase of 59.2±57.3 seconds for the control group and 180.3±46.6 seconds for the intervention group ($p\leq0.05$). Although there was no significant difference when comparing the two groups, a treatment medium to large standardized effect size was found to be 0.62 (95% CI, −0.23 to +1.44). Hall et al., in an observational study of 16 participants, demonstrated that patients significantly improved their maximal symptom-

limited work capacity from 4.1±0.35 to 6.6±0.4 METs ($p<0.001$) with an intensive 26-day high-complex- carbohydrate, high-fiber, low-fat diet plus exercise program (30). No systematic measurement of exercise capacity was included in the case report publication by the same author, although it was mentioned that by the end of the 26-day program the patient was able to walk pain-free for a distance of 3 miles in comparison to the resting leg pain that was reported at baseline (31).

Health-related and disease specific quality of life measures

There was only one trial reporting quality of life outcomes. Collins et al. (29) found a significant effect of polestriding on only the physical function subscale of the SF36 quality of life questionnaire. There was also a significant increase of PAD specific quality of life as measured by the WIQ (Walking Impairment Questionnaire) in subscales of perceived walked distance and speed which increased by 121% ($p<0.0001$) and 71% ($p=0.02$) respectively. However, no effects of vitamin E on the WIQ or SF36 subscales were found.

Limb blood flow

All four studies measured lower extremity blood flow with the ankle-brachial index (ABI). Collins et al. (29) reported no polestriding or vitamin E effect on post-exercise ABI. On the other hand, Woessner et al. described an ABI increase of 0.16±0.11 ($P\leq0.05$) in their intervention group and no change in the control group with a standardized effect size of 0.88 (95% CI, −0.01 to +1.70) (28). Hall et al., in their observational study reported a post-exercise right ABI increase from 26±3.8 to 40.7±5.5 percent ($p<0.001$) and a left ABI increase 30±4.4 to 44.6±7.5 percent ($p<0.001$) (30). In a case report that used the same intervention, Hall et al. reported a baseline absence of pulses below the femoral

arteries, with an arteriogram showing 100% bilateral occlusion of both femoral arteries with collateralization and reconstitution at the popliteal region. After the 26-day program, an ABI 0.60 in the right leg and 0.67 in the left leg was reported suggesting improvement in collateral flow (31).

Furthermore, Woessner et al.(28) showed that peak reactive hyperemic blood flow did not change in the control group (0.74+2.67 mL blood per 100-mL tissue per minute) but increased in the beetroot plus exercise intervention group by 2.57±2.65 mL blood per 100-mL tissue per minute ($P \leq 0.05$). They also showed a significant reduction in desaturation rate in the intervention group compared to the control group. Nevertheless, indices of gastrocnemius perfusion and limb blood flow at rest showed similar responses in both groups.

Clinical outcomes

None of the selected publications examined the impact of a nutrition and exercise program on the need for revascularization surgery or its impact on postoperative outcomes if participants decided to undergo revascularization following the study.

9.5. DISCUSSION

To our knowledge, this is the first systematic review that aims to investigate the effects of a combined nutrition and exercise intervention on functional capacity, pain-free walking distance, quality of life and limb blood flow. Other reviews have looked at the effects of lifestyle modifications on mortality and major cardiovascular events in PAD patients (32), none of the studies have included patient centered outcomes. Both interventions, nutrition and exercise, could be placed under the umbrella of behavioral interventions, and as such, they need to be very well-designed interventions. This is

especially true for the exercise component of most of the behavioral strategies for PAD patients with claudication. Frequently in the literature, the word exercise and promotion of physical activity are used indistinctively when discussing non-medical interventions for PAD patients. Although walking advice and promotion of physical activity is highly encouraged in the PAD population, it cannot be considered as an exercise therapy unless the type, the duration, the intensity and the frequency of the exercise is specified to the patient. Unfortunately, the vast majority of research confuses those two terms and insufficiently reports the exercise intervention (33-37). Furthermore, non-structured exercise programs have been shown to have worse result than supervised structured exercise programs and highly structured home-based programs (8, 11, 12, 38). Taking into consideration the complexity of the PAD population, which is characterized by multiple concomitant comorbidities, poor health habits and a reluctance to undergo

lifestyle modifications, our authors believe that this population is particularly unsuited to an unstructured exercise intervention. Therefore, our systematic review was designed to ensure that all included publications rigorously reported a structured exercise protocol and any articles reporting promotion of physical activity alone were excluded.

The combination of structured exercise and nutrition seems to be beneficial at increasing exercise tolerance (28, 30, 31). However, the benefits obtained in combining nutritional and exercise modalities were not statistically significant compared to exercise alone, although a moderate to strong effect size was observed with beetroot juice supplementation in the Woessner RCT, suggesting that the study was underpowered (28). Increased limb blood flow was also observed with the addition of beetroot juice extract group in the aforementioned study (28) and in the non-randomized uncontrolled before-and-after publications by Hall et al.(30, 31) with the use of a high- complex-carbohydrate,

high-fiber, low-fat diet, which is a diet rich in antioxidants and nitric oxide (NO) precursors. These studies suggest that NO improves limb blood flow in PAD patients with intermittent claudication and could potentially increase exercise performance in PAD patients. The effect of NO in blood flow and exercise tolerance has been previously studied, although more evidence is required to prove this hypothesis (13, 39-42). Vitamin E has antioxidant and antiplatelet adhesion actions, and has been shown to be beneficial in cardiovascular disease (43). Collins et al. (29) therefore hypothesized that it would have a positive effect on exercise tolerance in PAD patients. Unfortunately, there was no effect of vitamin E in combination with polestriding above that seen with polestriding alone on exercise capacity, quality of life or limb blood flow. The authors suggest that reasons for their negative results could be due to an insufficient vitamin E dosage, insufficient time, or simply that vitamin E has no effect on exercise performance or that its effect is curtailed by atherosclerotic plaques. Nevertheless, it must be taken into account that in this study up to a 30% of the recruited subjects were excluded after a baseline screening and that the non-randomized population had a tendency to be older and with more comorbidities, thus potentially excluding the subjects who could have benefited the most from vitamin E supplementation.

Surprisingly, quality of life was not the primary outcome in any of the publications and it was only measured in one of the trials (29). Furthermore, the need for revascularization surgery and surgical outcomes was assessed in none of the trials. More studies that evaluate the impact of non-medical interventions, such as exercise and nutrition on quality of life, and the need for revascularization are needed. This is especially important as quality of life plays a large role in deciding whether patients with intermittent claudication are offered surgical revascularization.

It is also worth noting that several protocols and trial registrations of ongoing research were found during our search that will hopefully shed some light to discern if programs that include a combination of nutrition and exercise are beneficial for PAD patients (44-46). Unfortunately, it was also observed that trials fitting our inclusion criteria were cancelled due to slow recruitment (47). This fact is also a result in and of itself; for the reasons already mentioned that the PAD population tends to have poor compliance with exercise and nutritional interventions and thus might not be adherent to these programs once clinically instituted (48). For this reason, we believe that the psychosocial aspect of PAD and motivational interviewing should be addressed as they will likely play important roles in engaging PAD patients with proposed lifestyle modifications (49, 50). It should be noted that the goal of this systematic review was to evaluate the combined effects of nutrition and exercise; however, it did not exclude trials where other concomitant interventions such as smoking cessation or psychological support were included as long as structured exercise and nutrition were present in the intervention. There are several articles that use multimodal and multidisciplinary programs that include walking advice or unstructured exercise, nutrition, smoking cessation, wound care, etc. to increase walking capacity, quality of life and reduce cardiovascular risk in the PAD population(33, 51, 52), but structured exercise and nutrition are often omitted or underused in their protocol. When designing multimodal approaches to treat and prevent PAD derived complications is pivotal that the interventions are structured and this should be emphasized for the design of future trials (11, 34, 36).

9.5. LIMITATIONS

The main limitation of the present systematic review is the inability to perform a pooled analysis across studies due to heterogeneity in study designs, interventions and outcomes.

Therefore, only a qualitative analysis was performed. Furthermore, only one trial included in the systematic review assessed quality of life, which was the primary outcome of this systematic review.

9.6. CONCLUSIONS

There are conflicting results and lack of quality data proving the benefit of nutrition and structured exercise programs on patient centered outcomes. Limb blood flow might be increased with the combination of a diet rich in inorganic nitrate and exercise. There is insufficient evidence to appreciate the effects of such programs on quality of life. Furthermore, there is no data regarding the effects of combined nutrition and exercise on the need for revascularization surgery or post-revascularization outcomes Therefore, more large randomized controlled trials are needed to assess the effects of multimodal interventions that include nutrition and structured exercise on patient centered outcomes and clinical outcomes in the PAD population.

9.8. CONFLICT OF INTEREST

All authors state that they have no conflict of interest.

9.9. ACKNOWLEDGMENTS

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9.11. TABLES AND FIGURES

Figure 1: PRISMA flow diagram describing systematic review search results, abstract screening and article selection

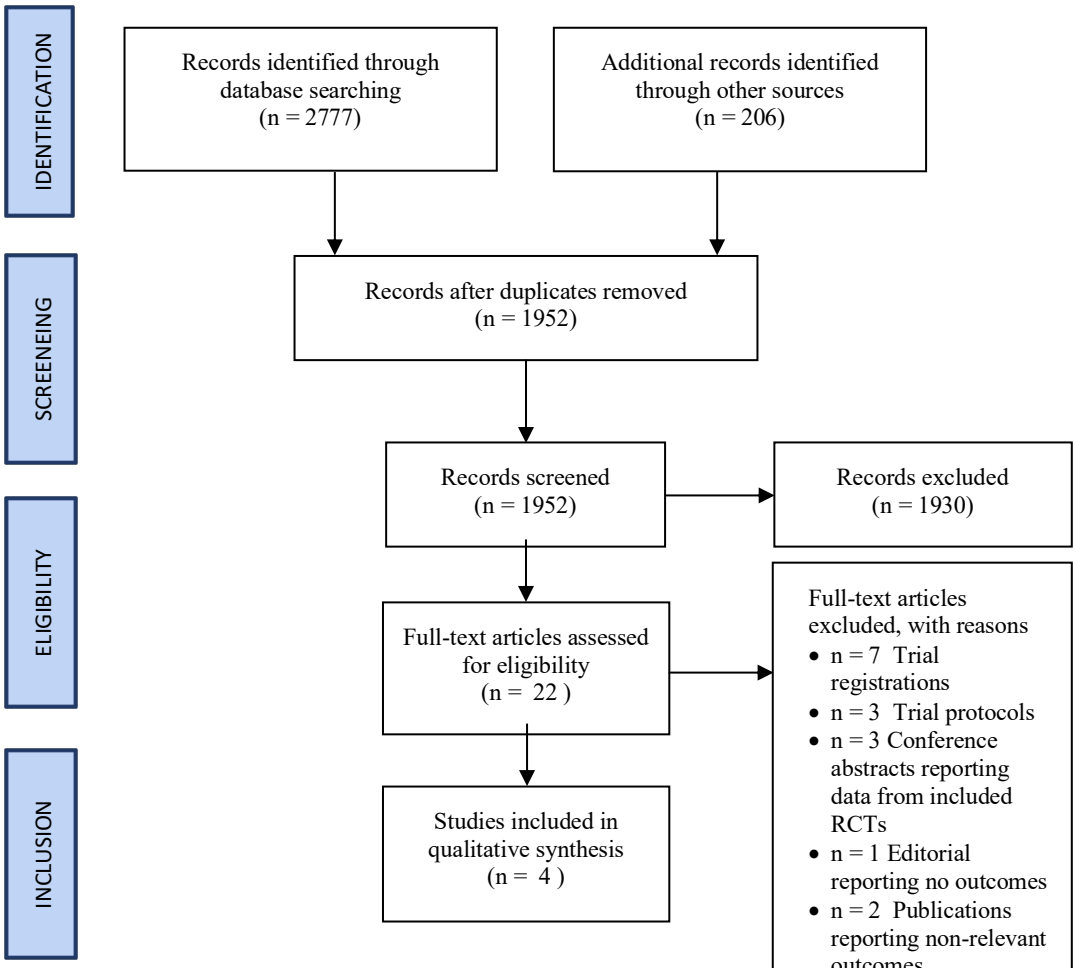

Table 1 Overview of study characteristics

Reference	Design	N	Age	Male	Control group	Exercise intervention	Nutritional intervention	Duration	Primary outcome
Collins E et al. Med Sci Sports Exerc. 2003	RCT 2x2 factorial	52	67.1 (7.8)	51 (98)	Placebo	3 times/week of polestriding	vitamin E 400 UI daily	24 weeks	Duration of incremental treadmill test
Woessner et al. *Circ Res. 2018*	RCT	35	69.7 (8.1)	15 (62.5)	Exercise	3 times/week of 30-minute treadmill walking	4.2 mmol beetroot juice extract (inorganic nitrate)	12 weeks	Claudication onset time
Hall et al. Journal of Cardiac Rehabilitation. 1982	Case series	16	61.5 (1.7)	14 (87.5)	NA	- 1 hour/ day of supervised treadmill walking, stretching and flexibility exercises - Twice/day 30-45 min. of unsupervised walking	high-complex-carbohydrate, high-fiber, low-fat diet	26 days	Exercise capacity measured with METS during treadmill test
Hall et al. Phys Sportsmed. 1982	Case report	1	46	1 (100)	NA	- 1 hour/ day of supervised treadmill walking, stretching and flexibility exercises - Twice/day 30-45 min. of unsupervised walking	high-complex-carbohydrate, high-fiber, low-fat diet	26 days	Walked distance

Data is presented as mean (SD) or n (%)

Table 2: Risk of bias of RCT* and non-randomized controlled trials** for combined nutrition and structured exercise interventions in PAD.

RCTs

Reference	Sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Collins E et al. Med Sci Sports Exerc. 2003	low	Some concerns	Some concerns	High	Some concerns	High
Woessner et al. Circulation Research. 2018	Some concerns	high	Low	High	Low	High

Non-randomized trials

Year Reference	Confounding	Selection of participants	Deviation from intended intervention	Missing data	Outcome measurement	Selective outcome reporting
Hall et al. Journal of Cardiac Rehabilitation. 1982	Critical risk	Critical risk	No information	No information	Serious risk	Moderate risk
Hall et al. Phys Sportsmed. 1982	Critical risk	Critical risk	No information	No information	Critical risk	Critical risk

**Each criterion has been evaluated as being "high," "low," or "some concerns" regarding the risk of bias following the RoB 2 tool for assessing risk of bias in randomized trials **Each criterion has been evaluated as being "low risk," "moderate risk," "serious risk", "critical risk", and "no information" regarding the risk of bias following the ROBINS-I tool for assessing risk of bias.*

9.12. APPENDIX 1: SEARCH STRATEGY

Exercise, Nutrition and Peripheral Artery Disease

Date:	*March 19, 2020*
From:	*Lindsay Hales (MUHC – MGH library; 43056)*
To:	*Miquel Coca Martinez*
Subject:	*Exercise, Nutrition and Peripheral Artery Disease*

Databases & Search Strategies

- **Biosis (Clarivate Analytics) [November 7, 2019]**

#	Searches	Results
1	TS=(peripher* NEAR/3 arter* NEAR/3 disease*)	12425
2	TS=((peripher* NEAR/3 arter*) and (PAD or PAOD))	3828
3	TS=(claudicat*)	5759
4	TS=(((arter* or arterial* or arteriosclero* or atheriosclero*) NEAR/3 (oblitera* or occlusion* or insufficien*)) and (peripher* or extremit* or PAD or PAOD))	4807
5	TS=(vascular* NEAR/3 occlusi* NEAR/2 disease*)	1403
6	1 or 2 or 3 or 4 or 5	22000
7	TS=((diet* or nutrition*))	1825758
8	TS=(((food* or herbal) NEAR/6 supplement*) or nutraceutic* or neutraceutic* or probiotic*)	82097
9	TS=((inorganic* or supplement*) NEAR/3 nitrate*)	2042
10	TS=(amino NEAR/1 acid*)	6842201
11	TS=(Arginine* or histidine* or isoleucine* or leucine* or lysine* or methionine* or phenylalanine* or threonine* or tryptophan* or valine*)	551977
12	TS=((Nutri*) NEAR/5 (supplement* or counsel* or interven* or advic* or advis* or assess* or status* or therap* or modifi* or modify* or support* or guid* or program*))	916107
13	TS=(immunonutri* or immuno-nutri* or micronutri* or macronutri* or micro-nutri* or macro-nutri*)	30135
14	TS=((supplement* or enrich*) NEAR/3 (protein* or fat* or fiber or fibre or sodium or carbs or carb or carbohydrate*)) or leucin* or whey* or omega-3* or vitamin* or mineral*)	2465740
15	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	9513418
16	TS=(exercis* or (physical* NEAR/2 (activit* or performance* or function*)))	417064
17	TS=((walk* or run or running or bike* or bicycl* or jog or jogging or jogs or swim*))	324031
18	16 or 17	685972
19	6 and 15 and 18	725
20	#18 AND #15 AND #6 **Refined by: PUBLICATION YEARS:** (2019)	21

- **Cochrane (Wiley) [November 7, 2019]**

#	Searches	Results
1	(peripher* NEAR/3 arter* NEAR/3 disease*):ti,ab,kw	3648
2	((peripher* NEAR/3 arter*) and (PAD or PAOD)):ti,ab,kw	1193
3	(claudicat*):ti,ab,kw	2397
4	(((arter* or arterial* or arteriosclero* or atheriosclero*) NEAR/3 (oblitera* or occlusion* or insufficien*)) and (peripher* or extremit* or PAD or PAOD)):ti,ab,kw	577
5	(vascular* NEAR/3 occlusi* NEAR/2 disease*):ti,ab,kw	75
6	#1 or #2 or #3 or #4 or #5	5520
7	(diet* or nutrition*):ti,ab,kw	102935
8	(((food* or herbal) NEAR/6 supplement*) or nutraceutic* or neutraceutic* or probiotic*):ti,ab,kw	8806
9	((inorganic* or supplement*) NEAR/3 nitrate*):ti,ab,kw	376
10	(amino acid*):ti,ab,kw	9284
11	(Arginine* or histidine* or isoleucine* or leucine* or lysine* or methionine* or phenylalanine* or threonine* or tryptophan* or valine*):ti,ab,kw	11287
12	((Nutri*) near/5 (supplement* or counsel* or interven* or advic* or advis* or assess* or status* or therap* or modifi* or modify* or support* or guid* or program*)):ti,ab,kw	20364
13	(immunonutri* or (immune NEXT nutri*) or micronutri* or macronutri* or (micro NEXT nutri*) or (macro NEXT nutri*)):ti,ab,kw	5001
14	(((supplement* or enrich*) NEAR/3 (protein* or fat* or fiber or fibre or sodium or carbs or carb or carbohydrate*)) or leucin* or whey* or (omega NEXT 3*) or vitamin* or mineral*):ti,ab,kw	49921
15	#7 or# 8 or #9 or #10 or #11 or #12 or #13 or #14	100043
16	(exercis* or (physical* NEAR/2 (activit* or performance* or function*))):ti,ab,kw	111106
17	(walk* or run or running or bike* or bicycl* or jog or jogging or jogs or swim*):ti,ab,kw	49837
18	#16 or #17	137089
19	#6 and #15 and #18	110
20	Limit to 2019	6

- **Embase (OVID) [November 7, 2019]**

Embase Classic+Embase <1947 to 2019 November 05>

#	Searches	Results
1	exp peripheral occlusive artery disease/	174919
2	intermittent claudication/	11250
3	(peripher* adj3 arter* adj3 disease*).tw,kw,dq.	27343
4	((peripher* adj3 arter*) and (PAD or PAOD)).tw,kw,dq.	9858
5	claudicat*.tw,kw,dq.	15819
6	(((arter* or arterial* or arteriosclero* or atheriosclero*) adj3 (oblitera* or occlusion* or insufficien*)) and (peripher* or extremit* or PAD or PAOD)).tw,kw,dq.	8769
7	(vascular* adj3 occlusi* adj2 disease*).tw,kw,dq.	2114
8	1 or 2 or 3 or 4 or 5 or 6 or 7	189726
9	dietary supplement/	10515
10	(((food* or herbal) adj6 supplement*) or nutraceutic* or neutraceutic* or probiotic*).tw,kw,dq.	53903
11	(nutrition* or diet*).tw,kw,dq.	1027524
12	exp essential amino acid/	326589
13	nitric acid derivative/	9749
14	((inorganic* or dietar* or supplement*) adj3 nitrate*).tw,kw,dq.	1717
15	amino acid*.tw,kw,dq.	539601
16	(Arginine* or histidine* or isoleucine* or leucine* or lysine* or methionine* or phenylalanine* or threonine* or tryptophan* or valine*).tw,kw,dq.	481354
17	exp diet therapy/	355061
18	exp food/	1090394
19	exp diet/	356617
20	(Nutri* adj5 (supplement* or counsel* or interven* or advic* or advis* or assess* or status* or therap* or modifi* or modify* or support* or guid* or program*)).tw,kw,dq.	133072
21	(immunonutri* or immuno-nutri* or micronutri* or macronutri* or micro-nutri* or macro-nutri*).tw,kw,dq.	32010
22	(((supplement* or enrich*) adj3 (protein* or fat* or fiber or fibre or sodium or carbs or carb or carbohydrate*)) or leucin* or whey* or omega-3* or vitamin* or mineral*).tw,kw,dq.	617331
23	or/9-22	3396071
24	8 and 23	8611
25	exp exercise/	351334
26	exp kinesiotherapy/	79029
27	fitness/	39708
28	(exercis* or (physical* adj2 (activit* or performance* or function*))).tw,kw,dq.	560395

29	(walk* or run or running or bike* or Bicycl* or jog or jogging or jogs or swim*).tw,kw,dq.	427956
30	25 or 26 or 27 or 28 or 29	1038107
31	24 and 30	981
32	remove duplicates from 31	972
33	limit 32 to (conference abstract or conference paper or "conference review")	188
34	32 not 33	784
35	limit 33 to yr="2017 -Current"	43
36	(201905* or 201906* or 201907* or 201908* or 201909* or 201910* or 201911* or 201912*).dc,dd.	1155489
37	34 and 36	25
38	35 and 36	9
39	("31211542" or "31206284" or "31182334" or "31159978" or "31224332" or "31262371" or "31623356").pm.	3
40	37 not 39	22
41	from 38 keep 1-9	9
42	from 40 keep 1-22	22

- **Global Health (OVID) [November 7, 2019]**

Global Health 1973 to 2019 Week 43, **Global Health Archive** 1910 to 1972

#	Searches	Results
1	(peripher* adj3 arter* adj3 disease*).ti,ab,id.	1125
2	((peripher* adj3 arter*) and (PAD or PAOD)).ti,ab,id.	507
3	claudicat*.ti,ab,id.	355
4	(((arter* or arterial* or arteriosclero* or atheriosclero*) adj3 (oblitera* or occlusion* or insufficien*)) and (peripher* or extremit* or PAD or PAOD)).ti,ab,id.	112
5	(vascular* adj3 occlusi* adj2 disease*).ti,ab,id.	68
6	1 or 2 or 3 or 4 or 5	1535
7	(diet* or nutrition*).ti,ab,id.	528782
8	(((food* or herbal) adj6 supplement*) or nutraceutic* or neutraceutic* or probiotic*).ti,ab,id.	35637
9	((inorganic* or supplement*) adj3 nitrate*).ti,ab,id.	364
10	amino acid*.ti,ab,id.	79412
11	(Arginine* or histidine* or isoleucine* or leucine* or lysine* or methionine* or phenylalanine* or threonine* or tryptophan* or valine*).ti,ab,id.	59939
12	(Nutri* adj5 (supplement* or counsel* or interven* or advic* or advis* or assess* or status* or therap* or modifi* or modify* or support* or guid* or program*)).ti,ab,id.	64872
13	(immunonutri* or immuno-nutri* or micronutri* or macronutri* or micro-nutri* or macro-nutri*).ti,ab,id.	17716
14	(((supplement* or enrich*) adj3 (protein* or fat* or fiber or fibre or sodium or carbs or carb or carbohydrate*)) or leucin* or whey* or omega-3* or vitamin* or mineral*).ti,ab,id.	250757
15	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	762993
16	(exercis* or (physical* adj2 (activit* or perfomance* or function*))).ti,ab,id.	84806
17	(walk* or run or running or bike* or bicycl* or jog or jogging or jogs or swim*).ti,ab,id.	50243
18	16 or 17	124996
19	6 and 15 and 18	59
20	limit 19 to yr="2019 -Current"	4

- **Medline (OVID)[November 7, 2019]**

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to November 05, 2019>

#	Searches	Results
1	Peripheral Arterial Disease/	6843
2	Peripheral Vascular Diseases/	12492
3	limit 2 to yr="1991 - 2010"	7582
4	arterial occlusive diseases/	26973
5	limit 4 to yr="1963 - 2010"	23053
6	Intermittent Claudication/	7800
7	(peripher* adj3 arter* adj3 disease*).tw,kf.	16803
8	((peripher* adj3 arter*) and (PAD or PAOD)).tw,kf.	5904
9	claudicat*.tw,kf.	10560
10	(((arter* or arterial* or arteriosclero* or atheriosclero*) adj3 (oblitera* or occlusion* or insufficien*)) and (peripher* or extremit* or PAD or PAOD)).tw,kf.	5484
11	(vascular* adj3 occlusi* adj2 disease*).tw,kf.	1373
12	1 or 3 or 5 or 6 or 7 or 8 or 9 or 10 or 11	57508
13	exp Dietary Supplements/	71606
14	exp diet/	270133
15	(diet* or nutrition*).tw,kf.	752031
16	(((food* or herbal) adj6 supplement*) or nutraceutic* or neutraceutic* or probiotic*).tw,kf.	39979
17	exp Amino Acids, Essential/	209461
18	Nitrates/	28275
19	((inorganic* or supplement*) adj3 nitrate*).tw,kf.	907
20	Amino Acids, Essential/	2266
21	amino acid*.tw,kf.	470377
22	(Arginine* or histidine* or isoleucine* or leucine* or lysine* or methionine* or phenylalanine* or threonine* or tryptophan* or valine*).tw,kf.	386680
23	exp Nutrition Therapy/	98298
24	exp Food/	1249511
25	(Nutri* adj5 (supplement* or counsel* or interven* or advic* or advis* or assess* or status* or therap* or modifi* or modify* or support* or guid* or program*)).tw,kf.	93735
26	(immunonutri* or immuno-nutri* or micronutri* or macronutri* or micro-nutri* or macro-nutri*).tw,kf.	23535
27	(((supplement* or enrich*) adj3 (protein* or fat* or fiber or fibre or sodium or carbs or carb or carbohydrate*)) or leucin* or whey* or omega-3* or vitamin* or mineral*).tw,kf.	456714
28	Food additives/	7837
29	limit 25 to yr="1966 - 1974"	626
30	Food fortified/	9128

31	limit 30 to yr="1972 - 1997"	4076
32	diet therapy.fs.	49790
33	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 29 or 31 or 32	2840350
34	exp Exercise/	184890
35	exp Exercise Therapy/	47870
36	exp Physical Fitness/	28267
37	(exercis* or (physical* adj2 (activit* or perfomance* or function*))).tw,kf.	391903
38	(walk* or run or running or bike* or bicycl* or jog or jogging or jogs or swim*).tw,kf.	300932
39	34 or 35 or 36 or 37 or 38	696109
40	12 and 33 and 39	334
41	(201905* or 201906* or 201907* or 201908* or 201909* or 201910* or 201911* or 201912*).dt.	654976
42	40 and 41	7

- Medline (OVID) [March 19, 2020]

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to March 18, 2020>

#	Searches	Results
1	Peripheral Arterial Disease/	7294
2	Peripheral Vascular Diseases/	12552
3	limit 2 to yr="1991 - 2010"	7581
4	arterial occlusive diseases/	27125
5	limit 4 to yr="1963 - 2010"	23053
6	Intermittent Claudication/	7862
7	(peripher* adj3 arter* adj3 disease*).tw,kf.	17340
8	((peripher* adj3 arter*) and (PAD or PAOD)).tw,kf.	6127
9	claudicat*.tw,kf.	10748
10	(((arter* or arterial* or arteriosclero* or atheriosclero*) adj3 (oblitera* or occlusion* or insufficien*)) and (peripher* or extremit* or PAD or PAOD)).tw,kf.	5583
11	(vascular* adj3 occlusi* adj2 disease*).tw,kf.	1392
12	1 or 3 or 5 or 6 or 7 or 8 or 9 or 10 or 11	58401
13	exp Dietary Supplements/	74179
14	exp diet/	275260
15	(diet* or nutrition*).tw,kf.	769049
16	(((food* or herbal) adj6 supplement*) or nutraceutic* or neutraceutic* or probiotic*).tw,kf.	42025
17	exp Amino Acids, Essential/	210139
18	Nitrates/	28625
19	((inorganic* or supplement*) adj3 nitrate*).tw,kf.	940
20	Amino Acids, Essential/	2284
21	amino acid*.tw,kf.	476723
22	(Arginine* or histidine* or isoleucine* or leucine* or lysine* or methionine* or phenylalanine* or threonine* or tryptophan* or valine*).tw,kf.	391911

23	exp Nutrition Therapy/	99800
24	exp Food/	1266198
25	(Nutri* adj5 (supplement* or counsel* or interven* or advic* or advis* or assess* or status* or therap* or modifi* or modify* or support* or guid* or program*)).tw,kf.	96253
26	(immunonutri* or immuno-nutri* or micronutri* or macronutri* or micro-nutri* or macro-nutri*).tw,kf.	24339
27	(((supplement* or enrich*) adj3 (protein* or fat* or fiber or fibre or sodium or carbs or carb or carbohydrate*)) or leucin* or whey* or omega-3* or vitamin* or mineral*).tw,kf.	466373
28	Food additives/	7928
29	limit 25 to yr="1966 - 1974"	626
30	Food fortified/	9244
31	limit 30 to yr="1972 - 1997"	4075
32	diet therapy.fs.	50532
33	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 29 or 31 or 32	2886120
34	exp Exercise/	190407
35	exp Exercise Therapy/	49435
36	exp Physical Fitness/	29168
37	(exercis* or (physical* adj2 (activit* or perfomance* or function*))).tw,kf.	402479
38	(walk* or run or running or bike* or bicycl* or jog or jogging or jogs or swim*).tw,kf.	308652
39	34 or 35 or 36 or 37 or 38	714185
40	12 and 33 and 39	343
41	(201905* or 201906* or 201907* or 201908* or 201909* or 201910* or 201911* or 201912*).dt.	871676
42	40 and 41	10
43	(201911* or 201912* or 202001* or 202002* or 202003* or 202004*).dt.	520472
44	40 and 43	7
45	44 not 42	5

- **Scopus (Elsevier) [November 7, 2019]**

#	Searches	Results
1	TITLE-ABS-KEY(peripher* W/3 arter* W/3 disease*)	44122
2	TITLE-ABS-KEY(((peripher* W/3 arter*) and (PAD or PAOD))	6652
3	TITLE-ABS-KEY(claudicat*)	19862
4	TITLE-ABS-KEY((((arter* or arterial* or arteriosclero* or atheriosclero*) W/3 (oblitera* or occlusion* or insufficien*)) and TITLE-ABS-KEY((peripher* or extremit* or PAD or PAOD))	20261
5	TITLE-ABS-KEY((vascular* W/3 occlusi* W/2 disease*))	2017
6	1 or 2 or 3 or 4 or 5	69189
7	TITLE-ABS-KEY(diet* or nutrition*)	1555703
8	TITLE-ABS-KEY((food* or herbal) W/6 supplement*)	22615
9	TITLE-ABS-KEY((nutraceutic* or neutraceutic* or probiotic*))	56823
10	TITLE-ABS-KEY((inorganic* or supplement*) W/3 nitrate*))	2740
11	TITLE-ABS-KEY(amino acid*)	1189865
12	TITLE-ABS-KEY(Arginine* or histidine* or isoleucine* or leucine* or lysine* or methionine* or phenylalanine* or threonine* or tryptophan* or valine*)	746185
13	TITLE-ABS-KEY((Nutri*) W/5 (supplement* or counsel* or interven* or advic* or advis* or assess* or status* or therap* or modifi* or modify* or support* or guid* or program*))	198067
14	TITLE-ABS-KEY((immunonutri* or immuno-nutri* or micronutri* or macronutri* or micro-nutri* or macro-nutri*)	45025
15	TITLE-ABS-KEY((supplement* or enrich*) W/3 (protein* or fat* or fiber or fibre or sodium or carbs or carb or carbohydrate*))	40492
16	TITLE-ABS-KEY(leucin* or whey* or omega-3* or vitamin* or mineral*)	1293322
17	7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	4192012
18	TITLE-ABS-KEY((physical* W/2 (activit* or performance* or function*)))	251513
19	TITLE-ABS-KEY(exercis*)	613646
20	TITLE-ABS-KEY(walk* or run or running or bike* or bicycl* or jog or jogging or jogs or swim*)	1189965
21	18 or 19 or 20	1865984
22	6 and 17 and 21	692
23	Limit to 2019	33

2. Additional Details

2.1. Duplication & Removal of Records

Database	Before Duplicate Removal	After Duplicate Removal	% Retained
Biosis – Clarivate Analytics	21	9	43%
Cochrane	6	3	50%
Embase	22	13	59%
Embase (Conference Abs.)	9	5	56%
Global Health	4	0	0
Medline	7	5	71%
Scopus	33	7	21%
Totals	***102***	***42***	**41%**

2.2. Legend for Databases

Legends for Medline (Ovid), Embase (Ovid) & CINAHL (Ebsco) are available on our website: http://www.muhclibraries.ca/Documents/Database_Legends.pdf

10. PREFACE TO CHAPTER 2

As seen in the previous chapter, studies that combine structured exercise and nutrition in PAD patients suffering from IC are scarce and evidence is of low quality. It has also been discussed in the previous chapter that there is indeed a call for a multimodal multidisciplinary optimization approach to treat and prevent worsening of PAD. This approach ideally should encompass lifestyle modifications namely exercise, healthy eating and smoking cessation along with disease teaching, medical optimization of underlying conditions and comorbidities and the rational use of endovascular revascularization. There have been some studies that have investigated the effects of multidisciplinary multimodal approaches on outcomes for PAD. Nevertheless, the common denominator in all those studies is that the exercise component is not structured and in most cases it is unsupervised[27,30,31].

Multimodal prehabilitation, understood as a multidisciplinary optimization tool to increase functional reserve before surgery in order to reduce postoperative complications and prevent postoperative functional decline has been studied mainly in the surgical cancer population[32-35]. Growing evidence supports its use as a preoperative optimization strategy to increase perioperative functional capacity, decrease postoperative complications and healthcare associated costs in the context of an Enhanced Recovery After Surgery (ERAS) program[36-38]. Prehabilitation experience in the cardiovascular domain is less abundant, but it has also been shown to be effective at increasing functional capacity, decreasing length of stay and reducing postoperative pulmonary complications in cardiac surgery and in abdominal aneurysm repair[39,40]. Nevertheless, multimodal prehabilitation in peripheral arterial disease has not yet been investigated. Consequently, in the following chapter the feasibility, safety and efficacy of a multimodal prehabilitation

program for peripheral arterial disease will be presented with a case series, as a proof of concept for multimodal prehabilitation in peripheral arterial disease.

11. CHAPTER 2

Multimodal Prehabilitation for Peripheral Arterial Disease: A Case Series.

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Key words: multimodal prehabilitation, peripheral arterial disease, intermittent claudication, quality of life, functional capacity

Conflict of interest and Funding:

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Type of Research: Single center prospective case series

Key Findings: A 12-week Multimodal Prehabilitation program was instituted in 5 patients with PAD and poor expected revascularization outcome. Median [IQR] adherence to each prehabilitation component was 91.7% [33.5] for supervised training, 91.7% [40] for home-based and 75% [50] for nutrition. No major adverse events occurred during the program.

Take home Message: Multimodal Prehabilitation is safe and feasible in patients PAD suffering from severe life limiting intermittent claudication whose surgical option entails a high-risk procedure or those who have no revascularization option at all . Multimodal Prehabilitation might be a suitable tool to increase quality of life, functional capacity and emotional status in this population.

Table of contents Summary: This prospective single center case series suggests that a 12-week multimodal prehabilitation is safe and feasible for patients with PAD poor expected revascularization outcome. The authors believe that this novel approach could be used to increase functional capacity, quality of life and emotional status in PAD patients whose surgical option entails a high-risk procedure or those who have no revascularization option at all.

11.1 ABSTRACT

The effects of a 12-week Multimodal prehabilitation (MMP) have not yet been investigated in PAD patients with severe life-limiting intermittent claudication and poor expected revascularization outcome. Five patients underwent a 12-week MMP program. No serious adverse events occurred throughout the program. Median [IQR] adherence to prehabilitation was 91.7% [40]. Functional capacity and quality of life improved in all patients after the program. MMP is safe, feasible and it could be used to increase functional capacity and quality of life for those patients whose surgical option entails a high-risk procedure or those who have no revascularization option at all.

11.2. INTRODUCTION:

Peripheral arterial disease (PAD) affects up to 10% of the worldwide population and the prevalence increases to 20% among patients 70 years of age and older[1]. Individuals with PAD are often sedentary, suffer from decreased functional capacity, severe disability, poor quality of life, and increased risk of premature mortality[2, 3]. Lifestyle modifications, especially smoking cessation, exercise, and nutrition are critical for patients with PAD and should be encouraged prior to contemplating surgery[4]. Despite the importance of lifestyle modifications, along with medical and nutritional optimization for PAD, there is a lack of implementation and consistency of all these elements in the clinical setting[5, 6].

Multimodal Prehabilitation (MMP), understood as multidisciplinary optimization strategy that includes structured exercise, nutrition, smoking cessation and psychological support has been shown to improve surgical outcomes in different types of surgeries, and it is postulated as one of the most promising approaches to optimize a patient's functional capacity before and after surgery[7]. There is no data regarding how a MMP program might impact outcomes in PAD patients. This multidisciplinary approach might the most suited method for PAD patients in whom the risks of revascularization surgery outweigh the potential benefits, or in patients with no surgical options.

11.3. METHODS

Patient selection and diagnosis of PAD:

Five consecutive patients with the diagnosis of severe life-limiting PAD and poor expected revascularization outcome were recruited at the outpatient vascular clinic of the McGill University Health Centre, agreed to participate in the program and signed the informed consent. Moderate to severe PAD diagnosis was made clinically by functional limitations in walking activity or pain at night, anatomically by imaging demonstrating arterial stenosis below the inguinal, and hemodynamically by an ABI $\leq$ 0.90. All patients were medically optimized and stable PAD condition. Poor expected revascularization outcome was defined by complex infrainguinal disease such as TASC II D lesions or previous failed bypass attempts[8].

Assessments and intervention

Baseline assessment was done before the start of the MMP program which included sociodemographic and anthropometric data, health-related quality of life (HRQoL) questionnaires, presence of anxiety or depression (HADS questionnaire[9]), and functional capacity (6-Minute Walk test[10], Gardner-Skinner's test[11], sit-to-stand test[12] and grip strength test[13]). Onset of claudication during the walk test was also recorded. After baseline assessment patients started a 12-week MMP program that is summarized in Table I and is fully detailed in the supplemental material.

Weekly compliance to both supervised and home-based exercise was recorded as well as adherence to nutritional recommendations. Any exercise-related adverse events occurring during the supervised session were recorded. A reassessment upon the 12-week prehabilitation program completion was performed.

11.4. RESULTS

A total of 5 patients with median age of 76 (57-80 years old) underwent the 12-week prehabilitation program. Four patients had severe intermittent claudication (Fontaine stage IIb), one patient had rest pain, he was unable to walk and was using a wheelchair. All five patients had cardiovascular risk factors such as hypertension, dyslipidemia and diabetes. There were 2 active smokers and 3 ex-smokers. Baseline functional capacity, HRQoL and other parameters collected are shown in table II.

There were no serious adverse events throughout the program, although one patient presented with a hypertensive peak (BP 210/90 mmHg) with symptomatology consisting of headache and dizziness upon arrival to one exercise session. He was immediately referred to the Emergency Department and did not perform the exercise session on that day. Insulin requirements for two of the patients with diabetes had to be lowered due to the improvement in glycemic control. Median [IQR] adherence to each prehabilitation component was 91.7% [33.5] for supervised training, 91.7% [40] for home-based and 75% [50] for nutrition. Three out of five patients underwent psychosocial intervention and all the active smokers enrolled on the smoking cessation program. Changes in functional capacity, quality of life and emotional status are summarized in table II. The increase in functional capacity and onset of pain was clinically significant in all subjects. Furthermore, the patient who used a wheelchair to ambulate at baseline became fully functional and stopped using the wheelchair after the 12-week program. HRQoL and walking impairment measured by the VascuQol and WIQ improved drastically with increases that in some cases almost doubled the baseline value.

11.5. DISCUSSION:

Structured walking protocols for PAD patients have been proven to be effective at increasing walking capacity and delaying onset of pain. They have been shown to be as effective as medication and endovascular revascularization with respect to increasing pain-free walking distance[14, 15]. Other interventions such as smoking cessation and healthy nutrition have also shown to impact PAD outcomes as well[16-19]. However, PAD individuals usually find it hard undergo lifestyle modifications without rigorous guides and supervision due to enrooted poor health behaviors and reluctance to change. Although it has been reported that walking advice increases walking capacity, for PAD patients this isolated unstructured intervention is not enough. It is not sufficient at creating a change in patient's lifestyle and patients stop walking at some point due to claudication pain and go back to old habits. Indeed, evidence shows that supervised training is better than unsupervised training in PAD patients[20, 21]. Moreover, PAD patients present with high anxiety and depression rates and they are in need of psychological support[22]. Good mental health is key to promote a change in patient mindset, therefore, psychological support, motivational interviewing, and patient empowering are key elements to achieve a successful lifestyle modification in this population[23]. International vascular surgery societies have underlined the importance of exercise, nutrition and smoking cessation for the disease prevention, control and to reduce symptomatology[8, 24, 25]. Nevertheless, there has been a lack of implementation of all these interventions or they have been partially implemented[26].

The feasibility and safety of a MMP program has been demonstrated in these 5 cases of patients with PAD and poor revascularization option. The improvements in functional capacity, HRQoL and emotional status shown in this case series are promising. It is clear

to us that in order to achieve a significant lifestyle change in the PAD population we need to provide them with a structured multidisciplinary team that accompanies and supervises closely their way through the lifestyle modification in order to improve their quality of life and increase their functional capacity. We believe that the reason for this significant improvement relies on the synergy created combining all the components (disease teaching, structured aerobic and resistance exercise, psychosocial support, nutritional counseling and smoking cessation), which provide a holistic approach to the patient and the disease. Furthermore, adherence to all components was higher compared to other trials with behavioral interventions in this population[27, 28]. This fact could be attributed to the incorporation of the psychosocial support intervention and disease teaching, which are key components for patient empowerment and engagement[29]

11.6. CONCLUSION:

Multimodal prehabilitation appears to be safe and feasible in PAD patients suffering from severe life limiting intermittent claudication whose surgical option entails a high-risk procedure or those who have no revascularization option at all. MMP could be an excellent tool to optimize this population in order to increase their quality of life and functional capacity. Further robust studies are needed to prove the effectiveness and impact of this multimodal approach in quality of life, functional capacity and need for surgery on this population.

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11.8. TABLES

Table I: Description of the 12-Week Multimodal Prehabilitation Program for PAD patients

Exercise - *12-week program* - *Goal progression every week if program well tolerated*	**Supervised** *1 time/week*	- Aerobic: 30-40 minutes of moderate intensity on treadmill. - Resistance: 20 minutes of whole-body resistance training with emphasis on lower limb exercises (calves, quadriceps and hamstrings).
	Home-based *3 times/week*	- Aerobic: 30-40 minutes of walking at moderate intensity. - Resistance: whole-body resistance training with elastic bands provided. Emphasis on lower limb exercises (calves, quadriceps and hamstrings). - Stretching exercises.
Nutrition - *1 first visit* - *1 follow-up visit*	**Nutritional education:** - Balanced meals - Correct portion size - Timing and spacing of meals - Mindful eating - Protein importance and sources	
	Nutritional intervention - Nutritional assessment - Ensure balanced macronutrient intake - Weight management - Optimize glycemic control - Adequate protein intake 1.2-1.5g/kg/day	
Psychosocial - *If score in HADS-A>6 or HADS-D >8*	- Cognitive reframing - Relaxation and deep breathing exercises - Anxiety coping strategies	
Smoking cessation	- Assessment by a smoking cessation specialist - Nicotine Replacement Therapy - Progress tracking with exhaled carbon monoxide analyzer	

HADS-A: Hospital Anxiety and Depression Scale – Anxiety; HADS-D: Hospital Anxiety and Depression Scale – Depression.

Table II: Change in body composition, functional capacity, quality of life, anxiety and depression after a 12-week multimodal prehabilitation program.

Measurement \ Patient	1		2		3		4		5	
	BL	12W (Δ%)	BL	12W (Δ%)	BL	12W (Δ%)	BL	12W (Δ%)	BL	12W (Δ%)
Body composition										
Weight (kg)	74.2	78.8 (+6.2)	88.3	83.5 (-5.4)	105.4	104.2 (-1.2)	92.6	91.8 (-0.9)	55.5	55.1 (-0.7)
BMI (kg/m^2)	26	27.5 (+5.7)	29.5	27.3 (-)	34	33.6 (-7.5)	31.3	31 (-0.9	20.9	20.7 (-1)
Body Fat (%)	26.4	30.7 (+16.2)	45.8	41.3 (-4.5)	38.5	35.3 (-8.3)	43.8	45.9 (4.8)	30.9	31.1 (+0.6)
Lean Body Mass (kg)	54.6	54.6 (0)	47.9	49.1 (+1.2)	64.8	67.4 (+4.0)	52	49.7 (-4.4)	38.3	38 (-0.8)
Functional capacity										
6-MWT distance (m)	303	494 (+63)	281	351 (+25)	285	389 (+36)	195	242 (+24)	312	362 (+16)
Onset of pain (s)	120	254 (+111)	98	270 (+175)	86	117 (+36)	130	145 (+11)	66	84 (+27)
Gardner's test (s)	318	600 (+88)	158	330 (+109)	97	182 (+87)	30	120 (+300)	60	84 (+40)
Timed Up and Go	5.89	3.71 (-37)	10.42	8.41 (-19.3)	8.35	6.74 (-19.3)	9.02	8.66 (-4.0)	7.94	6.69 (-15.7)
Bicep curl test (reps)	19	28 (+47)	16	19 (+19)	18	21 (+17)	14	14 (0)	16	19 (+19
Sit-to-stand test (reps)	17	24 (+41)	9	12 (+33)	12	14 (+17)	7	5 (-28)	6	11 (+83)
Grip strength (kg)	43	50 (+16)	35	38 (+9)	28	36 (+29)	20	20 (0)	16	22 (+37)
Quality of life										
VascuQol										
Total	3.13	4.84 (+54.6)	5.92	6.04 (+2.0)	3.14	4.01 (+27.7)	3.47	4.91(+41.5)	4.20	4.74 (+12.8)
Pain domain	2.75	4.00 (+45.5)	6.00	5.50 (-8.3)	2.25	2.75 (+22.2)	3.25	5.00 (+53.8)	2.75	3.75 (+36.4)
Social domain	3.5.0	5.00 (+42.9)	7.00	6.00 (-14)	4.00	4.00 (0.0)	4.50	5.50 (+22.2)	5.00	6.00 (+20.0)
Activity domain	2.62	5.00 (+90.8)	4.50	6.00 (+33.3)	2.75	4.20 (+52.7)	2.65	3.50 (+32.1)	4.12	4.25 (+3.1)
Symptoms domain	3.50	5.25 (+50.0)	6.25	6.25 (0)	3.45	4.48 (+29.9)	3.25	6.00 (+84.6)	6.00	6.25 (+4.2)
Emotional domain	3.29	4.88 (+48.3)	5.86	6.29 (+0.7.3)	3.27	4.63 (+41.6)	3.71	4.57 (+23.2)	3.14	3.43 (+9.2)
WIQ										
WIQ total	18.0	45.2 (+151)	17.8	54.6 (+36.8)	25.6	37.1 (+44.9)	18.5	46.9(+153)	6.3	12 (+90.5)
WIQ distance	22.0	37.1 (+68.6)	5.9	59.5 (+53.6)	26.0	44.6 (+71.5)	3.8	26.5(+597)	0.5	4.1 (+720)
WIQ speed	4.5	31.8 (+606)	14.1	50 (+35.9)	21.7	50 (+130)	9.8	39.1 (+299)	14.1	15.2 (+7.8)
WIQ stairs	29.2	66.7 (+128)	33.3	54.2(+20.9)	29.2	16.7(-42.8)	41.7	75 (+79.9)	4.2	16.7 (+298)
HADS										
HADS-A	4	3 (-25)	3	1 (-2)	9	6 (-33)	10	6 (-40)	10	4 (-60)
HADS-D	7	3 (-57)	2	2 (0)	9	4 (-55)	15	9 (-40)	1	2 (-100)

BL: baseline assessment; 12W: 12-week assessment; Δ%: increase from baseline in percentage; BMI: body mass index; 6-MWT: 6-Minute Walk Test; VascuQol: Vascular Quality of Life Questionnaire; WIQ: Walking Impairment Questionnaire; HADS-A: Hospital Anxiety and Depression Scale – Anxiety; HADS-D: Hospital Anxiety and Depression Scale – Depression.

11.9. SUPPLEMENTAL MATERIAL

Detailed 12-week multimodal prehabilitation program intervention

a) Supervised exercise session: Supervised training was performed in-hospital under the supervision of a kinesiologist once per week and typically lasted a total of 1 hour. The training session was divided as follows:

   i. The aerobic component consisted of a 5-minute of warm-up in a recumbent stepping device (NuStep, Inc., Ann Arbor, M) followed by a 30 to 40 minutes of accumulated moderate intensity treadmill walking (not including rest periods). The walking treadmill exercise prescription was tailored to each patient according to their baseline functional capacity results and intensity during training was measured by the Borg scale of perceived exertion[41]. Patients were encouraged to continue walking until they reached their maximal claudication pain. Exercise and rest periods were repeated during each session until the minimum total of 30 minutes of walking time was reached in each session. Workload progression every week if tolerated. Blood pressure was monitored before the training session and at the end. Heart rate, perceived effort, and claudication pain were monitored throughout the period of exercise.

   ii. The resistance training component consisted of ten exercises targeting all major muscle groups of the body, with special emphasis on lower extremities. Intensity of resistance training was based on strength tests performed at baseline and progression of strength exercise was made

b) Home-based exercise: Patients received a motivational interview underlining the importance of physical activity and its relationship with PAD disease and were

encouraged to keep active throughout the day (promotion of physical activity). They were advised to walk for at least 30-40 minutes at moderate intensity 3 times/week. They were also instructed on how to conduct resistance exercise at home with elastic bands that were provided during the first supervised exercise session along with flexibility exercises prescription and promotion of physical activity. Whole-body muscular resistance training was carried out also three times a week to avoid muscle soreness and was mainly focused on lower limb strength. Patients were instructed to do push-ups, sit-ups, calf raises, hamstring kickbacks and standing strides (lunges) until volitional fatigue, increasing this number to reach 12 repetitions. The difficulty chosen for strengthening of biceps, deltoids and quadriceps was based on what the person was able lift to reach volitional fatigue with 8 repetitions.

c) Nutrition counseling and supplementation: the nutritional status and dietary intake of patients were assessed by a registered dietitian at baseline using Patient Generated Subjective Global Assessment (PG-SGA), a 3-day food diary, anthropometric measurements, and bio impedance (InBody 270, Biospace, Seoul, Korea). Based on the status and conditions of the patient, an individualized nutrition intervention was provided, promoting dietary changes to ensure balanced intake with adequate protein, weight management, and the regulation of glycemic control. Nutrition education sessions with a registered dietitian included learning correct portion sizes, building a balanced plate, learning sources and importance of protein, importance of timing and spacing of meals, along with practicing mindful eating. The goals of the nutrition intervention included:

i. Balanced intake: correct distribution of macronutrients, including adequate protein and a variety of fruits and vegetables.

ii. Adequate protein: 1.2-1.5 g/kg/day.

iii. Weight management to fall within healthy body mass index (BMI) range of 19 – 25 kg/m2.

iv. Optimize glycemic control: 5-7mmol/L before meals, 7.8-11 mmol/L 2 hours after meals, A1C <7%.

d) Smoking cessation: patients who were active smokers were assessed using the Fagerstrom Test for Nicotine Dependence and they were encouraged to cease cigarette smoking. They were offered to meet a smoking cessation specialist and to start nicotine replacement therapy. Progress was monitored using the exhaled carbon monoxide test.

e) Psychosocial intervention: patients were seen by a physician at baseline assessment who reviewed and optimized, if necessary, the pharmacological treatment. Disease teaching, underlining the importance of risk factor reduction and a plain explanation of the physiopathology of PAD was also performed at baseline by a physician. Patients that scored more than 6 points in the HADS-Anxiety or more than 8 in the HADS-Depression received a personalized psychological intervention conducted by a psychosocial specialist. The intervention consisted of relaxation and deep breathing exercises, anxiety coping strategies and cognitive reframing. Patients were also provided with a relaxation CD to take home.

12. DISCUSSION

Optimal medical optimization and risk factor reduction are fundamental to control PAD progression and to decrease the incidence of cardiovascular events, which are very prevalent in this population. PAD population is characterized by presenting multiple comorbidities that are related to an unhealthy lifestyle and poor risk factor control[42]. Lifestyle modifications such as exercise and nutrition are a powerful tool to treat and prevent PAD, yet they are still undervalued and underutilized by healthcare professionals and, in most cases, not funded by healthcare systems[43-46].

Despite the fact that evidence points towards supervised exercise as being more effective than unsupervised exercise and equally effective to endovascular revascularization surgery, it is still unclear what type and modality of structured supervised exercise is more effective at increasing exercise capacity in PAD since all but a few of the studies done to date on structured exercise programs have concentrated on walking protocols[47]. Moreover, many patients with intermittent claudication symptoms find it difficult to partake in walking programs, and many prefer the immediate resolution of symptoms offered with surgery. However, surgery does not appear to result in long term functional gains.

One of the key features of PAD disease evolution is the progressive deterioration of the patient's quality of life that is correlated to his/her functional capacity[48]. PAD patients with IC might find it hard to perform simple everyday life activities, such as walking one block or even crossing a street without stopping due to pain. As a result of this they might feel dependent and become cumbersome for themselves and their care givers due to their functional limitations. In fact, quality of life plays a large role in deciding whether patients

with intermittent claudication are offered surgical revascularization. Interestingly, there is lack of evidence on how exercise interventions impact general or disease specific quality of life. Only a few studies have looked at the impact of exercise training on health related quality of life improvement despite of its importance in this disease[19].

Nutrition seems to play an important role in the development and progression of PAD[20,21,49,50]. In addition to a healthy diet, different nutritional supplements have been proposed to enhance walking capacity and reduce cardiovascular risk in this population, such as the supplementation with long chain n3 Polyunsaturated Fatty Acids (PUFA), folate, vitamins B6, B12, E or coenzyme Q10[51]. There is currently not enough evidence to support any of the aforementioned supplementation for treatment of PAD. There is, however, emerging evidence on the use of inorganic nitrate precursors such as beetroot juice extract to increase blood flow and exercise tolerance. This increase in blood flow and exercise tolerance seems to be mediated through the nitric oxide (NO) vasodilator effects[52-54]. PAD patients present changes in tissue structure and characteristics in response to chronic poor perfusion, among which stand out vascular endothelial dysfunction and reduced nitric oxide (NO) bioavailability. Exogenous administration of NO precursors (inorganic nitrate) seems to function as pool of NO that is released and converted to NO under hypoxic and acidic conditions[55], which are present in patients in the lower extremities of patients with PAD suffering from IC . Therefore, these patients could benefit from this therapy since inorganic nitrate would target the peripheral tissues that are poorly perfused because of the occlusive vascular disease[56].

As discussed in chapter 1, the evidence for holistic approaches that include nutrition and structured exercise interventions to treat PAD is very low. Nonetheless, it seems rather

logical to think that a multimodal multidisciplinary approach might exert a greater benefit than just applying the components separately, increasing exercise capacity, improving quality of life and maybe sparing surgery for some patients[57].

Multimodal prehabilitation is a multidisciplinary holistic approach that aims to improve functional reserve before a stressor or surgery. It takes advantage of the synergistic anabolic effects between nutrition and exercise and it includes factors that have shown to impair postoperative recovery such as active smoking or anxiety and depression[58]. The term prehabilitation initially appeared in 1946, in a military postwar context, in an article published in the British Medical Journal[59]. In the article it is described how "good food, lodging, hygiene, and recreation combined with controlled physical training and education" improved overall health in a group of men enrolled in a military program. Later on, the term was redefined to its current meaning and context in the perioperative setting. While prehabilitation initially focused on exercise as a single modality intervention, in recent years it has incorporated smoking cessation, nutrition and psychosocial interventions, becoming multimodal[33]. This model, therefore, represents a much more holistic approach and it is based on the understanding that functional capacity, optimal nutrition and emotional wellbeing are closely interrelated, thus complementing each other. For this reason, we hypothesized that multimodal prehabilitation could be the best tool to optimize PAD patients who suffer from intermittent claudication. This thesis, therefore, provides evidence on the feasibility safety and efficacy of a prehabilitation program for PAD patients with moderate to severe intermittent claudication. The findings shown in this thesis will serve to foster further research on the effectiveness of prehabilitation at improving health related quality of life, exercise capacity and emotional status in PAD patients. Multimodal prehabilitation seems to be a promising tool to help

optimize PAD patients and could potentially be implemented as first line treatment for PAD patients with intermittent claudication prior considering endovascular revascularization, although further research is needed.

13. CONCLUSION

The first chapter of this thesis was intended to review the current evidence for exercise and nutrition optimization interventions for PAD by performing a systematic review, that would yield the bases for introducing the concept of multimodal prehabilitation. The second chapter was intended to assess the feasibility, safety and efficacy of this approach in PAD patients with moderate to severe intermittent claudication and poor revascularization options and it was done by presenting a case series of 5 patients who underwent a 12-week multimodal prehabilitation program.

In conclusion, there is still a lack of evidence on how interventions that include nutrition and exercise impact quality of life, exercise capacity, limb blood and need for surgery of patients who suffer from PAD and intermittent claudication. Multimodal multidisciplinary programs that include structured exercise, nutrition, psychological coping and smoking cessation, could be used as an optimization tool in this population. Multimodal prehabilitation seems to be safe, feasible and efficacious in PAD patients, although further research is needed to determine its effectivness and cost-benefit.

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15. APPENDICES

The following questionnaires were used for assessing health-related quality of life**,** walking impairment and emotional state at baseline and after completion of the 12-week multimodal prehabilitation program.

15.1. VASCULAR QUALITY OF LIFE (VASCUQOL)

Instructions: These questions ask you how you have been affected by poor circulation to your legs over the last two weeks.
You will be asked about the symptoms you have had, the way that your activities have been affected and how you have been feeling.
Please read each bit of the answer and then tick the one that applies best to you.
If you are unsure about how to answer a question, please give the best answer you can.
There is no right or wrong answer.
Please answer every question. Thank you.

1. In the last two weeks **I have had pain in the leg (or foot) when walking** *(tick one)*

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

2. In the last two weeks **I have been worried that I might injure my leg** *(tick one)*

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

3. In the last two weeks **cold feet have given me** *(tick one)*

1. A very great deal of discomfort or distress ☐ 1
2. A great deal of discomfort or distress ☐ 2
3. A good deal of discomfort or distress ☐ 3
4. A moderate amount of discomfort or distress ☐ 4
5. Some discomfort or distress ☐ 5
6. Very little discomfort or distress ☐ 6
7. No discomfort or distress ☐ 7

4. In the last two weeks, because of the poor circulation to my legs, **my ability to take exercise or to play any sports has been** *(tick one)*

1. Totally limited, couldn't exercise at all ☐ 1
2. Extremely limited ☐ 2
3. Very limited ☐ 3
4. Moderately limited ☐ 4
5. A little limited ☐ 5
6. Only very slightly limited ☐ 6
7. Not at all limited ☐ 7

5. In the last two weeks **my legs have felt tired or weak** *(tick one)*

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

6. In the last two weeks, because of the poor circulation to my legs, **I have been restricted in spending time with my friends or relatives** *(tick one)*

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

7. In the last two weeks **I have had pain in the foot (or leg) after going to bed at night** *(tick one)*

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

8. In the last two weeks **pins and needles or numbness in my leg (or foot)** have caused *(tick one)*

1. A very great deal of discomfort or distress ☐ 1
2. A great deal of discomfort or distress ☐ 2
3. A good deal of discomfort or distress ☐ 3
4. A moderate amount of discomfort or distress ☐ 4
5. Some discomfort or distress ☐ 5
6. Very little discomfort or distress ☐ 6
7. No discomfort or distress ☐ 7

9. In the last two weeks **the distance I can <u>walk has improved</u>** *(tick one)*

1. Not at all (distance is unchanged or has decreased) ☐ 1
2. A little ☐ 2
3. Somewhat ☐ 3
4. Moderately ☐ 4
5. A good deal ☐ 5
6. A great deal ☐ 6
7. A very great deal ☐ 7

10. In the last two weeks, because of the poor circulation to my legs, **my ability to walk has been** *(tick one)*

1. Totally limited, couldn't walk at all ☐ 1
2. Extremely limited ☐ 2
3. Very limited ☐ 3
4. Moderately limited ☐ 4
5. A little limited ☐ 5
6. Only very slightly limited ☐ 6
7. Not at all limited ☐ 7

11. In the last two weeks **being (or becoming) housebound has been a concern of mine** *(tick one)*

1. A very great deal ☐ 1
2. A great deal ☐ 2
3. A good deal ☐ 3
4. Moderately ☐ 4
5. Somewhat ☐ 5
6. A little ☐ 6
7. Not at all ☐ 7

12. In the last two weeks **I have been concerned about having poor circulation to my legs** *(tick one)*

1. All of the time ☐ 1

2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

13. In the last two weeks **I have had pain in the foot (or leg) when I am at rest** *(tick one)*

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

14. In the last two weeks, because of the poor circulation to my legs**, my ability to climb stairs has been** *(tick one)*

1. Totally limited, couldn't climb stairs at all ☐ 1
2. Extremely limited ☐ 2
3. Very limited ☐ 3
4. Moderately limited ☐ 4
5. A little limited ☐ 5
6. Only very slightly limited ☐ 6
7. Not at all limited ☐ 7

15. In the last two weeks, because of the poor circulation to my legs**, my ability to take part in social activities has been** *(tick one)*

1. Totally limited, couldn't socialise at all ☐ 1
2. Extremely limited ☐ 2
3. Very limited ☐ 3
4. Moderately limited ☐ 4
5. A little limited ☐ 5
6. Only very slightly limited ☐ 6
7. Not at all limited ☐ 7

16. In the last two weeks, because of the poor circulation to my legs**, my ability to perform routine household work has been** *(tick one)*

1. Totally limited, couldn't perform housework at all ☐ 1
2. Extremely limited ☐ 2

3. Very limited ☐ 3
4. Moderately limited ☐ 4
5. A little limited ☐ 5
6. Only very slightly limited ☐ 6
7. Not at all limited ☐ 7

17. In the last two weeks **ulcers in the leg (or foot) have given me pain or distress** *(tick one)*

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time (tick this if you do not have leg ulcers) ☐ 7

18. Because of poor circulation to my legs, **the overall range of activities that I would have liked to do in the last two weeks has been** *(tick one)*

1. Severely limited – most activities not done ☐ 1
2. Very limited ☐ 2
3. Moderately limited – several activities not done ☐ 3
4. Slightly limited ☐ 4
5. Very slightly limited – very few activities not done ☐ 5
6. Hardly limited at all ☐ 6
7. Not limited at all – have done all the activities I wanted ☐ 7

19. In the last two weeks **the poor circulation to the legs have made me feel frustrated** *(tick one)*

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

20. In the last two weeks **when I do get pain in my leg (or foot) it has given me** *(tick one)*

1. A very great deal of discomfort or distress ☐ 1
2. A great deal of discomfort or distress ☐ 2
3. A good deal of discomfort or distress ☐ 3

4. A moderate amount of discomfort or distress ☐4
5. Some discomfort or distress ☐5
6. Very little discomfort or distress ☐6
7. No discomfort or distress ☐7

21. In the last two weeks **I have felt guilty about relying on friends or relatives** *(tick one)*

1. All of the time ☐1
2. Most of the time ☐2
3. A good bit of the time ☐3
4. Some of the time ☐4
5. A little of the time ☐5
6. Hardly any of the time ☐6
7. None of the time ☐7

22. In the last two weeks, because of the poor circulation to my legs**, my ability to go shopping or carry bags has been** *(tick one)*

1. Totally limited, couldn't go shopping at all ☐1
2. Extremely limited ☐2
3. Very limited ☐3
4. Moderately limited ☐4
5. A little limited ☐5
6. Only very slightly limited ☐6
7. Not at all limited ☐7

23. In the last two weeks **I have worried I might be in danger of losing a part of my leg or foot** *(tick one)*

1. All of the time ☐1
2. Most of the time ☐2
3. A good bit of the time ☐3
4. Some of the time ☐4
5. A little of the time ☐5
6. Hardly any of the time ☐6
7. None of the time ☐7

24. In the last two weeks **the distance I can walk <u>has become less</u>** *(tick one)*

1. A very great deal ☐1
2. A great deal ☐2
3. A good deal ☐3
4. Moderately ☐4

5. Somewhat ☐ 5
6. A little ☐ 6
7. Not at all – distance is unchanged or has increased ☐ 7

25. In the last two weeks **I have been depressed about the poor circulation to my legs** *(tick one)*

1. All of the time ☐ 1
2. Most of the time ☐ 2
3. A good bit of the time ☐ 3
4. Some of the time ☐ 4
5. A little of the time ☐ 5
6. Hardly any of the time ☐ 6
7. None of the time ☐ 7

Thank you for completing this questionnaire

15.2. WALKING IMPAIRMENT QUESTIONNAIRE (WIQ)

1. *Please place a √ in the box that best describes how much difficulty you have had walking due to pain, aches or cramps during the last week. The response options range from 'No Difficulty' to 'Great Difficulty.'*

***During the last week,** how much difficulty have you had walking due to:*	**No Difficulty**	**Slight Difficulty**	**Some Difficulty**	**Much Difficulty**	**Great Difficulty**
a. Pain, aching, or cramps in your calves?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5
b. Pain, aching, or cramps in your buttocks?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5

For the following questions, the response options range from 'No Difficulty' to 'Unable to Do.' If you **cannot physically perform** a specified activity, for example walk 2 blocks without stopping to rest because of symptoms such as leg pain or discomfort, please place a √ in the box labeled 'Unable to Do.'

However, if you **do not perform** an activity for reasons unrelated to your circulation problems, such as climbing a flight of stairs because your home is one level or your apartment has an elevator, please place a √ in the box labeled 'Don't Do For Other Reasons.'

2. *Please place a √ in the box that best describes how hard it was for you to walk on level ground without stopping to rest for each of the following distances during the last week:*

***During the last week**, how difficult was it for you to:*	**No Difficulty**	**Slight Difficulty**	**Some Difficulty**	**Much Difficulty**	**Unable to Do**	**Didn't Do for Other Reasons**
a. Walk indoors, such as around your home?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
b Walk 50 feet?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
c. Walk 150 feet? (1/2 block)?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
d. Walk 300 feet? (1 block)?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
e. Walk 600 feet? (2 blocks)?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
f. Walk 900 feet? (3 blocks)?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
g. Walk 1500 feet? (5 blocks)?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

3. *Please place a √ in the box that best describes how hard it was for you to walk one city block on level ground at each of these speeds without stopping to rest during the last week. Please note 1 block is roughly equivalent to 300 feet.*

***During the last week**, how difficult was it for you to:*	**No Difficulty**	**Slight Difficulty**	**Some Difficulty**	**Much Difficulty**	**Unable to Do**	**Didn't Do for Other Reasons**
a. Walk 1 block slowly?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
b. Walk 1 block at average speed?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
c. Walk 1 block quickly?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
d. Run or jog 1 block?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

4. *Please place a √ in the box that best describes how hard it was for you to climb stairs without stopping to rest during the last week. Please note 1 flight of stairs is roughly equal to 14 steps.*

***During the last week**, how difficult was it for you to:*	**No Difficulty**	**Slight Difficulty**	**Some Difficulty**	**Much Difficulty**	**Unable to Do**	**Didn't Do for Other Reasons**
a. Climb 1 flight of stairs?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
b. Climb 2 flights of stairs?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6
c. Climb 3 flights of stairs?	❑ 1	❑ 2	❑ 3	❑ 4	❑ 5	❑ 6

15.3. HOSPITAL ANXIETY AND DEPRESSION SCALE

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions