RENAN LIMA MONTEIRO

Efeitos do fortalecimento dos músculos dos pés na atividade física de vida diária e funcionalidade de tornozelo e pé de pessoas com polineuropatia diabética: um ensaio clínico controlado randomizado

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Doutor em Ciências.

Programa de Ciências da Reabilitação

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SÃO PAULO

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Dedico este trabalho aos meus pais.

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NORMATIZAÇÃO ADOTADA

Esta tese está de acordo com as seguintes normas, em vigor no momento desta publicação:

Referências: adaptado de *International Committee of Medical Journals Editors* (Vancouver).

Universidade de São Paulo. Faculdade de Medicina. Divisão de Biblioteca e Documentação. *Guia de apresentação de dissertações, teses e monografias*. Elaborado por Anneliese Carneiro da Cunha, Maria Julia de A. L. Freddi, Maria F. Crestana, Marinalva de Souza Aragão, Suely Campos Cardoso, Valéria Vilhena. 3a ed. São Paulo: Divisão de Biblioteca e Documentação; 2011.

Abreviaturas dos títulos dos periódicos de acordo com *List of Journals Indexed in Index Medicus*.

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O aumento acelerado do número de casos de pessoas com diabetes está contribuindo para um rápido aumento no número de casos de complicações associadas, como a neuropatia periférica diabética (NPD), o que leva essas pessoas a conviverem com incapacidades e funcionalidade reduzida por um longo período de suas vidas devido ao comprometimento sensorial e musculoesquelético. De acordo com o Global Burden of Diseases, Injuries, and Risk Factors Study (2019) a necessidade de reabilitação pode ser necessária para qualquer pessoa com condições de saúde que levam a déficits de mobilidade sensoriais ou cognitivas, sendo os déficits musculoesqueléticos os com maior prevalência. Entretanto, atualmente há pouca e fraca evidência de estratégias terapêuticas para mitigar e reabilitar déficits musculoesqueléticos oriundos da NPD, o que contribui para a negligência dos serviços de reabilitação no tratamento e prevenção dessas complicações funcionais. Dessa forma, esta tese buscou propor, testar a viabilidade e a eficácia por meio de um ensaio clínico randomizado e controlado de um programa de exercícios terapêuticos para os pés de 12 semanas nos níveis de atividade física e velocidade da marcha de pessoas com NPD, bem como seus efeitos em desfechos clínicos e funcionais relacionados à NPD, tais como amplitude de movimento do tornozelo, sensibilidade tátil e vibratória, sintomas da NPD (desfechos que são fatores de risco para úlceras plantares), qualidade de vida, saúdes dos pés, força muscular e incidência de úlceras. Além da avaliação baseline, foram feitas reavaliações após 6, 12, 24 semanas e 1 ano. 78 participantes foram divididos em grupos: grupo intervenção (n=39, 61,6 $\pm$ 11,6 anos) e grupo controle (n=39, 60,0 $\pm$ 9,0 anos). A primeira etapa na construção desta tese foi a elaboração de um protocolo de exercícios fisioterapêuticos que focasse nos déficits musculoesqueléticos relacionados à NPD. Inicialmente, foi discutido com profissionais especialistas na área de NPD e fisioterapeutas especialistas em reabilitação do pé a cascata de complicações oriundos da NPD, bem como a definição dos principais desfechos do estudo. Os níveis de atividade física, medidos por meio do número de passos, e velocidade da marcha foram definidos como desfechos principais pois refletem diretamente a capacidade funcional física da pessoa com diabetes. Em seguida, foram discutidas estratégias de reabilitação com foco nos déficits funcionais físicos, como perda da força muscular intrínseca e extrínseca dos pés, rigidez articular e diminuição de mobilidade, e a partir de tais déficits foi desenvolvido o protocolo de reabilitação por meio de exercícios de fortalecimento e mobilidade, bem como exercícios funcionais. A realização dos exercícios em grupos de até 8 pessoas e progressão dos exercícios de forma individual foram estratégias adotadas para aumentar a adesão e potencializar os efeitos dos exercícios. Após o desenvolvimento e publicação do protocolo do estudo, a segunda etapa desta tese foi avaliar a viabilidade do ensaio clínico e do protocolo de exercícios, pois a escassez de estudos na área e o protocolo de exercícios inovador nos levaram a questionar a viabilidade do mesmo, bem como a satisfação e adesão dos participantes ao protocolo. O programa de exercícios foi viável, com base em uma taxa

moderada de recrutamento e uma população aderente (80%) e satisfeita (satisfação média 4,6 de 5), e a intervenção mostrou efeitos preliminares positivos ao longo do tempo em comparação com o grupo controle. A terceira e última etapa para a construção dessa tese foi o desenvolvimento do ensaio clínico propriamente dito. Os resultados deste ensaio clínico mostraram que 12 semanas de exercícios específicos para os pés com foco nos déficits musculoesqueléticos de pessoas com NPD foram capazes de aumentar a velocidade da marcha rápida e amplitude de movimento do tornozelo, melhorar a sensibilidade vibratória e qualidade de vida em comparação com o grupo controle após 12 semanas. Após 24 semanas, a intervenção proposta resultou em uma melhor qualidade de vida em relação ao grupo controle. E após 1 ano de acompanhamento, a velocidade de marcha rápida e a sensibilidade vibratória melhoraram no grupo intervenção em comparação ao grupo de controle. Assim, podemos concluir que o protocolo de reabilitação é viável, resultou em desfechos positivos para a pessoa com diabetes e NPD e pode-se sugerir a inclusão dessa abordagem como uma alternativa de tratamento e prevenção de complicações musculoesqueléticas relacionadas à NPD, embora ainda sem evidências na redução da incidência de úlceras plantares.

Descritores: Complicações do diabetes; Neuropatias diabéticas; Articulações do pé; Pesquisa de reabilitação; Terapia por exercício; Úlcera do pé.

ABSTRACT

Monteiro, R.L. *Effects of foot muscle strengthening on physical activity of daily living and ankle and foot functionality in people with diabetic polyneuropathy: a randomized controlled clinical trial.* [thesis] São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2021.

The increase in the number of cases of people with diabetes is contributing to a rapid increase in the number of cases of associated complications, such as diabetic peripheral neuropathy (DPN), which leads these people to live with disabilities and reduced functionality for a long period of their lives due to sensory and musculoskeletal impairment. According to the Global Burden of Diseases, Injuries, and Risk Factors Study (2019), the need for rehabilitation may be necessary for anyone with health conditions that lead to mobility, sensory or cognitive deficits, with musculoskeletal deficits being the most prevalent. However, currently there is little and weak evidence of therapeutic strategies to mitigate and rehabilitate musculoskeletal deficits arising from DPN, which contributes to the neglect of rehabilitation services in the treatment and prevention of these functional complications. Thus, this thesis sought to propose, test the feasibility and effectiveness through a randomized and controlled clinical trial of a 12-week therapeutic foot exercise program on the levels of physical activity and gait speed of people with DPN, as well as its effects on DPN-related clinical and functional outcomes, such as ankle range of motion, tactile and vibratory sensitivity, DPN symptoms (outcomes that are risk factors for plantar ulcers), quality of life, foot health, muscle strength and incidence of ulcers. In addition to the baseline assessment, reassessments were performed after 6, 12, 24 weeks and 1 year. 78 participants were allocated into groups: intervention group (n=39, 61.6 $\pm$ 11.6 years) and control group (n=39, 60.0 $\pm$ 9.0 years). The first step in the construction of this thesis was the elaboration of a physical therapy exercise protocol that focused on DPN-related musculoskeletal deficits. Initially, the cascade of complications arising from DPN, as well as the definition of the main outcomes of the study, was discussed with specialists in the field of DPN and physiotherapists specialized in foot rehabilitation. Physical activity levels, measured by the number of steps, and gait speed were defined as the main outcomes as they directly reflect the physical functional capacity of the person with diabetes. Then, rehabilitation strategies were discussed focusing on physical functional deficits, such as loss of intrinsic and extrinsic muscle strength of the feet, joint stiffness and decreased mobility, and from these deficits, the rehabilitation protocol was developed through exercises for strengthening and mobility, as well as functional exercises. Performing the exercises in groups of up to 8 people and progressing the exercises individually were strategies adopted to increase adherence and enhance the effects of the exercises. After the development and publication of the study protocol, the second step of this thesis was to assess the feasibility of the clinical trial and the exercise protocol, as the scarcity of studies in the area and the innovative exercise protocol led us to question its feasibility, as well as the satisfaction and adherence of the participants to the protocol. The exercise program was feasible, based on a moderate recruitment rate and an adherent (80%) and satisfied population (mean satisfaction 4.6 out of 5), and the intervention showed positive preliminary effects over time compared with the group control. The third and final step for the construction of this thesis was the development of the clinical trial itself. The results of this clinical trial showed that

12 weeks of foot-specific exercises focusing on the musculoskeletal deficits of people with DPN were able to increase fast gait speed and ankle range of motion, improve vibratory sensitivity and quality of life in comparison with the control group after 12 weeks. After 24 weeks, the proposed intervention resulted in a better quality of life compared to the control group. And after 1 year of follow-up, fast gait speed and vibratory sensitivity improved in the intervention group compared to the control group. Thus, we can conclude that the rehabilitation protocol is viable, resulted in positive outcomes for people with diabetes and DPN, and it is possible to suggest the inclusion of this approach as an alternative treatment and prevention of musculoskeletal complications related to DPN, although there is still no evidence in reducing the incidence of plantar ulcers.

Descriptors: Diabetes complications; Diabetic neuropathies; Foot joints; Rehabilitation research; Exercise therapy; Foot ulcer.

CAPÍTULO 1 - ESTRUTURA DA TESE, OBJETIVOS E HIPÓTESES

1.1. Estrutura da tese

Diante do cenário atual a respeito das evidências científicas para o tratamento das complicações oriundas da neuropatia periférica diabética (NPD) e prevenção de úlceras plantares, pode-se observar que há carência de mais estudos para suportarem a recomendação do fortalecimento da musculatura dos pés como estratégia de tratamento e prevenção. Dessa forma, essa tese visa contribuir na melhora da evidência a respeito desta temática. Em 2019 o International Working Group on Diabetic Foot (1) recomendou exercícios para os pés de pessoas com risco de úlcera, entretanto tal recomendação tem baixa evidência.

Esta tese de doutorado contém três estudos originais precedidos de uma introdução que possui uma contextualização geral sobre o tema, estrutura e os objetivos da tese. Todos os estudos originais apresentados são relacionados à investigação dos efeitos de um programa de fortalecimento da musculatura dos pés nos níveis de atividade física e velocidade da marcha de pessoas com NPD. Investigamos como um protocolo terapêutico inovador focado no fortalecimento na musculatura dos pés, realizado em grupo e com evolução dos exercícios de forma personalizada, poderia mudar os desfechos clínicos da NPD, funcionais e de mobilidade. Nossa hipótese é que essa intervenção proposta possa aumentar o número de passos e velocidade da marcha de pessoas com NPD, bem como melhorar sintomas da NPD e sensibilidade plantar, qualidade de vida, saúde dos pés, força e amplitude de movimento do complexo tornozelo-pé e incidência de úlceras.

O capítulo II descreve o protocolo do ensaio clínico randomizado e controlado, o programa de exercícios fisioterapêuticos para os pés e descreve ainda, com detalhes, o racional que levou ao desenvolvimento deste ensaio. Parte do desenvolvimento desta pesquisa se deu por meio de discussões e ideias com vários especialistas da área de reabilitação musculoesquelética e especialistas na área de NPD, incluindo o Professor Sicco Bus da Universidade de Amsterdã e editor-chefe do International Working Group on Diabetic Foot. O capítulo II apresenta então o artigo do protocolo publicado na revista BMC Musculoskeletal disorders (FI = 1.879).

O capítulo III é composto de mais um estudo original que avaliou a viabilidade do ensaio clínico randomizado. A dificuldade em desenvolver um ensaio clínico nessa temática pouco explorada, bem como o questionamento sobre a aceitação dos pacientes ao protocolo inovador nos levou ao desenvolvimento dessa análise de viabilidade do protocolo e do programa fisioterapêutico. Os resultados deste estudo mostram que o ensaio clínico e o protocolo de exercícios são viáveis, foi bem aceito entre as pessoas com diabetes e com relativa boa aderência, embora as dificuldades de recrutamento sejam evidentes. Este estudo de viabilidade foi publicado na revista SENSOR (FI= 3.275) em uma edição especial sobre Biomecânica.

Após a análise de viabilidade do ensaio clínico, o capítulo IV apresenta os resultados do ensaio clínico randomizado em formato de artigo, que foi submetido para a revista Scientific Reports (IF= 4.379). Os resultados são otimistas, pois 12 semanas de exercícios para os pés foram capazes de aumentar a velocidade da marcha de pessoas com NPD, bem como a melhora na sensibilidade tátil e amplitude de movimento do tornozelo, o que pode contribuir para a redução do risco de desenvolvimento de úlcera plantar.

Por fim, o capítulo V apresenta as considerações finais sobre os artigos publicados/submetidos que compuseram esta tese. Nossos resultados sugerem que este estudo tem um protocolo inovador, com um ensaio clínico viável, bem como resultados clínicos relevantes para o tratamento fisioterapêutico de pessoas com NPD.

1.2. Contextualização do tema da tese

O Diabetes Mellitus é uma doença crônica que, segundo a Federação Internacional de Diabetes 2019 (FID)(2) , está diagnosticada em mais de 463 milhões de pessoas em todo o mundo. De acordo com Global Burden of Diseases, Injuries, and Risk Factors Study 2019 (3), as doenças que mais necessitam de reabilitação são de origem musculoesquelética, pois comprometem muitos anos da vida do paciente com incapacidade. Entretanto as alterações musculoesqueléticas oriundas da Diabetes poucos são discutidas na literatura, bem como intervenções eficazes para reverter esse quadro.

Dentre as complicações que podem potencializar o comprometimento musculoesquelético em pessoas com diabetes, podemos citar a NPD que é uma doença crônica presente em até 50% da população com diabetes (4). A progressão da NPD afeta a integridade de estruturas neurais e, principalmente, pequenas articulações e músculos intrínsecos do pé e tornozelo (5–9). Esses efeitos específicos de um pé com NPD são os principais fatores para o desenvolvimento de deformidades, pressões plantares elevadas e aumento do risco de ulceração plantar. Desta forma, as alterações desencadeadas afetam a estabilidade dinâmica do pé, gerando uma inadequada mobilidade para as tarefas de vida diária (8–11).

Fagour et al., (2013) (12) afirma que pessoas com DM do tipo 2 possuem menores níveis de atividade física de vida diária quando comparados aos indivíduos do mesmo sexo e idade, porém sem Diabetes. Hanewincke et al., (2017) (13) afirma ainda que a NPD se associa fortemente a uma dificuldade na capacidade de realizar atividades físicas de vida diária e se relaciona com uma biomecânica da marcha alterada e um aumento na prevalência de quedas. Estudos epidemiológicos indicam que pessoas com Diabetes são 2 a 3 vezes mais propensas a reportar uma incapacidade de deambular, subir 10 degraus ou executar tarefas domésticas comparadas a pessoas de idade similar sem Diabetes (14).

Diante desta situação, diversos estudos buscaram avaliar os níveis de atividade de vida diária de pessoas com Diabetes, em especial com NPD, por meio da contagem do número de passos (15–18). Tais estudos baseiam-se na premissa de que a melhora dos níveis de atividade da vida diária é particularmente importante para pessoas com Diabetes, não somente para a melhora do controle glicêmico e saúde cardiovascular, mas também porque pessoas com diabetes têm duas vezes mais chances de ter limitações na mobilidade (comparados aos que não tem diabetes)(19). Entretanto, as causas das limitações na mobilidade física de pessoas com NPD ainda não parecem estar esclarecidas. Sobre isso, Tuttle et al. (2011) (16) aponta que o número de passos de pessoas com NPD são inversamente proporcionais à quantidade de tecido adiposo intramuscular nos pés e pernas, o que sugere que o comprometimento muscular seja um dos fatores para a diminuição da atividade física. Outros estudos sugerem que déficits motores e sensitivos (20) e a perda da amplitude de movimento no complexo do pé e tornozelo (21,22) estejam diretamente relacionados com a diminuição nos níveis de atividade física, bem como na redução da qualidade de vida e diminuição da velocidade da marcha de pessoas com NPD (20).

Diversos estudos controlados e não controlados que buscaram avaliar os efeitos de várias modalidades de exercícios, como exercícios para os pés, treinamento de equilíbrio e exercícios de resistência com descarga de peso em diferentes desfechos relacionados a complicações decorrentes de NPD (23–26) foram incluídos em uma revisão sistemática (27) e forneceram a base para o International Working Group on Diabetic Foot - IWGDF (2020) para recomendar exercícios para os pés e exercícios relacionados com a mobilidade como estratégias de tratamento e prevenção de úlceras nos pés. Esses estudos mostraram que exercícios para os pés podem melhorar os sintomas da NPD e aumentar a amplitude de movimento da articulação do tornozelo, mas ainda não está claro se eles poderiam melhorar a força muscular do pé-tornozelo e a funcionalidade em pessoas com risco baixo ou risco moderado de ulceração do pé (27). Além disso, a qualidade da evidência ainda é fraca porque a maioria dos ensaios clínicos incluídos eram de baixa qualidade, apresentavam tamanhos de efeito pequenos, envolviam pouco exercícios que visavam especificamente a principal disfunção musculoesquelética em pessoas com NDP o que dificulta uma conclusão definitiva sobre sua eficácia (27). Portanto, para a disseminação mais ampla e a adoção desta recomendação em políticas públicas de saúde para pessoas com NPD, mais estudos são necessários para melhorar a qualidade das evidências.

1.3. Objetivos

i. Investigar a viabilidade do ensaio clínico randomizado e controlado e a eficácia preliminar de 12 semanas de um programa fisioterapêutico de exercícios para os pés em pessoas com NPD.

ii. Investigar o efeito em 6 semanas após a randomização na velocidade da marcha auto selecionada, velocidade da marcha rápida, sensibilidade tátil e vibratória, sintomas da NPD, qualidade de vida, amplitude de movimento passiva de tornozelo, saúde e funcionalidade dos pés, força dos músculos do pé em pessoas com NPD.

iii. Investigar o efeito imediatamente após o período de intervenção (12 semanas após a randomização) na incidência de úlceras plantares, sensibilidade tátil e vibratória, sintomas da NPS, qualidade de vida, amplitude de movimento passiva de tornozelo, saúde e funcionalidade dos pés e força dos músculos do pé em pessoas com NPD.

iv. Investigar o efeito em 24 semanas e um ano de *follow-up* após a randomização no nível de atividade física diária, velocidade da marcha auto selecionada, velocidade da marcha rápida, sensibilidade tátil e vibratória, sintomas da NPD, qualidade de vida, amplitude de movimento passiva de tornozelo, saúde e funcionalidade dos pés e força dos músculos do pé em pessoas com NPD.

1.4. Hipóteses

Nossas hipóteses foram:

a) O ensaio clínico e o protocolo fisioterapêutico de exercícios serão viáveis, bem aceitos pelas pessoas, gerando boa adesão, satisfação e seu desenvolvimento será exequível.

b) Os resultados da intervenção fisioterapêutica mostrarão:

- aumento dos níveis de atividade física diária;
- aumento da velocidade de marcha rápida e auto selecionadas;
- aumento da amplitude de movimento passiva do tornozelo;
- melhora na sensibilidade tátil e vibratória plantar;

- aumento na força muscular isométrica dos dedos do pé e hálux;
- melhora da qualidade de vida e da saúde e funcionalidade dos pés;
- diminuição dos sintomas da NPD;
- reduzir a incidência de úlcera plantar em 1 ano.

1.5. Referências capítulo 1

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CAPÍTULO 2 - PROTOCOLO DO ENSAIO CLÍNICO RANDOMIZADO

2.1 Protocol for evaluating the effects of a foot-ankle therapeutic exercise program on daily activity, foot-ankle functionality, and biomechanics in people with diabetic polyneuropathy: a randomized controlled trial

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Protocol for evaluating the effects of a foot-ankle therapeutic exercise program on daily activity, foot-ankle functionality, and biomechanics in people with diabetic polyneuropathy: a randomized controlled trial

Renan L. Monteiro[1,2], Cristina D. Sartor[1,3], Jane S. S. P. Ferreira[1], Milla G. B. Dantas[1,4], Sicco A. Bus[5] and Isabel C. N. Sacco[1*]

Abstract

Background: Diabetic polyneuropathy (DPN) negatively affects foot and ankle function (strength and flexibility), which itself affects the daily physical activity and quality of life of patients. A physical therapy protocol aiming to strengthen the intrinsic and extrinsic foot muscles and increase flexibility may be a promising approach to improve lower-extremity function, prevent further complications, and improve autonomy for daily living activities in these patients. Thus, the inclusion of a specific foot-related exercises focused on the main musculoskeletal impairments may have additional effects to the conventional interventions in the diabetic foot. Methods/design: A prospective, parallel-group, outcome-assessor blinded, randomized controlled trial (RCT) will be conducted in 77 patients with DPN who

will be randomly allocated to usual care (control arm) or usual care with supervised foot-ankle exercises aiming to increase strength and flexibility twice a week for 12 weeks and remotely supervised foot-ankle exercises for a year through a web software. Patients will be evaluated 5 times in a 1-year period regarding daily physical activity level, self-selected and fast gait speeds (primary outcomes), foot ulcer incidence, ulcer risk classification, neuropathy testing, passive ankle range of motion, quality of life, foot health and functionality, foot muscle strength, plantar pressure, and foot-ankle kinematics and kinetics during gait. Discussion: This study aims to assess the effect of a foot-ankle strength and flexibility program on a wide range of musculoskeletal, activity-related, biomechanical, and clinical outcomes in DPN patients. We intend to demonstrate evidence that the year-long training program is effective in increasing gait speed and daily physical activity level and in improving quality of life; foot strength, functionality, and mobility; and biomechanics while walking. The results will be published as soon as they are available. Trial registration: This study has been registered at ClinicalTrials.gov as NCT02790931 (June 6, 2016) under the name "Effects of foot muscle strengthening in daily activity in diabetic neuropathic patients". Keywords: Clinical trial; Diabetic foot; Diabetic neuropathies; Exercise; Foot ulcer; Physical therapy.

Background

Foot disorders are a major issue related to diabetic polyneuropathy (DPN) [1,2]. Several sensorial and motor dysfunctions are directly related to ulcer formation and amputation [2]. Recent papers that focused on musculoskeletal foot-ankle complications and strategies to overcome them have been inconclusive[3–7] in defining the best strategy in preventing chronic complications related to DPN.

The progression of DPN affects the integrity of small joints and intrinsic muscles [3,8–12]. These effects are the main factors for the development of deformities, elevated plantar pressures, and increased risk of plantar ulceration [8,13–17]. These alterations affect the dynamic stability of the foot, generating an inadequate mobility for daily living activities [11,12,18,19].

Recent guidelines for treating and preventing diabetic foot complications are based on the management/control of diabetes, integrated foot care, patient education, and self-management of foot care [20]. Besides these, foot orthosis and special shoes are recommended for reducing tissue mechanical stress and injuries [20]. Considering other rehabilitation approaches, including exercise therapy, showed to be beneficial in diabetic foot outcomes, particularly in increasing nerve velocity conduction of the lower limbs. Additional benefits can be induced by exercise in diabetic patients, such as skin sensitivity and intraepidermal nerve fiber density, which can delay the usual course of DPN, delay skin damage and ulceration [21]. Specific foot-ankle therapeutic exercises, have also shown promising results for improving sensitivity, foot-ankle range of motion and DPN symptoms [22], as well as for redistributing plantar pressure during locomotion [21,23], but these are not part of the guidelines and require adequate investigation in well-designed studies prior to complementary recommendation in integrated care [20]. Many foot and lower limb disorders that result from diabetes, such as deformity, muscle weakness, decreased range of motion, rigidity of connective tissue, poor balance, and coordination, can potentially be restored or prevented by specific interventions. These neuromusculoskeletal alterations are common in DPN patients, and interventions such as strengthening, stretching, balancing, and gait training may be beneficial in preventing foot ulcers and amputation, fall risk reduction,

improvement of daily physical activity level and quality of life, which can all reduce mortality and comorbidity rates.

Previous studies have reported the benefits of foot-ankle therapeutic exercises. A protocol performed at home for one month reduced peak plantar pressures during gait in DPN patients [24]. Likewise, personalized foot-ankle therapeutic exercise protocols to strengthen foot-ankle muscles showed positive results in satisfactorily redistributing plantar pressures during gait [4,24], resulting in a better physiological pattern in foot-ankle rollover, and improvement of clinical measures of balance control [21].

DPN is also strongly associated with an inability to perform physical daily living activities, altered gait biomechanics, and increased number of falls [25]. Previous studies discussed diabetic patients' reduced activity levels [26–29], which are important not only for glycemic control and cardiovascular health, but also patient mobility, as persons with diabetes are twice as likely to have mobility limitations compared to non-diabetics [30]. Tuttle et al. (2011) [28] showed that the number of steps of DPN patients are inversely proportional to the amount of intramuscular adipose tissue, suggesting that muscular impairment is caused by decreased physical activity levels. Motor and sensory deficits [31] and impaired foot range of motion [32,33] severely reduce gait speed, affecting quality of life [31]. Unfortunately, there has not yet been any study reporting on the clinical effects of a specific foot-ankle exercise program and on falls incidence and daily physical activity levels.

Although there is evidence of profound changes in foot structure and function in DPN patients, whole body strengthening programs mostly neglect distal muscle groups, such as the ankle extrinsic and foot intrinsic muscles. The primary objective of this randomized controlled trial (RCT) is to investigate the effects of a 12-week therapeutic foot and ankle exercise program on daily physical activity level and self-selected and fast gait

speeds at 12 weeks and after 1 year follow-up in patients with DPN. The secondary objectives of this study are to investigate the effects of this intervention at 6, 12, and 24 weeks and 1 year on foot ulcer incidence, ulcer risk classification, sensitivity, DPN symptoms, quality of life, foot health and functionality, foot muscle strength, and gait biomechanics.

Hypotheses

Our hypotheses are that a 12-week foot-ankle therapeutic exercise protocol will:

- H 1. Increase daily physical activity levels
- H 2. Increase self-selected and fast gait speeds
- H 3. Reduce foot ulcer incidence in 1 year
- H 4. Not increase ulcer risk classification
- H 5. Increase foot tactile sensitivity
- H 6. Increase foot vibration sensitivity
- H 7. Decrease tactile sensory threshold
- H 8. Increase passive ankle range of motion
- H 9. Reduce DPN symptoms
- H 10. Improve health-related quality of life
- H 11. Improve foot health and functionality status
- H 12. Increase foot muscle strength
- H 13. Improve plantar pressure distribution
- H 14. Produce beneficial biomechanical changes during gait that denote an improvement in the mechanical efficiency of absorbing loads and propelling the body while walking and improve foot-ankle mobility. Such changes would include an increase in (1) the foot-ankle range of motion during stance phase, (2) ankle

extensor moment and concentric power during propulsion phase, and (3) ankle flexor moment and eccentric power during heel-strike phase.

Methods/Design

Overview of the research design

This study is designed as a two-arm parallel-group, outcome-assessor blinded RCT that is prospectively registered in Clinical Trials number NCT02790931. The trial follows all recommendations established by SPIRIT [34].

The trial will be conducted in patients with DPN who are randomly allocated to:

- Control group (CG) - patients will not receive any specific intervention beyond usual care, which includes treatment recommended by the medical team, pharmacological treatment, and self-care guidelines, which are maintained in both groups [20].
- Intervention group (IG) - patients will receive usual care with additional foot-ankle exercises supervised by a physiotherapist twice a week and remotely-supervised exercises through Educational Diabetic Foot Software (SOPeD) twice a week for 12 weeks. After the 12-week period, the IG will continue exercising for the completion of the study (9 months) using the remotely supervised web software twice a week. http://www.usp.br/labimph/soped/

Patients of both groups will be evaluated five times in a 1 year period: at baseline (T0), after 6 (T6), 12 (T12), and 24 weeks (T24), and after 1 year (1y follow-up). All outcomes will be evaluated at each visit except for the biomechanical variables evaluated at T0 and T12. The primary outcome of daily physical activity will be evaluated at all instances except T6 for technical purposes.

The design and flowchart of the protocol are presented in Fig. 1. All procedures of this study follow the norms of an Operational Procedure Manual developed specifically for this research. The study will be conducted at the outpatient physiotherapy clinic of the primary care center *Centro de Saúde Escola Barra Funda Dr. Alexandre Vranjac* and the assessments will be performed at the *Laboratório de Biomecânica, movimento e postura humana* (LaBiMPH) at the Physical Therapy, Speech and Occupational Therapy department of the School of Medicine of the University of São Paulo, São Paulo, Brazil.

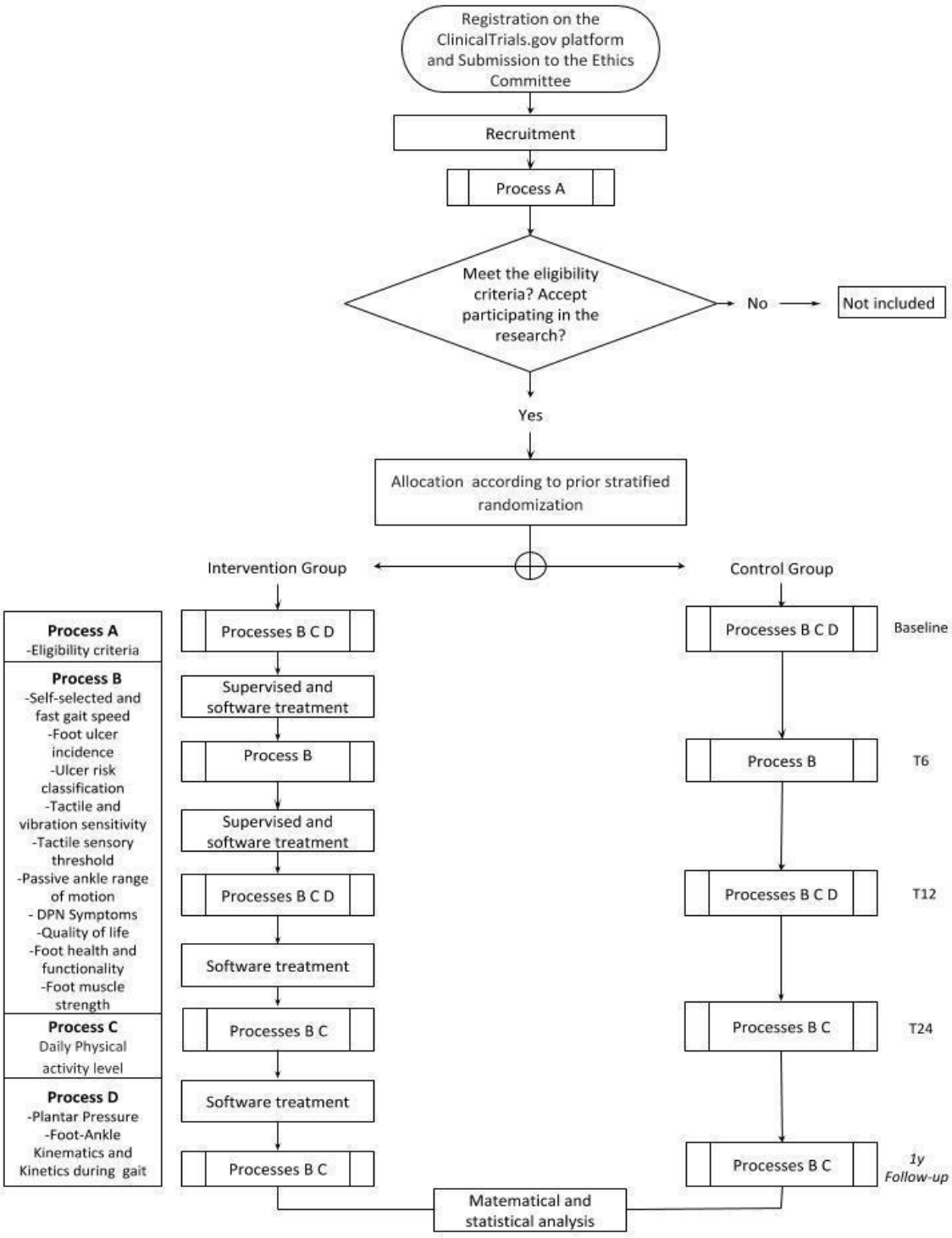

Figure 1 - Flow chart illustrating the process of the study.

Participants and recruitment

This study is currently recruiting patients (study start date: December 2017).

The inclusion criteria are:

- Either gender

- Adults up to 75 years
- Diabetes Mellitus type 1 or 2 diagnosed, with moderate or severe DPN confirmed by a Fuzzy software [9]
- Independent walking ability for at least 10 m
- A maximum of one amputated toe, not being the hallux
- Accessibility to electronic devices with internet that allow access to the web software

The exclusion criteria are:

- Presence of an active plantar ulcer
- History of surgical procedure at the knee, ankle, or hip or indication of surgery throughout the intervention period
- Arthroplasty and/or orthosis of lower limbs or indication of lower limb arthroplasty throughout the intervention period
- Diagnosis of neurological diseases
- Dementia or inability to give consistent information
- Receiving any physiotherapy during the intervention period
- Major vascular complications and/or severe retinopathy

Randomization, allocation, and blinding

Both groups will be stratified according to the degree of DPN and gait speed, since both variables can highly influence clinical and biomechanical outcomes. Stratification will be performed according to the degree of DPN indicated by Fuzzy software (2–7.5: moderate degree of DPN, 7.6–10: severe degree of DPN) [9] and gait speed (slow: < 1.1 m/s, fast: ≥ 1.1 m/s) [35].

The randomization schedule will be prepared using Clinstat software (University of York, UK) by an independent researcher (Researcher #1) who will not be aware of the numeric code for the CG and IG groups. This sequence will be generated in blocks of random sizes (1–8) with random orders. The numerical sequence will be kept in opaque envelopes, numbered sequentially, following an order generated by the software. The randomization procedure will follow the instructions of Randelli et al. (2008)[36]. This sequence will be kept private and stored in a location where blind assessors do not have access.

After receiving the patients' informed consent to participate, the random allocation to either the intervention or control group will be made by another independent researcher (Researcher #2), who will also be unaware of the codes. Only the physiotherapist (Researcher #3), responsible for locally supervised training, will know the group allocation of participants. Researcher 3 will also be responsible for the remote monitoring of the web software training. All patients' personal data will be kept confidential before, during, and after the study by encoding participant's names. Only the physiotherapist and the person receiving treatment will be aware of the meaning of each code. Patients will be allocated to study groups 1 week after baseline evaluation. The envelope with the initially-generated numerical sequence will then be opened, signed, and dated by the independent researcher, who will make the allocation (Researcher 2). Four physiotherapists (Researchers #4), also blind to treatment allocation, will be responsible for all clinical, functional, and biomechanical outcome assessments.

To guarantee the blindness of Researcher 4, before each evaluation, patients will be instructed not to reveal whether they are in the CG or IG; their questions should be asked only of the physiotherapist who is treating them (Researcher #3). The data tabulation and

processing and trial statistician will also be blind to treatment allocation until completion of the main treatment analysis.

Treatment Arms

CG patients will not receive any specific intervention beyond treatment recommended by the health care team, which includes pharmacological treatment and self-care guidelines, and which will be maintained in both groups. The self-care guidelines adjusted for our setting in Sao Paulo include: performing daily inspection of the feet, using socks without elastic and sewing, cutting the nails in a square shape, avoiding cutting calluses or blisters without supervision, avoiding walking barefoot or wearing shoes without socks or wearing slippers, and seeking medical assistance whenever identifying problems in their feet. The IG patients will receive a therapeutic foot-ankle exercise protocol for strengthening and improving functionality under the supervision of a physiotherapist twice a week for 12 weeks, and a series of foot-ankle exercises will be performed under remote supervision through SOPeD twice a week for the entire 1-year study period. The web software will include written descriptions, photos, and audiovisual resources for each exercise. The supervised therapeutic routine will take approximately 50 minutes to complete, and the remotely-supervised routine will take a maximum of 20 minutes at home.

Intervention

CONTROL GROUP

Patients allocated to the control group will not receive any specific intervention other than the treatment recommended by the medical staff and consensus of the International Working Group on the Diabetic Foot (IWGDF) 20, which includes:

1. Examine the feet annually for signs or symptoms of peripheral neuropathy and peripheral artery disease.

2. Screen for a history of foot ulceration or lower-extremity amputation, peripheral artery disease, foot deformity, pre-ulcerative signs on the foot, poor foot hygiene, and ill-fitting or inadequate footwear.
3. Instruct patient to inspect feet and the insides of shoes daily, wash feet daily (with careful drying, particularly between the toes), avoid using chemical agents or plasters to remove calluses or corns, use emollients to lubricate dry skin, and cut toe nails straight across.

Provide education aimed at improving foot care knowledge and behavior, as well as encouraging the patient to adhere to this foot care advice.

INTERVENTION GROUP

Patients allocated to the IG will receive a foot-ankle therapeutic exercise protocol for muscle strengthening and improving functionality. Part of the exercise protocol will be performed twice a week under the supervision of a physiotherapist for 12 weeks. A series of foot-ankle exercises will also be performed twice a week, remotely supervised through SOPeD. After 12 weeks of supervised and remote intervention, patients will continue home exercise practice using SOPED twice a week until the end of the study (for an additional 9 months).

The simplicity and practicality of this exercise protocol is an excellent tool for the management of the diabetes musculoskeletal complications in the primary and secondary care of public health systems. Both protocols (SOPeD and supervised therapeutic exercises) were designed following the same criteria: (a) warming exercises, (b) strengthening of the intrinsic foot muscles, (c) strengthening of the extrinsic ankle muscles, and (d) functional exercises, such as balance and gait training.

The following muscle groups were targeted in both protocols:

- Medial-plantar aspect: abductor hallucis, flexor hallucis brevis, and adductor hallucis
- Lateral-plantar aspect: abductor digiti minimi, flexor digiti minimi brevis, and opponens digiti minimi
- Middle-plantar aspect: flexor digitorum brevis, quadratus plantae, lumbrical muscles, plantar interosseous, and dorsal interosseous muscles
- Dorsal-foot aspect: extensor digitorum brevis and extensor hallucis brevis

The following joints were targeted in both protocols:

- Interphalangeal, metatarsophalangeal, and ankle joints

Supervised treatment will include 8 to 15 exercises to guarantee the four previously described criteria throughout the duration of the protocol (Additional file 1: Table 2). To promote long-term participation, each supervised session will be conducted in groups of 5–8 participants[37], and the duration of a session will be at least 50 minutes.

Remote exercise protocols will have a total of 8 exercises combined to provide the four previously described criteria through the duration of the protocol. To avoid monotony and enhance motivation, the exercises will change from session to session, and the maximum duration of a session will not be more than 20 minutes. A number of studies with diabetic patients have been conducted using e-health technologies that allowed people to engage in activities in their preferred environment, thereby taking up less of the health professional's time and decreasing demands on health centers[38].

The web software exercise protocol was developed to provide autonomy and reduce the need for professional supervision. It contains clear video instructions (as well as text and audio) and preserves the safety of the target population during exercise. Furthermore, it establishes training volume, progression criteria, and guidelines for discontinuing the protocol. This tool personalizes the progress of a foot-ankle exercise program based on

individual capabilities, similar to conventional physiotherapy, through a visual analogue scale, represented by a ruler and faces, which quantifies the level of effort required to perform each exercise so that daily progress can be customized. If the effort score ranges from 0.0–2.0 on the visual scale, the patient progresses to the next level the following day; from 2.1–7.0, the patient advances to the next level after two days; and from 7.1–10, the patient returns to the previous level.

To make the software more motivational, it has many game components [39]. Thus, users are rewarded in various ways: after finishing each stage, completing the self-assessment, and performing all the exercises that week. Users are also rewarded for dedication and persistence, not just physical ability. Each exercise and its training volume will be progressively modified based on the patients' needs.

According to Huijgen et al. (2008)[40], rehabilitation systems with remote supervision have good acceptance and similar adherence to supervised interventions, with about 13% loss in their remote intervention group versus 15% in the control group. The increased adherence to treatment at home and its effectiveness are likely due to the remote intervention enhancing patient motivation in addition to prescribing progressive exercises aligned with their needs.

Data on exercise practice and foot evaluation will be summarized by the software and made visible to the patient. In addition, patients' responses to the exercise software will be stored and accessible to researchers at any time. If any subject fails to login to the web software for more than 5 consecutive days, an e-mail will automatically be sent asking the subject to login and report training data (or lack thereof) for the past week.

The discontinuation criteria for exercise during any session include cramps, moderate to intense pain, fatigue, dizziness, fear, or any other condition that exposes the

patient to any discomfort. Subjects in both groups will be advised to avoid other concomitant types of care such as physical therapy, acupuncture, or unconventional medical treatment during the study. In cases where treatment is indispensable, the patient must advise the investigators.

Assessments

The scheme of evaluation processes is illustrated in Figure 2. Four physiotherapists (Researchers #4) who are blind to group allocation will perform all assessments. The first assessment will consist of collecting personal details, anthropometry data, and all outcomes. After baseline assessment, all subjects will be scheduled for 4 assessments: at 6, 12, and 24 weeks, and at 1 year.

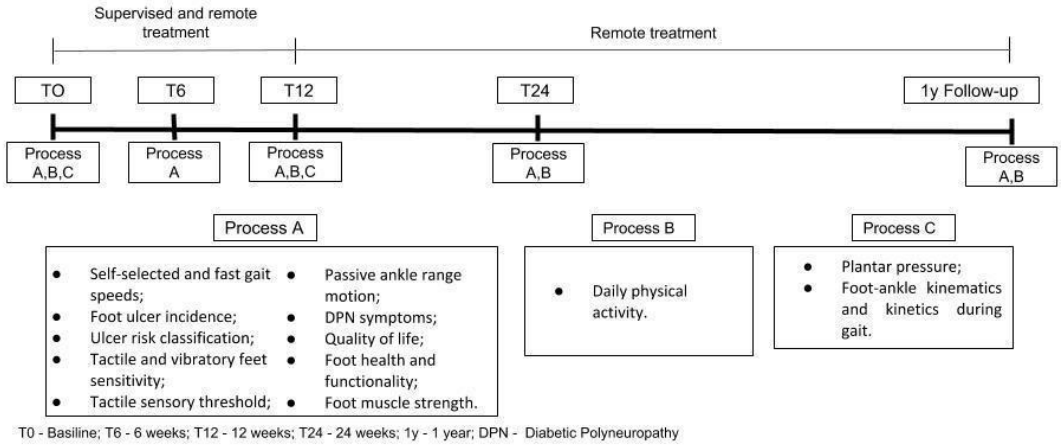

Figure 2 - Timeline of the evaluation processes throughout the clinical trial.

PRIMARY OUTCOMES

Daily physical activity level (number of steps)

Daily physical activity levels will be measured for 6 days by counting the number of steps using a 3D accelerometer (Power Walker-610, Yamax, Japan). This equipment measures the total number of steps and distance covered and has been previously validated

with older people and patients with DPN [41,42]. Before receiving the equipment, the accelerometer will be adjusted to the body weight and step length of each subject. To measure step length, the subject will be asked to walk comfortably in a 10-step interval. Thereafter, the mean step size will be calculated by measuring the 10 steps (toe to toe) divided by the number of steps. Each patient will be instructed to use the accelerometer daily, except during bathing and rest, for 6 days.

Self-selected and fast gait speeds

Patients will first walk barefoot on a 10 m track at a comfortable pace to determine self-selected gait speed and then as fast as possible to determine fast gait speed. For both speeds, 3 trials will be conducted, and the average will be calculated and used for analysis. Two photocells (CEFISE, Speed Test Fit Model, Nova Odessa, Brazil) located in the middle 6 m of a 10 m walking track will be used to measure walking time and calculate gait speed.

SECONDARY OUTCOMES

Foot ulcer incidence

Throughout the study period, the presence of and moment of occurrence of plantar foot ulcers will be assessed. At each study visit (T0, T6, T12, T24, and Follow-up 1 year), two blind assessors will examine the entire surface of patients' feet, including interdigital areas, to identify unreported or hidden foot injuries, in addition to asking the patient about foot wounds in the previous months since the last study visit. If an ulcer occur either during the intervention or the follow-up period, two blind assessors will check photographs of the patient´s foot and define if the occurrence is indeed an ulcer. Therapists will teach patients to inspect their own feet every morning to identify any evidence of skin lesions (e.g., abrasions, lacerations, blisters, and macerations) at or below the malleolus. A diabetic foot

ulcer is defined as a "full thickness lesion of the skin distal to the malleoli in a person with diabetes mellitus" [43].Patients will be instructed to contact the research team immediately if these lesions are identified[29]. If a patient develops a plantar foot ulcer during the study, the intervention will be discontinued, and the patient will be followed up with the intention-to-treat analysis.

Ulcer risk classification

Ulcer risk classification will be performed according to the International Working Group on the Diabetic Foot (IWGDF) [43], in which Group 0 (no risk) patients do not present with DPN, with or without deformity, Group 1 (low risk) patients with only DPN, Group 2 (high risk) DPN patients with foot deformity or vascular disease, and Group 3 (severe risk) DPN patients with a history of foot ulceration or amputation. The presence of DPN will be assessed by Fuzzy software developed by our group and published previously[9], and the peripheral arterial disease will be classified using the ankle-brachial index defined by Boulton et al. (2008)[44]. Values less than 0.5 indicate severe vascular disease, 0.5–0.9 indicate vascular disease, and 0.9–1.2 are considered normal.

Tactile sensitivity

Tactile sensory deficits will be assessed by a 10 g monofilament [44,45] in four plantar areas (plantar surface of the hallux and heads of the 1st, 3rd, and 5th metatarsals). This instrument has good reliability and validity in elderly individuals [46]. The monofilament will be applied perpendicularly to the skin surface 3 times on the tested areas with sufficient force to cause the filament to bend or buckle. The sequence of the tested areas will be randomized. The patient will not be able to see the monofilament or where it is being applied. The number of areas in which the patient does not feel pressure will be recorded

[47]. The greater the number of areas marked, the greater the impairment of tactile sensitivity.

Vibration sensitivity

Vibration testing will be conducted with the timed method using a 128 Hz tuning fork applied to the dorsal surface of the distal phalanx of the hallux. The time (in seconds) at which vibration sensation diminishes beyond the examiner's perception will then be recorded from both sides on a standardized form[48]. Values less than 10 seconds are classified as present vibratory sensitivity, greater than 10 seconds are classified as decreased vibratory sensitivity, and no perception is classified as absent vibratory sensitivity.

Tactile sensory threshold

The tactile sensory threshold will be assessed in the dorsal surface of the hallux using 6 monofilaments: 0.05 g, 0.2 g, 2 g, 4 g, 10 g, and 300 g. Patients will lay in prone position with the leg resting comfortably on a stretcher. Both feet are evaluated. Monofilaments are applied in order of increasing stiffness. A positive threshold will be recorded when the subject can feel the filament[49].

Passive ankle range of motion

The passive ankle range of motion will be evaluated bilaterally using an ankle electrogoniometer (model SG110/A, Biometrics, Gwent, UK). The biaxial electrogoniometer has two endblocks: a mobile (telescopic) and a fixed block joined by an instrumented spring with strain gauge. These endblocks attach to the ankle joint. The fixed endblock is positioned parallel to the major axis of the foot, below the lateral malleolus, and the telescopic endblock is aligned with the major axis of the leg. The strain gauge spring is kept

tense and its center is coincident to the ankle joint axis (over the lateral malleolus) with the sensor attached to the subject. The system is calibrated with the ankle in its mechanical neutral position: standing in a relaxed posture in stationary equilibrium, with the body weight distributed equally between the feet and the output value defined as the zero angle of the goniometer. Forward motion of the lower segment is regarded as flexion (negative values) and backward motion as extension (positive values)[50]. After setting the zero angle, the patient will lie down and the assessor will measure the passive range of motion.

DPN symptoms

Patients will answer the Brazilian version of the Michigan Neuropathy Screening Instrument (MNSI)[51]. This questionnaire has 15 questions about the sensitivity of the legs and feet and is self-administered. Answers of "yes" for questions 1, 2, 3, 5, 6, 8, 9, 11, 12, 14, and 15 receive a score of 1. A "no" answer for questions 7 and 13 score 1. Question 4 is a measure of circulatory deficit and question 10 is a measure of general asthenia and are not included in the score. The sum of all scores ranges from 0 to 13 (13 representing a worse DPN).

Quality of life

Patients will answer the EQ-5D questionnaire[52], which is a generic instrument for measuring health-related quality of life that allows the assessor to generate an index representing the individual's health status. It is based on a classification system that describes health in five dimensions: mobility, personal care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three associated severity levels, corresponding to no problems (level 1), some problems (level 2), and extreme

problems (level 3). The EQ-5D associates a value between -0.59 and 1.00, which represents the health status of a patient (1 being perfect health).

Foot health and functionality

This study will use a Brazilian-Portuguese version of a foot-health status questionnaire (FHSQ-BR) translated and validated by Ferreira et al. (2008)[53]. Section I evaluates foot health in four domains: foot pain, foot function, footwear, and general foot health. Section I is composed of questions with answer options presented in affirmative sentences and corresponding numbers. Section III collects general demographic data. This study will only use the scores from Section I because Section II refers to general health. Each domain scores from 0 to 100 points, where 100 is the best condition and 0 the worst. The Scores will be calculated using the FHSQ software version 1.03 (Care Quest, Australia).

Foot muscle strength

Foot muscle isometric strength will be measured according to Mickle et al. (2006)[54] using a pressure platform (emed q-100, Novel, Munich, Germany). Subjects will stand and push down on the platform two times, as hard as possible, with their hallux and toes, which controls for excessive body sway. The maximum force under the hallux and toes normalized by bodyweight are outcomes of this measurement.

Dynamic plantar pressure distribution during gait

A 700 × 403 × 15.5 mm pressure platform (emed q-100, Novel, Munich, Germany) with 6080 sensors and 4 sensors per cm^2 that collects data at 100 Hz will be used to assess walking plantar pressure distribution. Participants will walk barefoot to the platform with a self-selected gait speed three times for 4 m. Both feet will be analyzed for each patient.

Based on the algorithm by Giacomozzi et al. (2000)[55], peak pressure, contact area, and pressure-time integral in seven anatomical plantar regions will be analyzed: heel, midfoot, medial forefoot, medium forefoot, lateral forefoot, hallux, and toes. This method relies on the integration of a 3D motion capture system (Vicon system), a pressure measurement device (emed q-100), a multi-segment foot model, and an algorithm to identify regions of interest.

Foot-ankle kinematics and kinetics during gait

Gait kinematics will be acquired using three-dimensional displacements of passive reflective markers (9.5 mm in diameter) tracked by eight infrared cameras at 100 Hz (VERO, Vicon Motion System Ltd., Oxford Metrics, UK) and the NEXUS 2.6 motion capture software (Vicon Motion System Ltd., Oxford Metrics, UK). Three-dimensional and force-platform motion capture data will be collected to quantify the magnitude and direction of biomechanical responses during gait. Forty-three markers will be placed on the subject (leg, ankle, and foot) according to the Oxford protocol.

The laboratory coordinate system will be established at one corner of the force plate and all initial calculations will be based on it. Each lower-limb segment (shank and thigh) will be modeled based on surface markers as a rigid body with a local coordinate system that coincides with the anatomical axes. Translations and rotations of each segment will be reported relative to the neutral positions defined during the initial static standing trial. All joints will be considered to be spherical (i.e., with three rotational degrees of freedom). Ground reaction forces will be acquired by a force plate (AMTI OR-6-1000, Watertown, MA, USA) with a sampling frequency of 1 kHz embedded in the center of the walkway. Force and kinematic data acquisition will be synchronized and sampled by an A/D board (Control Box LOCK VICON, 192 kHz, 24 bits).

Five valid steps will be acquired from the same foot as the pressure distribution measurements on a 10 m walkway. The bottom-up inverse dynamics method will be used to calculate the ankle force moments in the sagittal plane, considering the inertial properties of segments[56]. For the calculation of ankle power, the calculated moment of force and the angular velocity of the ankle in the sagittal plane will be considered. Calculation of all variables will be performed using a custom-written MATLAB function (MathWorks, Natick, MA, USA).

The kinematic and kinetic outcomes that will be analyzed are: (a) the total sagittal plane ankle range of motion during gait stance phase (degrees); (b) the ankle angle in three planes at the heel strike (degrees); (c) the ankle angle in three planes at the final phase of push off (degrees); (d) range of dorsiflexion during gait stance phase (degrees); (e) dorsiflexor ankle moment peak at the heel strike and approximately 80% of gait support phase, corresponding to the beginning of the propulsion; (f) the ankle power peak at approximately 80% of the stance phase (W/kg) corresponding to the propulsion phase; (g) deformation of the medial longitudinal arch angle; (h) rotation between forefoot and rearfoot; (i) angle in the transversal plane between first and second metatarsals and between second and fifth metatarsals; and (j) maximum inversion and eversion (frontal plane).

Evaluation of the outcome-assessor blinding

To evaluate whether or not there was a failure in blinding of the outcome assessor, assessors will be asked to guess which group the patients belonged to at the end of 12 weeks of treatment. Then the evaluators will classify the certainty of their opinions according to a scale (1 = not sure, 5 = completely sure). To ensure that the evaluator is not

induced to correctly guess the participants' allocation, the patient will be instructed to not disclose any behavior details during the previous 12 weeks.

Outcome measurements

The outcome measurements are described in Table 1.

Table 1 - Outcomes Measurements.

Outcome		**When will they be evaluated**				
Primary	**Measures**	***Baseline***	**6 weeks**	**12 weeks**	**24 weeks**	***Follow-up*** **1 year**
Daily Physical Activity level	Number of steps by Accelerometers	**X**		**X**	**X**	**X**
Self-selected and fast gait speed	Speed in m/s measured by Photoelectric Cells	**X**	**X**	**X**	**X**	**X**
Secondary	**Measures**					
Foot ulcer incidence	Number of new cases of ulcers in 12 months of the study	**X**	**X**	**X**	**X**	**X**
Ulcer risk classification	Classification according to IWGDF	**X**	**X**	**X**	**X**	**X**
Tactile sensitivity	Number of non-sensitive areas measured by 10g monofilaments	**X**	**X**	**X**	**X**	**X**
Vibration sensitivity	Classification the ability to feel the vibration measured by tuning fork	**X**	**X**	**X**	**X**	**X**
Tactile sensory threshold	Tactile sensitivity threshold between different monofilament thicknesses	**X**	**X**	**X**	**X**	**X**
Passive ankle range of motion	Ankle angle measured by a digital electrogoniometer	**X**	**X**	**X**	**X**	**X**
DPN Symptoms	Score of Michigan Neuropathy Screening Instrument (MNSI)	**X**	**X**	**X**	**X**	**X**
Quality of life	Score of EQ-5D questionnaire	**X**	**X**	**X**	**X**	**X**
Foot health and functionality	Scores of FHSQ-BR questionnaire	**X**	**X**	**X**	**X**	**X**
Foot muscles strength	Maximum force obtained on EMED pressure platform	**X**	**X**	**X**	**X**	**X**
Plantar pressure	Peak pressure obtained on EMED pressure platform	**X**		**X**		

Foot-ankle kinematics and kinetics during gait	Three-dimensional motion capture and a force platform	**X**		**X**		

Sample size and statistical analysis

The sample size was calculated using the GPower v. 3.1 program [57] based on the following outcomes: daily physical activity level (number of steps) and self-selected and fast gait speeds. These three outcomes were chosen because they reflect important functional gains for patients with DPN. Thus, three sample calculations were performed and selected, which resulted in the largest number of participants. For fast gait speed, effect size was calculated based on a study that evaluated the effect of exercise on the fast gait speed in elderly patients, which had an increase in gait velocity from 151.9 ± 5.5 to 162.7 ± 6.9 cm/s after 3 months of intervention[58]. For self-selected gait speed, the effect size was based on the minimal clinical difference in self-selected gait speed (0.17), as it may be useful for establishing therapeutic goals and interpreting patient progress to treatment [59]. For number of steps, effect size was calculated based on a study that evaluated the effect of interactive balance training on daily number of steps in individuals with DPN, for which there was an increase from 8.656 ± 4.589 to 11.052 ± 5.365 after 4 weeks of intervention[30].

Considering the primary outcome tested; a statistical design of F-test repeated measures and interaction between and within factors with 3 repeated measures and two study groups; a statistical power of 0.80; an alpha of 0.05; and a size of effect of 0.175, 0.170, and 0.154 for fast gait speed, self-selected gait speed, and number of steps, respectively, the resulting sample sizes were 54, 58, and 70 individuals, respectively. Therefore, the number of participants is based on the measurement for number of steps, which resulted in the largest number of participants (n = 70). Assuming a 10% dropout rate during the study, a sample size of 77 patients is needed.

Inferential statistical analysis will be done using an intention-to-treat and per protocol analysis. The missing data will be treated by imputation methods depending on the type: missing completely at random, missing at random, or not at random[60]. The per-protocol analysis will include only those patients who completed follow up in the allocated intervention group.

After confirmation of normality (Kolmogorov-Smirnov test), homoscedasticity (Levene test), and imputation of the means for the missing data of variables with normal distribution, ANOVA 2 factors for repeated measures will be performed, followed by Newman posttest Keuls, to obtain the group effect (intervention and control), time (between T0, T6, T12, T24, and Follow-up 1year), and group x time interaction.

Significant differences will be considered with $\alpha = 5\%$, but for the description of the effect of the intervention, the effect size (Cohen coefficient) and difference between the means will be calculated with their respective 95% confidence intervals.

Discussion

We have presented the rationale and design of a Randomized Controlled Trial on the efficacy of foot-ankle therapeutic exercise training in DPN patients. This RCT will provide important data on foot-ankle training effectiveness on daily physical activity levels and clinical and biomechanical outcomes. The outcomes may contribute to the design of future studies on clinical and biomechanical changes resulting from the strengthening of the foot-ankle complex.

Some studies have sought to evaluate the effects of strengthening on several outcomes in patients with DPN. Ten studies used generic lower limb exercises that did not focus specifically on musculoskeletal deficits related to diabetes: balance training, non-weight-bearing and weight-bearing strengthening, aerobic exercises, and multimodal

manual treatment treatment[29,30,53,61–67].Four studies that sought to evaluate the effects of specific foot-ankle training had methodological biases, such as lack of a control group[68], lack of DPN clinical outcomes[4], low number of participants[24], and short-term effects [25].

The RCT introduced here will have a longer period of follow-up (12 months), several clinical DPN outcomes, and a calculated sample size to achieve enough power within a cohort of patients with moderate and severe DPN. In addition, this trial proposes a specific training protocol for intrinsic and extrinsic foot-ankle muscle strengthening focusing on DPN deficits, including several easy-to-perform exercises that do not require continuous supervision by a health-care professional. The innovative and original exercise program presented in this RCT will be a promising approach to treat and prevent foot complications in this population and improve their autonomy for daily living activities.

Declarations

Ethics approval and consent to participate

This trial was approved by the Ethics Committee of the School of Medicine of the University of São Paulo (Protocol 1.464.870). All patients will be asked for written informed consent according to the standard forms and the researcher will obtain them.

Consent for publication

Written informed consent for publication of all images was obtained from the models.

Availibility of data and material

All personal data from potential or enrolled patients will be maintained confidential before, during and after the trial by encoding participant's name. All data access and storage

are in keeping with National Health and Medical Research Council guidelines, as approved. All files will be available from the database published at figshare.com. All important protocol amendments will be reported to investigators, review boards and trial registration by the Researcher.

Competing Interests

The authors affirm that this study has not received any funding/assistance from a commercial organization which may lead to a conflict of interests.

Authors'contributions

All authors have made substantial contributions to all three of sections (1), (2) and (3): (1) The conception and design of the study, or acquisition of data, or analysis and interpretation of data (2) drafting the article or revising it critically for important intellectual content (3) final approval of the version to be submitted. And in the protocol the following roles will be played by the authors: RLM is responsible for the study design, intervention, interpretation of the data, writing the report and submission of the manuscript. JSSPF is responsible for the study design, data collection, management, analysis, and interpretation, writing the report and submission of the manuscript. ICNS, CDS, MGBD and SAB is responsible for the study design, interpretation of the data, writing the report and submission of the manuscript.

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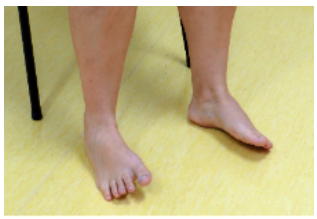
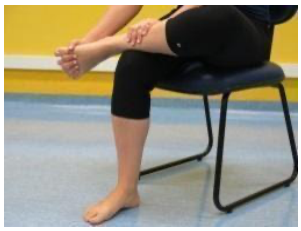
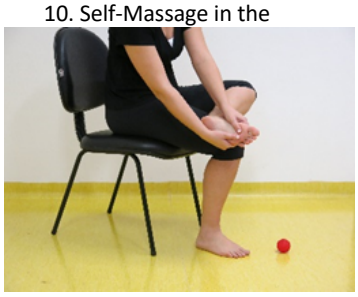
Additional file 1 - Protocol for evaluating the effects of a foot-ankle therapeutic exercise

Table 2 – Foot-ankle exercises protocol.

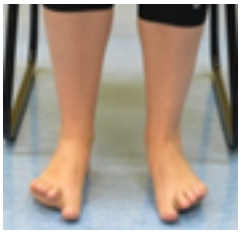
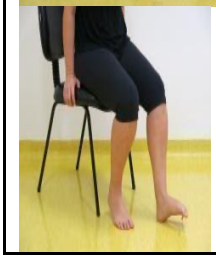
WARMING EXERCISES

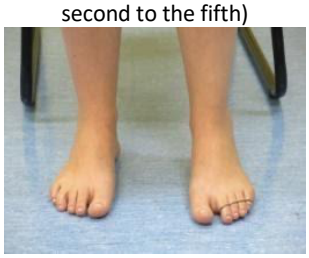
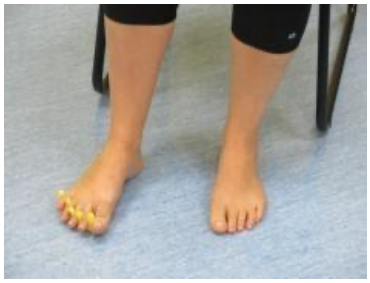
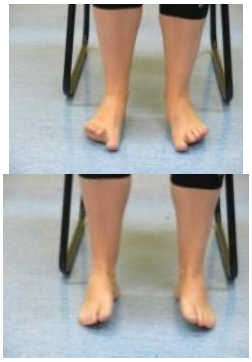
Exercise	Performance	Volume and progression	Approximate total duration
1. Stretching of the sole of the foot 	Sitting, cross your leg over your knee. With one hand, pull your toes back. With the other hand, massage the area on the bottom of your foot just in front of your heel.	Massage 1 min each foot	2 – 3 min
2. Massage with the ball 	Sitting, put a ball under your foot and massage back and forth (forward and backward); To one side and the other.	Massage 1 min each foot.	2 – 3 min
3. Move your feet up, down and in circles  	Sitting, move your feet up and down, and then move in circles. First: flexion and extension exercise. Second: Clockwise circles Third: Counterclockwise Circles	1: 1x10 rep; 2: 2x10 rep; 3: 1x10 rep; 4: 2x20 rep.	3 – 4 min
4. Writting words with your feet	Sitting down, write words in the air with your feet.	__	__

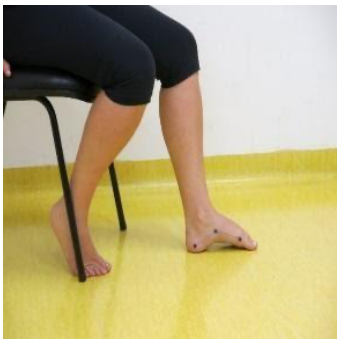
5. Calf muscle stretching 	Standing in front of a chair or wall, keep one leg in front of the other. The front leg with the knee flexed and the rear leg withe the knee extended. Lean forward at the ankle, keeping both heel on the ground, stretching the calf muscles.	1 x 20 s each leg.	1 min
6. Support on the lateral and medial border of the foot 	Sitting, knees bent and feet flat on the floor. Support both feet by the lateral edge of the foot, followed by the support of the medial edge of the foot.	1:1x10 rep holding each position for one second. 2:2x10 rep; 3:2x20 rep.	2 – 6 min
7. Interlacing your fingers and toes and making circular movements 	Sitting, cross one leg over the other and interlacing your fingers on your toes and perform circular motions.	1 x 20 s each foot.	1 min
8. Toes Manipulation 	Sitting, with one leg crossed over the other, hold each toe and slowly spin side to side, like a screw. Do it all your toes.	1x 15 rep each toe	1-2 min
9. Massage with the ball without contact of the heel 	Sitting, place a ball under your foot and press it toward the floor. Do not place the heel on the floor.	Press during 1 min each foot.	2-3 min

10. Self-Massage in the feet 	Sitting with one leg crossed over the other, massage the soles of your feet with both hands for 20 seconds. In a circular motion using the thumb, go in the direction of the heel up to the fingers. Do the same with the other foot.	1 x 20 s	1 min
11. Alternate toe support (sitting) 	Sitting on a chair, stand on tiptoe, alternating feet.	1:1x10 rep 2:2x10 rep 3:2x20 rep	1 – 4 min

INTRINSIC MUSCLES EXERCISES

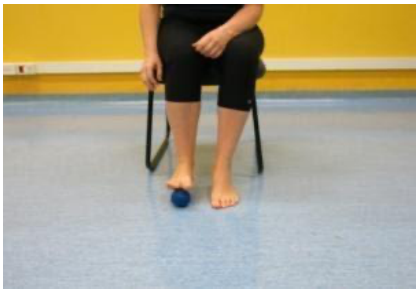
Exercise	Performance	Volume and progression	Approximate total duration
12. Toe alternate 	Sitting, with the heel fixed and contacting the floor, alternately touch the first and fifth on the floor. Do not move your knees. Do it slowly and under complete control.	1: 1x 10 rep; 2: 1x 10 (standing);	2-3 min
13. Pick up objects with your toes (1st cotton / pencil / ball)  	After placing an object on the floor (cotton, ball and pencil), take it with your toes	1:1x5 rep. holding for 5 seconds 2:2x5 (standing 3: 3x5 (standing	2 – 3 min

14. Wringing towel with feet 	Sitting, with the heel fixed and in contact with the floor, pull the towel with your toes without suspending the heel (Both feet)	1: 1x10 rep; 2: 1x15 rep;	1 – 2 min
15. Open and close the toes (from the second to the fifth) 	With an elastic between the second and fifth toe, perform the opening / separating movement of the fingers against the resistance of an elastic	1:1 x 10 rep (sitting). 2: 2x15 (standing) 3: 3x20 (Standing).	1-2 min
16. Squeeze toes separators 	Sitting, with 90 degrees of the knee and ankle flexion, adduct and abduct, squeeze the toes separators for one second Always keeping the heel fixed on the ground.	1: 1x10 rep eac foot; 2: 2x10 rep; 3: 3x10 rep.	1 min
17. Toe toes 	Sitting on a chair with your feet flat on the floor, tap one toe at a time, starting with the little toe, on the floor continuously. Doing a similar movement while strumming. After performing the same movement starting with the big toe.	1: 1x10 rep (sitting); 2: 1x10 (Standing); 3: 1x20 (Standing).	2 – 6 min
18. Toes flex with theraband 	Sitting, with the heel resting on the floor, flexion of the toes without moving the ankle.	1: 1x10; 2: 2x10; 3: 2x20.	1 min

19. Plantar arch raise 	Sitting, raise the plantar arch in na arch shape. The heel and fingertips should not get off the ground.	1: 1x10; 2: 2x10; 3: 3x10.	1-2 min
20. Short-foot exercise	Sitting, with 90 degrees of knee and ankle. Approximate the head of the first metatarsal toward the heel without toe flexion,“ shortening“ the feet. The forefoot and heel should not get off the ground.	1: 1x10; 2: 2x10; 3: 3x10.	1-2 min

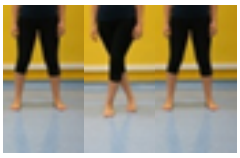
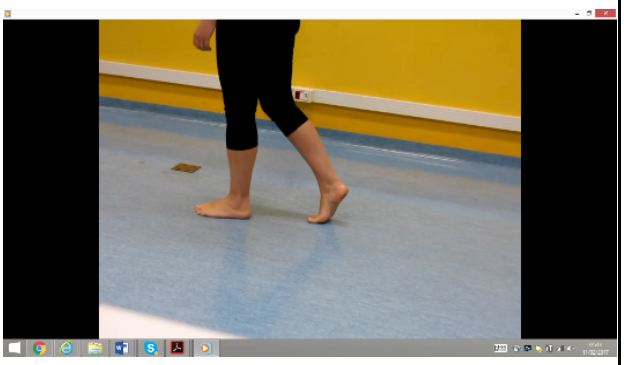
ANKLE EXERCISES

Exercise	Performance	Volume and progression	Approximate total duration
21. Climb on the tip Feet 	Using a support, chair or any other stable furniture, stand on tiptoe and return to the starting position.	1: 1x5 rep; 2: 1x10 rep; 3: 1x15 rep.	1 – 2 min
22. Kick the floor 	Sitting with feet flat on the floor, tapping the front of the foot repeatedly on the floor, with a fast speed, as if "impatient." Do one foot at a time.	1: 1x30 rep; 2: 2x30 rep; 3: 2x40 rep.	2 – 3 min

23. One Foot Balance 	Stand on one foot only. Do one side and then the other.	1: 1x10 rep; 2: 2x10 rep; 3: 1x10 rep; 4: 2x20 rep.	3 – 4 min
24. Tighten the ball 	Sitting, put your foot on a ball and press it down. The heel should rest flat on the floor.	1: 1x10 rep; 2: 1x15 rep; 3: 1x20 rep.	1 min
25. Strengthening the medial musculature of the foot 	Placing an elastic band around the medial part of the foot (below the big toe) and with the other foot stepping on the elastic band to give resistance. Make a movement against the elastic band, as if you would step on the floor with the lateral edge of the foot.	1: 1x10 rep (yellow elastic band); 2: 1x10 rep (blue elastic band)	1 – 2 min
26. Strengthening the lateral musculature of the foot 	Placing an elastic band around the lateral of the foot (below the little toe) and with the other foot stepping on the elastic band to give resistance. Make a movement against the elastic band, as it would walk with floor with the medial edge of the foot.	1: 1x10 rep (yellow elastic band); 2: 1x10 rep (blue elastic band)	1 – 2 min

FUNCTIONAL EXERCISES

Exercise	Performance	Volume and progression	Approximate total duration

27. Walk with open toes 	Walk slowly keeping your toes apart as long as your foot stays flat on the floor.	1: 1x10 rep 2: 2x10 rep 3: 2x20 rep	1 – 2 min
28. Walking across the steps. 	Walk to the side by crossing one leg in front and then crossing back. Return side the same way to the starting position.	1: 1x10 rep; 2: 2x15 rep; 3: 2x20 rep.	2 – 3 min
29. Step forward and backward 	Unload the weight forward and backward associated with ankle flexion and extension (Simulating the gait).	1: 2x15 rep 2: 2x20 rep 3: 2x30 rep	3 – 4 min
30. Walk with your toes pressed to the floor 	Walk with your toes pressing toward the ground, as if you were pushing the ground with your toes as you walk.	1: 1 x 10 step holding for 1 2: 2x10 steps 3: 3x10 step	2-3 min

CAPÍTULO 3 - VIABILIDADE DO ENSAIO CLÍNICO RANDOMIZADO

3.1 Feasibility and preliminary efficacy of a foot-ankle exercise program aiming to improve foot-ankle functionality and gait biomechanics in people with diabetic neuropathy: a randomized controlled trial

sensors

MDPI

Article

Feasibility and Preliminary Efficacy of a Foot-Ankle Exercise Program Aiming to Improve Foot-Ankle Functionality and Gait Biomechanics in People with Diabetic Neuropathy: A Randomized Controlled Trial

Renan L. Monteiro [1,2], Jane S.S.P. Ferreira [1], Érica Q. Silva [1], Asha Donini [1], Ronaldo H. Cruvinel-Júnior [1], Jady L. Verissímo [1], Sicco A. Bus [3] and Isabel C.N. Sacco [1,*]

1 Departamento de Fisioterapia, Fonoaudiologia e Terapia Ocupacional da Faculdade de Medicina da Universidade de São Paulo, Rua Cipotânea, 51-Butantã, São Paulo, SP 05360-000, Brazil; renanlm@usp.br (R.L.M.); janesuelen@usp.br (J.S.S.P.F.); ericaqueiroz10@usp.br (É.Q.S.); thales.panissa@usp.br (A.D.); ronaldocruvinel@usp.br (R.H.C.-J.); jady.verissimo@usp.br (J.L.V.)

2 Department of Physical Therapy, Federal University of Amapá, Rod. Juscelino Kubitschek, km 02-Jardim Marco Zero, Macapá, AP 68903-419, Brazil

3 Amsterdam UMC, University of Amsterdam, Department of Rehabilitation Medicine, Amsterdam Movement Sciences, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands; s.a.bus@amsterdamumc.nl

* Correspondence: icnsacco@usp.br; Tel.: +55-11-3091-8426; Fax: +55-11-3091-7462

Abstract

Foot-ankle strengthening and mobility exercises are part of international guideline recommendations for people at risk of diabetic foot disease. We examined the feasibility and preliminary efficacy of a 12-week foot-ankle exercise program on clinical, functional and biomechanical outcomes in people with diabetic neuropathy (DPN). We randomly allocated 30 people with DPN to usual care (control) or usual care plus a supervised exercise program (intervention). For feasibility, we assessed recruitment rate and participant

adherence and satisfaction. For program efficacy, we assessed baseline to 12-week changes in daily physical activity level, gait speed, tactile sensitivity, ankle range of motion, DPN symptoms, quality of life, foot health and functionality, foot strength and plantar pressure during gait, using paired t-tests ($p < 0.05$). In 52 weeks, we recruited 45 eligible participants (0.90/week). Program adherence was 80% and participants' satisfaction had a mean (SD) of 4.57 (0.70) out of 5. The intervention group significantly improved on toes strength, contact time during gait and DPN symptoms, and peak forefoot pressures increased over time; controls showed significantly increased heel peak pressures and force. The exercise program was feasible, based on a moderate recruitment rate and an adherent and satisfied population, and the intervention showed several positive preliminary effects over time compared to usual care.

Background

Diabetic neuropathy (DPN) is a symmetrical disorder, either clinically evident or subclinical, that occurs in people with diabetes; DPN is attributable to metabolic and microvascular alterations resulting from chronic hyperglycemia exposure as well as to cardiovascular risk covariates [1]. As DPN progresses, it affects the integrity of neural structures and, especially, small joints and intrinsic muscles of the foot-ankle [2–6]. These specific DPN consequences are the main factors for the development of foot deformities, increased plantar pressures during walking, and consequently the risk for plantar ulceration [2,7–9].

Supervised foot-related exercises combined with a health-promoting program were shown to effectively reduce DPN symptoms [10,11], improve vibration perception [12], recover foot and ankle joint mobility [12–16], redistribute pressure during walking [12,13,15,17–20] and increase foot strength and function [10,21,22]. All of these benefits

mitigate the risk factors for foot ulceration in diabetes. Several foot-related exercises have been recommended in international guidelines to help reduce the incidence of foot ulceration in people at risk. However, because the quality of the evidence supporting the beneficial effects of foot-related exercises remains weak [23], physiotherapy interventions have not yet been implemented worldwide for preventing the progression of the musculoskeletal deficits in people with diabetes and DPN. For this reason, it is still unclear how the compliance with this type of preventive programs would be in this population and whether the recruitment for a trial that tests the efficacy of these physiotherapy programs would be feasible. Although the performance of exercises has been effective for improving the musculoskeletal health [17,20,24,25] and functional balance [21,26] of people with DPN, the recommended exercises usually target larger joints and muscles of the lower limbs and focus mainly on gait and balance training. These exercises do not address the specific musculoskeletal deficits of distal and smaller joints and muscles, which affect the functionality and biomechanics of daily living activities. Some of the most recommended foot-related exercises in the literature that have to be part of an intervention program are based on short foot exercises and Vele´s forward and reverse tandem gait exercise [10,27,28]. Therefore, more high-quality well-designed controlled trials are warranted to strengthen the level of evidence supporting the use of specific foot-ankle therapeutic exercises to mitigate the risk factors of, and help prevent, foot ulceration in people with diabetes. A few randomized controlled trials (RCTs) evaluated the effects of foot-related strengthening and mobility exercises in different domains (i.e., clinical, functional, and biomechanical); the majority of these RCTs were of low quality, presented small effect sizes, and did not involve exercises that specifically target the main musculoskeletal dysfunction in people with DPN [23]. As regards the development of a guideline for foot ulcer

prevention [29], only three studies [10,13,15] assessed the effects of foot-ankle exercise on DPN-related outcomes. All of this makes it difficult to design an RCT on this topic involving the investigated population and to determine what makes a preventive program relevant in terms of exercise inclusion, frequency and intensity of sessions, outcomes used and level of adherence and motivation to the program. Therefore, aspects of the feasibility and the preliminary efficacy of a more comprehensive training program should first be investigated. The present work presents the results of a feasibility study involving a superiority RCT and preliminary efficacy analysis of a 12-week therapeutic foot-ankle exercise program for people with DPN [30]. It is also our intention with this paper to stress the use of biomechanical sensors to guide therapeutic strategies and rehabilitation of the dysfunctions related to DPN. These sensors are neither regularly applied to this population nor applied in clinical settings where this population is treated. Thus, besides the feasibility purposes, we aimed to emphasize the importance of the biomechanical sensor for trials that focus on therapeutic strategies for musculoskeletal deficits in the diabetic population. The parameters investigated were derived from biomechanical sensors and other clinical tools: foot functionality and clinical and biomechanical outcomes, such as gait speed, foot strength and plantar pressure during gait, as well as the aspects of recruitment, adherence to training protocol and participant satisfaction. Our hypotheses were as follows: (1) the program will be feasible and (2) the preliminary results of the intervention will show an increase in the toe and hallux isometric muscle strength, daily physical activity levels, self-selected and fast gait speeds, and passive ankle range of motion; an improvement in the foot tactile and vibration sensitivity, health-related quality of life and foot health and functionality; a decrease in the tactile sensory threshold and DPN symptoms; and an

improvement in the foot rollover as represented by a more homogeneous plantar pressure distribution during gait.

Methods

Study Design and Ethics

Data for this feasibility study were collected between November 2017 and November 2018 (Figure 3) in the outpatient physiotherapy clinic of Centro de Saúde Escola Barra Funda Dr. Alexandre Vranjac, a primary care center; the assessments were performed at the physical therapy department of the School of Medicine of the University of São Paulo. All subjects gave their informed consent to participate in this study. The trial was conducted in accordance with the Declaration of Helsinki, was approved by the Ethics Committee of the School of Medicine of the University of São Paulo (Resolution 196/96 of the National Health Council; Research protocol No. 1.464.870), and was prospectively registered at ClinicalTrials.gov as NCT02790931. The research protocol ha2790931. The research protocol has been published elsewhere [30].

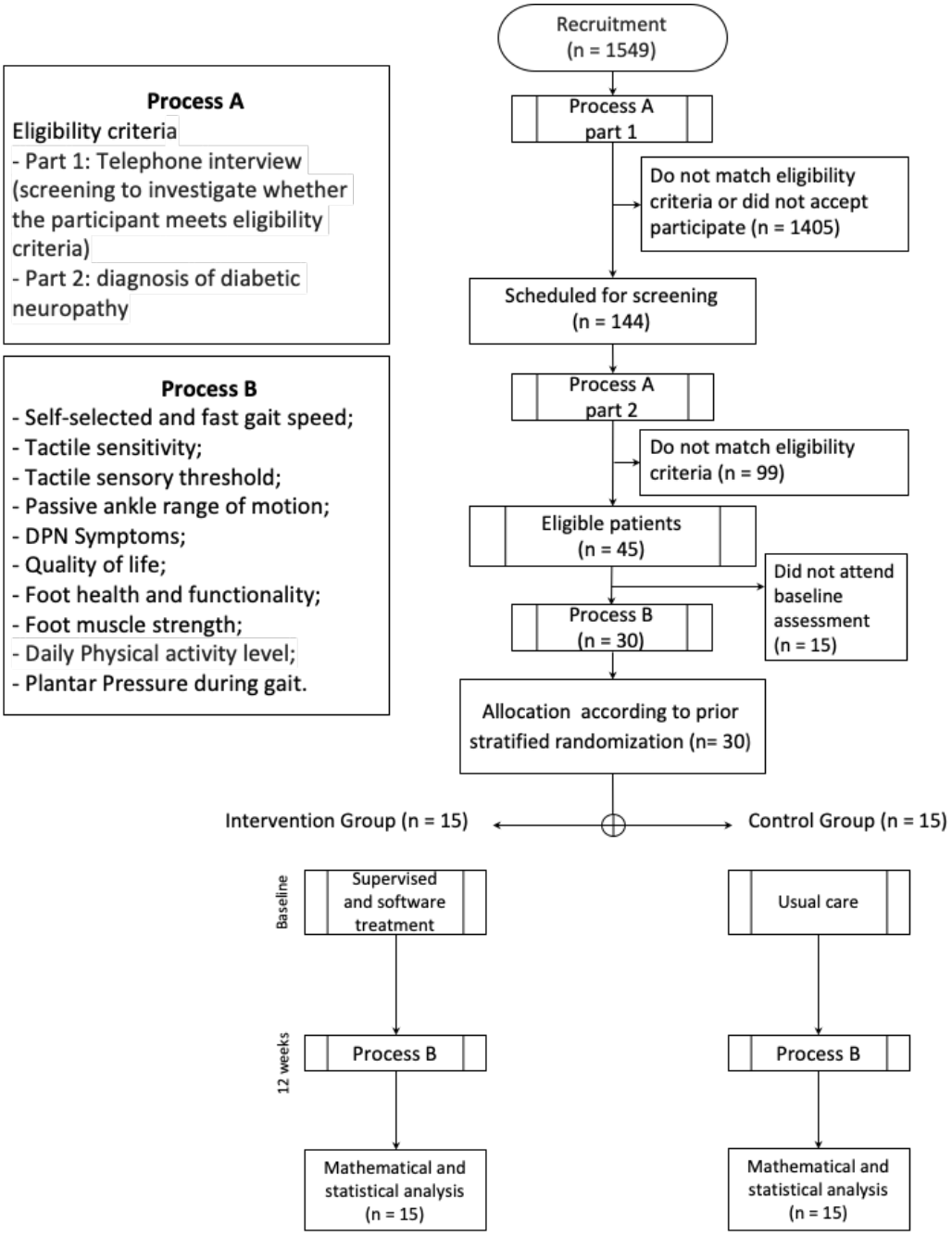


Figure 3 - Flowchart of the feasibility study. DPN - Diabetic neuropathy.

Participants

The first 30 participants who were selected via convenience sampling were recruited, allocated, and completed the exercise program. Feasibility studies usually entail a smaller sample size compared with a full randomized trial as no formal calculation of power is required in the former [31]. Adults of up to 75 years of age with moderate or severe DPN

were recruited through digital advertisement and through direct recruitment of people with diabetes during the health campaigns promoted by the State of São Paulo. Individuals were eligible if they had type 1 or 2 diabetes mellitus; with moderate or severe DPN as diagnosed by the fuzzy decision support system [3]; able to walk independently for at least 10 m; with a maximum of one amputated toe, not being the hallux; and with Internet access that allows the use of a web-based software for the supervised exercise sessions. Individuals were excluded if they had the following: plantar ulcer; history of a surgical procedure in the knee, ankle, or hip or an indication of lower limb arthroplasty; the need to use a walking aid, such as a walker or cane; diagnosis of other neurological diseases besides DPN; dementia or inability to give consistent information; received any physiotherapy during the intervention period; diagnosis of a major vascular complication and/or severe retinopathy, as determined from their medical records. The participants' eligibility was checked by physiotherapists who were responsible for the outcome assessments in the trial and who were blinded to the treatment allocation. These physiotherapists collected the demographic, anthropometric, and clinical (history) data, as well as the data on foot and ankle function and plantar pressure during walking in a baseline assessment. At baseline, the participants were scheduled for a final assessment at the end of the 12-week follow-up period.

Randomization, Allocation and Blinding

The randomization scheme was prepared with the Clinstat software (University of York, York, UK) by an independent researcher who was blinded to the group allocation. A numerical sequence was placed in opaque envelopes that were numbered sequentially based on the order generated by the software. This sequence was kept private and stored

in a location that is inaccessible to the blinded outcome assessors. Only the physiotherapist responsible for the supervised physiotherapy session was aware of the group allocation. The participants' personal data were kept confidential before, during and after the study through the assignment of a research code for each participant. Apart from the physiotherapist who was responsible for the randomization, the participant was also aware of his/her own code assignment. Two other physiotherapists, both blinded to the treatment allocation, were responsible for all clinical, functional, and biomechanical outcome assessments. The participants were instructed not to reveal their treatment allocation to the physiotherapist who conducted the assessments.

Intervention Protocol

The control group participants received the usual care recommended by medical staff and by the guidelines of the International Working Group on the Diabetic Foot (IWGDF) [29], as follows:(1) screening for a history of foot ulceration or lower-extremity amputation, peripheral artery disease, foot deformity, pre-ulcerative signs on the foot, poor foot hygiene, and ill-fitting or inadequate footwear;(2) inspecting the feet and the insides of shoes daily, washing the feet daily (with careful drying, particularly between the toes), avoiding the use of chemical agents or plasters to remove calluses or corns, using emollients to lubricate dry skin, and cutting toe nails straight across; (3) providing education aimed to improve foot care knowledge and behavior, as well as encouraging the participants to adhere to this foot care advice. All of these usual care orientations were given during the baseline session by the physiotherapist who conducted the study. The intervention group participants received the usual care, along with a 12-week therapeutic exercise program that strengthens the muscles and improves the functionality of the foot-ankle complex.

A part of the exercise protocol was performed twice a week under the supervision of a physiotherapist, and a series of foot and ankle exercises was performed twice a week by the participant alone, who was remotely supervised through the Educational Diabetic Foot Software (SOPeD, www.soped.com.br).The exercise protocol was designed to be as simple and practical as possible to effectively manage the musculoskeletal complications related to diabetes and to facilitate its implementation in primary and secondary public health care units. Both protocols (SOPeD and supervised therapeutic exercises) were designed to consist of the same set of modules: (a) warm-up exercises, (b) strengthening of the intrinsic foot muscles, (c) strengthening of the extrinsic foot muscles, and (d) functional exercises, such as balance and gait training. The SOPeD consisted of eight exercises that were divided into four modules. To promote long-term participation, each supervised session was conducted in groups of five to eight participants [26] with a minimum duration of 50 min. The exercise progression was customized to each patient as the supervised exercises were a face-to-face intervention that were executed according to the criteria set in physiotherapy programs. To avoid monotony and to increase motivation, the exercises were varied every session, and the maximum duration of each session was 20 min.

Outcomes

For the purpose of this study, the intervention was considered feasible based on the following criteria: (a) the adherence to the 12-week intervention protocol and to the final outcomes assessment was>80%; (b) the participant's recruitment rate was close or equal to what the laboratory restrictions for the outcomes assessment require (10 participants/week); and (c) the participant satisfaction toward the intervention was>4

on a 5-point Likert scale. The preliminary efficacy of the training program was assessed based on whether the intervention group displayed significantly improved toe and hallux isometric muscle strength between baseline and after 12 weeks (T12). In the full RCT, the primary outcomes are the daily ambulatory activity level and self-selected and fast gait speeds, and the secondary outcomes are the foot isometric muscle strength, ankle joint range of motion, tactile sensitivity, DPN symptoms, quality of life, foot health and functionality and plantar pressure distribution during walking.

Outcomes for Feasibility

Recruitment

Recruitment was assessed in terms of recruitment rate and recruitment success. The recruitment rate is the ratio between the number of eligible individuals and the duration of the recruitment period (52 weeks); it is expressed as individuals per week. The challenges in recruitment were described qualitatively. Recruitment success is the ratio between the number of individuals who underwent baseline assessment and the number of eligible individuals who were contacted within the 52-weekrecruitment period.

Adherence to the Exercise Program and to the Assessments and Dropout Rate

The adherence to the foot and ankle exercise program is the percentage of participants who completed more than 80% of the 24 face-to-face sessions in 12 weeks. The dropout rate is the proportion of participants who terminated their participation in the therapeutic exercise program and dropped out of the study. The adherence to final outcomes assessment is the proportion of participants who had completed the T12 assessment.

Participant Satisfaction

The participant satisfaction with the therapeutic exercise program was evaluated by using a questionnaire at the end of the 12-week program. The items where the 5-point Likert scale was used included affirmative statements: (1) “I am satisfied with the exercise protocol”; (2) “The exercise protocol is easy to perform”; (3) “The exercise protocol is fun to perform”; (4) “The exercise protocol reached my expectations”; (5) “The exercise protocol somehow improved my walking practice”. The participants knew that their responses were anonymous, that is, the investigators do not know their identity. The score for each item ranged from 1 (strongly disagree) to 5 (absolutely agree), with the higher scores indicating greater participant satisfaction.

Outcomes of the Efficacy of the Exercise Program

Most of outcomes used to test the preliminary efficacy of the exercise program were derived from biomechanical sensors that have previously demonstrated their important clinical repercussions for individuals with DPN [23].

Toe and Hallux Isometric Muscle Strength

Toe and hallux isometric muscle strength was measured according to the method of Mickle et al. (2009) [32] wherein a pressure platform (emed q-100, Novel, Munich, Germany) was used. The subjects were asked to stand and push down on the platform two times and as hard as possible with their hallux and toes, which prevents excessive body sway. The maximum force under the hallux and toes normalized by bodyweight (BW) were the outcomes for this measurement.

Daily Physical Activity Level (Number of Steps)

The level of daily physical activity was inferred from the number of steps taken for six continuous days as determined by using a 3D accelerometer (Power Walker-610, Yamax, Japan). This equipment measures the total number of steps and the distance covered, and it has been previously validated with older people and individuals with DPN [33,34].

Self-Selected and Fast Gait Speeds

In our gait lab, the participants first walked barefoot on a 10-meter track at a comfortable pace to determine their self-selected gait speed and then as fast as possible on the same track to determine their fast gait speed. For both speeds, two trials were conducted, and their average speed was calculated and used for analysis. Two photocells (CEFISE, Speed Test Fit Model, Nova Odessa, Brazil) located in the middle (at the 6 m mark) of the 10-meter walking track were used to measure the walking time and to calculate the gait speed. Gait speed is of great clinical value, as it is closely related to mortality; White et al. (2013) [35] have shown that older adults, as our participants, with fast decline in gaits peed had a 90% greater risk of mortality than those with slow decline over time. Thus, even with a basic biomechanical sensor such as photoelectric cells, the outcome gait speed can be of paramount importance for monitoring the health status of DPN individuals.

Plantar Pressure during Gait

A 700×403 mm pressure platform (emed q-100) with 6080 sensors (4 sensors/cm2) that collects data at 100 Hz was used to assess the plantar pressure distribution during barefoot walking. The participants walked three times barefoot over the platform at a self-selected gait speed. A foot mask with five regions of interest (ROI) (rearfoot, midfoot, forefoot, hallux and toes) was applied to assess the maximum force (% Body Weight - BW),

peak pressure (kPa), contact area (cm2), contact time (ms), pressure-time integral ((kPa)·s), and force-time integral (% BW·s) per ROI. The average of the three trials was used for analysis.

Tactile Sensitivity

Tactile sensory deficits were assessed using a 10 g monofilament in four plantar areas (plantar surface of the hallux and heads of the 1st, 3rd, and 5th metatarsals) in both feet, which were tested in randomized order [36,37]. The number of areas where the participant did not feel the pressure applied by the monofilament was recorded [38]. This method demonstrated a moderate reliability by the intraclass correlations between assessors (ICC(2,3)>0.73) [39].The tactile sensory threshold was assessed on the dorsal surface of the hallux by using six monofilaments with different degrees of stiffness. Each sensitivity threshold value was transformed into a specific numerical value: 0.05 g, 0.2 g, 2 g, 4 g, 10 g, 300 g, and no sensitivity were represented by1, 2, 3, 4, 5, 6, and 7, respectively. Both feet were evaluated. Monofilaments were applied in order of increasing stiffness. A positive threshold was recorded when the subject could feel the pressure applied by the filament [40]. This method demonstrated a moderate reliability by the intraclass correlations between assessors (ICC(2,3)>0.55) [39].

Passive Ankle Range of Motion

The passive ankle joint range of motion was evaluated bilaterally by using an ankle electrogoniometer (model SG110/A, Biometrics, Gwent, UK). A forward motion of the lower segment was regarded as flexion (negative values) and a backward motion was regarded as extension (positive values) [41]. After setting the zero angle (90 degrees of the

ankle joint flexion angle while lying),the assessor measured the passive range of motion of the participant in supine position. This method demonstrated a moderate, good and poor reliability by the intraclass correlations between assessors(ICC(2,3)>0.60 (flexion right foot); 0.84 (flexion left foot); 0.00 (extension right foot); 0.41 (extension left foot), respectively [39].

DPN Symptoms

The participants answered the Brazilian version of the Michigan Neuropathy Screening Instrument (MNSI) [42]. This questionnaire includes 15 items on the sensitivity of the legs and feet. The confirmatory answers for questions 1, 2, 3, 5, 6, 8, 9, 11, 12, 14 and 15 received a score of 1. A negative answer for questions 7 and 13 also scored 1. Question 4 measures circulatory deficit and question 10 measures general asthenia, and both were not included in the scoring. The total scores therefore ranged from 0 to 13 (13 representing the worst DPN condition).

Quality of Life

The participants answered the EuroQoL 5-dimensions (EQ-5D) questionnaire [43], which is a generic instrument used to measure the health-related quality of life and allows an assessor to generate an index representing an individual's health status. It is based on a classification system that describes health in five dimensions: mobility, personal care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D associates a value between−0.59 and 1.00, which represents the health status of an individual (1.00 being the best possible health condition).

Foot Health and Functionality

This study used the Brazilian-Portuguese version of a foot health status questionnaire (FHSQ-BR) translated and validated by Ferreira et al. (2008) [44]. Section I evaluates foot health in four domains: foot pain, foot function, footwear, and general foot health. Section II consists of questions with answer options written in affirmative sentences, along with their corresponding numerical value. Section III collects general demographic data. This study used the scores from Section I only because Section II refers to general health. Each domain was scored from 0 to 100 points, wherein 100 represents the best possible condition and 0 represents the worst condition. The scores were calculated using FHSQ software, version 1.03 (Care Quest, Australia).

Statistical Analysis

According to some authors, the analysis in any type of a pilot or feasibility study should be primarily descriptive [45] and may focus on estimating the confidence interval [46]. Pilot and feasibility studies are treated as independent studies, and whether they should be analyzed using hypothesis testing is controversial [47,48]. Given that it is inappropriate to assign undue significance to the results of hypothesis testing as no formal calculation of power was performed in these studies, such studies should not be analyzed using hypothesis testing. When a sample size is small, it is likely that an imbalance exists in the pre-randomization covariates, which would require adjustments to the analysis. In addition, the confidence interval is likely inaccurate, even when significant differences exist. The results of any hypothesis testing should therefore be treated as preliminary and must be interpreted with caution, and within-group analyses should therefore be favored. We therefore focused on intra-group comparisons (paired t tests) and reported the mean or

median differences and 95%confidence interval. Baseline assessment outcomes between study groups were compared by Mann–Whitney tests when data were non-normally distributed (Shapiro–Wilk test p>0.05) and by independent t-tests when data were normally distributed. Comparisons between assessments (baseline and T12) within each group were done using paired t-tests for toe and hallux strength and for all plantar pressure variables. In dealing with bilateral data from two legs, conceptual problems led to the recommendation against pooling of data in most situations in foot and ankle research [49]. According to Menz (2004) [49],and given that DPN is a symmetrical disease [1], we chose one side for analysis by randomly selecting a single foot (i.e., the right foot) for biomechanical analysis. For the clinical data, given their non-normal distribution, the following variables were compared between assessments and within groups using Wilcoxon tests: tactile sensitivity and threshold, FHSQ function and shoes and health domains. The remaining variables (age, body mass, height, body mass index, DPN severity fuzzy score, ankle range of motion (ROM), MNSI, FHSQ pain, EQ-5D,gait speeds and number of steps) were compared between assessments within groups using paired t-tests. The adopted alpha was 0.05.

Results

The groups did not significantly differ in any of the outcomes at the baseline assessment (Table 3).

Table 3 - Baseline participants' characteristics from the control and intervention groups.

Outcomes	Control Group (n = 15)	Intervention Group (n = 15)	p-value
Age (years)	62.5 (6.8)	64.6 (6.9)	0.220 [1]
Body mass (kg)	78.4 (17.5)	78.6 (20.0)	0.485 [1]
Height (m)	1.6 (0.1)	1.7 (0.1)	0.178 [1]
Body Mass Index (kg/m^2)	28.9 (5.3)	28.1 (7.0)	0.364 [1]
Type of diabetes	DM1= 0% DM2= 100 %	DM1=33.3% DM2=66.7%	0.063 [3]
Sex	M-7 F-9	M-9 F-5	1.000 [3]
DPN severity (Fuzzy Score)	4.4 (2.2)	5.6 (3.0)	0.105 [1]
MNSI (score)	6.1 (2.2)	6.3 (3.8)	0.816 [1]
Tactile sensitivity (number of areas)	2.4 (2.4)	3.3 (2.9)	0.445 [2]
Tactile sensitivity threshold right	3.0 (2–7)[¶]	3.0 (2–7) [¶]	1.000 [2]
Tactile sensitivity threshold left	3.0 (2–7) [¶]	3.0 (2–7) [¶]	1.000 [2]
Self-selected gait speed (m/s)	1.0 (0.2)	1.1 (0.4)	0.478 [1]
Fast gait speed (m/s)	1.5 (0.4)	1.6 (0.3)	0.694 [1]
Daily activity level (number of steps)	8134.6 (5055.2)	7810.8 (4268.3)	0.844 [1]
FHSQ pain (score)	58.7 (24.6)	54.2 (35.8)	0.651 [1]
FHSQ function (score)	70.4 (25.8)	72.9 (30.6)	0.600 [2]
FHSQ shoes (score)	39.4 (33.7)	48.9 (41.8)	0.501 [2]
FHSQ health (score)	37.5 (31.2)	32.5 (23.0)	1.000 [2]
EQ-5D (score)	0.4 (0.2)	0.4 (0.2)	0.581 [1]
Ankle dorsiflexion ROM right (◦)	19.0 (5.8)	16.6 (7.7)	0.555 [1]
Ankle dorsiflexion ROM left (◦)	21.7 (7.5)	17.3 (6.2)	0.215 [1]
Ankle plantarflexion ROM right (◦)	25.7 (8.4)	28.67 (10.0)	0.331 [1]
Ankle plantarflexion ROM left (◦)	30.5 (8.7)	31.9 (9.8)	0.883 [1]

Data are presented as mean (SD) or as n or %. ¶ Mode (minimum–maximum range). 1 t-test; 2 Mann–Whitney test; 3 Chi-square test. MNSI- Michigan neuropathy Screening Instrument questionnaire.

Feasibility Outcomes

Recruitment

In the first year of recruitment (52 weeks) by using digital advertisements and outpatient clinic databases and via direct contact with people with diabetes through the health campaigns at the university campus, we identified 1549 people with diabetes whose ages fell within the age range set for this study. These individuals were further screened for eligibility by telephone interview (Figure 3, part 1). A total of 144 (9.3%) people were initially found to be eligible for the subsequent laboratory screening based on the inclusion and exclusion criteria, and were willing to participate (Figure 3, part 2). Based on the laboratory screening results, 99 of these 144 potential participants failed to satisfy the eligibility criteria, mainly the requirement for having a moderate or severe DPN. The 45 other participants (31%) were confirmed eligible; thus, the recruitment rate was 0.9 participants/week.

Of the 45 eligible individuals, 30 were included in the baseline assessment (16 males and 14 females), resulting in a recruitment success rate of 66%; for the 15 other individuals, some could not attend the baseline assessment within the period of this feasibility study due to their unavailability, whereas the others provided no reason. The number of participants who were scheduled for the baseline assessment out of the total number of individuals screened within a fixed period (52 weeks) indicated a “successful recruitment,” and the figure is a better predictor of the number of individuals that must be recruited to reach the desired number of included subjects. Based on the 66% recruitment success rate,

for a full-blown RCT, 119 individuals must be screened in order to reach the desired number of included participants, which is 77.

Adherence to the exercise program and to the assessments and dropout rate

Out of the 15 intervention group participants, 3 (20%) failed to complete at least 80% of the 24 supervised training sessions, that is, the mean adherence was 80%. None of the 30 participants withdrew from this study (0% dropout), and the adherence to the final assessments at T12 was 100%.

The reported reasons for not joining a supervised training session included a conflicting schedule for hospital-related appointments and the unavailability of a family member who will take the participant to the supervised session. Whenever a participant missed a scheduled session, we rescheduled the session within the same week.

Participant satisfaction

Overall, the average score for the participants' satisfaction with the therapeutic foot and ankle exercise program was 4.6 (SD 0.70) on a 5-point Likert scale (Figure 4).

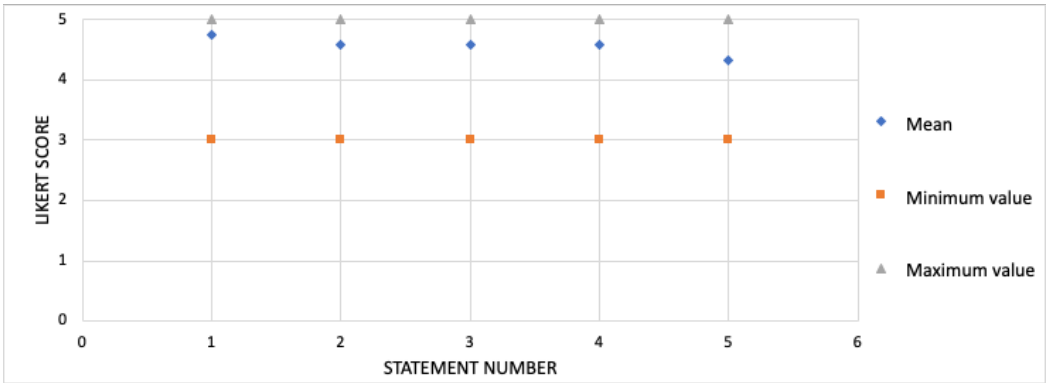


Figure 4 - Participant satisfaction with the exercise protocol (n = 15). Scores are shown on a 5-point Likert scale. Data are shown as mean, maximum and minimum. Statement number: (1) "I am satisfied with the exercise protocol"; (2) "The exercise protocol is easy to perform"; (3) "The exercise protocol is fun to perform"; (4) "The exercise protocol met my expectations"; (5) "The exercise protocol somehow improved my walking practice".

Program Efficacy Outcomes

The MNSI score significantly decreased from the baseline to T12 in both the intervention ($p = 0.049$) and control ($p = 0.023$) groups. Moreover, the FHSQ foot pain score improved in both the intervention ($p = 0.046$) and control ($p = 0.033$) groups (Table 4). In the intervention group, the maximum toe strength significantly increased from the baseline to T12 ($p = 0.001$), a pattern not observed in the control group ($p = 0.668$) (Table 5).

In the intervention group, the contact time for the toes after 12 weeks of exercise training increased significantly compared with the baseline ($p = 0.025$, Table 6). Additionally, the forefoot peak pressure ($p = 0.001$) and the pressure-time integral ($p = 0.006$) significantly increased in the intervention group. In the control group, the midfoot pressure-time integral significantly decreased ($p = 0.047$), the maximum normalized heel force significantly increased ($p = 0.049$), and the heel peak pressure significantly increased ($p =$

0.049) at T12 compared with the baseline. No other significant time effects were observed in the study groups.

Table 4 - Clinical outcomes and foot health and functionality of each group (control and intervention).

Outcomes	Control Group		Control Effect		Intervention Group		Intervention Effect	
	Baseline (n = 15)	T12 (n = 15)	p value	Difference (CI 95%)	Baseline (n = 15)	T12 (n = 15)	p value	Difference (CI 95%)
MNSI questionnaire (mean Score)[1]	6.1 (2.0)	4.9 (3.1)	**0.023***	1.2 (0.1 to 2.1)	6.3 (3.8)	5.2 (3.1)	**0.049***	1.1 (−0.0 to 2.3)
Tactile sensitivity (number of areas)[2]	2.4 (2.4)	2.7 (2.7)	0.559	−0.3 (−1.5 to 0.9)	3.2 (2.9)	3.0 (2.6)	0.739	0.2 (−1.0 to 1.4)
Tactile sensitivity threshold Right[2]	3.0 (2.0–7.0) |	3.0 (1.0–7.0) |	0.957	-	3.0 (2.0–7.0) |	3.0 (2.0–7.0) |	1.000	-
Tactile sensitivity threshold Left [2]	3.0 (2.0–7.0) |	3.0 (1.0–7.0) |	1.000	-	3.0 (2.0–7.0) |	3.0 (2.0–7.0) |	1.000	-
EQ-5D questionnaire (Score)[1]	0.36 (0.1)	0.40 (0.1)	0.352	-0.04 (-0.14 to 0.06)	0.36 (0.1)	0.41 (0.2)	0.161	−0.05(−0.10 to 0.02)
FHSQ—foot pain (Score)[1]	58.7 (24.6)	66.3 (23.0)	**0.033***	−7.6 (−14.5 to −0.7)	54.2 (35.7)	68.9 (23.6)	**0.046***	−14.7 (−29.9 to 0.5)
FHSQ—foot function (Score)[2]	70.4 (25.8)	69.7 (23.2)	0.888	0.7 (−9.7 to 11.1)	72.9 (30.5)	79.2 (26.1)	0.181	−6.3 (−15.8 to 3.3)
FHSQ—shoes (Score)[2]	39.4 (33.6)	40.1 (34.8)	0.902	−0.7 (−12.2 to 10.8)	48.9 (41.1)	42.2 (39.2)	0.417	6.7 (−10.4 to 23.8)
FHSQ—foot health (Score)[2]	37.5 (31.2)	46.0 (26.0)	0.089	−8.5 (−18.5 to 1.5)	32.5 (23.0)	44.2 (21.4)	0.097	−11.7 (−25.8 to 2.4)

Data are presented as mean (SD) and mean differences with 95% confidence intervals (CI). [1] p values related to paired t-tests, [2] p values related to Wilxocon matched pairs. * and bold p values represents difference between baseline and T12 within the group. | represents mode (minimum–maximum). MNSI—Michigan Neuropathy Screening Instrument, FHSQ—foot health status questionnaire.

Table 5 - Functional outcomes of each group (control and intervention).

Outcomes	Control Group		Control Effect		Intervention Group		Intervention Effect	
	Baseline (n = 15)	T12 (n = 15)	p value	Mean Difference (CI 95%)	Baseline (n = 15)	T12 (n = 15)	p value	Mean Difference (CI 95%)
Ankle ROM dorsiflexion right (°)	19.0 (5.7)	16.7 (6.1)	0.214	2.3 (−1.5 to 6.0)	16.6 (7.1)	19.3 (6.1)	0.137	−2.7 (−6.4 to 0.98)
Ankle ROM dorsiflexion left (°)	21.7 (7.5)	18.5 (5.0)	0.113	3.2 (−0.8 to 7.2)	17.3 (6.2)	18.0 (4.8)	0.637	−0.7 (−3.6 to 2.3)
Ankle ROM plantarflexion right (°)	25.7 (8.4)	29.9 (7.4)	0.019	−4.2 (−7.7 to −0.8)	28.7 (9.9)	28.8 (7.3)	0.947	−0.1 (−4.4 to 4.1)
Ankle ROM plantarflexion left (°)	30.5 (8.7)	30.9 (13.4)	0.701	−0.4 (−3.03 to 2.10)	31.9 (9.7)	32.0 (7.5)	0.951	−0.1 (−4.7 to 4.4)
Self-selected gait speed (m/s)	1.03 (0.23)	1.02 (0.31)	0.986	0.01 (−0.16 to 0.16)	1.14 (0.36)	1.06 (0.16)	0.342	0.08 (-0.10 to 0.25)
Fast gait speed (m/s)	1.50 (0.38)	1.44 (0.35)	0.444	0.06 (−0.40 to 0.23)	1.56 (0.33)	1.70 (0.44)	0.142	−0.14 (−0.30 to 0.05)
Number of steps for 6 days	8135 (5055)	7280 (3393)	0.367	854 (−1110 to 2819)	7811 (4268)	9137 (4964)	0.337	−1326 (−4189 to 1536)
Maximum force—hallux (%BW)	10.8 (3.8)	9.6 (4.3)	0.368	1.2 (−1.5 to 3.9)	11.8 (5.9)	12.1 (6.0)	0.727	−0.3 (−2.0 to 1.4)
Maximum force—toes (%BW)	7.5 (4.3)	7.2 (4.0)	0.668	0.3 (−1.2 to 1.8)	6.4 (2.8)	8.9 (4.0)	**0.001***	−2.5 (−3.8 to 1.2)
Maximum force—all toes (%BW)	11.3 (3.4)	10.8 (4.1)	0.676	0.5 (−2.1 to 3.1)	12.0 (5.9)	13.2 (4.8)	0.161	−1.2 (−3.1 to 0.6)

Data are presented as mean (SD) and mean differences with 95% confidence intervals (CI). p values related to paired t-tests. * and bold p values represents difference between baseline and T12 within the group. BW—body weight; ROM—range of motion.

Table 6 - Plantar pressure distribution variables during gait of each group (control and intervention).

Plantar Pressure During Gait									
Region of Interest	**Parameters**	**Control group**		**Control Effect**		**Intervention Group**		**Intervention Effect**	
		Baseline (n = 15)	**T12 (n = 15)**	**p value**	**Difference (CI 95%)**	**Baseline (n = 15)**	**T12 (n = 15)**	**p value**	**Difference (CI 95%)**
Toes	CA [cm²]	9.3 (4.0)	9.1 (3.8)	0.675	0.2 (−0.9 to 1.3)	7.4 (3.2)	8.1 (3.0)	0.291	−0.7 (−2.2 to 0.7)
	MF [%BW]	6.3 (3.7)	6.7 (4.1)	0.523	−0.4 (−1.9 to 0.9)	6.3 (5.7)	6.0 (3.8)	0.751	0.3 (−1.6 to 2.1)
	PP [kPa]	174 (111)	174 (103)	0.994	0.1 (−37.1 to 37.4)	268 (172)	244 (136)	0.494	24.0 (−50.1 to 98.2)
	CT [ms]	562 (162)	501 (124)	0.060	61.2 (8.9 to 113.6)	519 (119)	578 (58)	**0.025***	−59.2 (−122.4 to 3.9)
	PTI [(kPa)*s]	58.0 (44.4)	50.8 (32.8)	0.279	7.2 (−6.7 to 21.0)	64.3 (47.0)	73.7 (35.2)	0.233	−9.4 (−25.8 to 6.9)
	FTI [%BW*s]	1.9 (1.4)	1.8 (1.2)	0.541	0.1 (−0.4 to 0.7)	1.5 (1.1)	1.7 (0.9)	0.346	−0.2 (−0.6 to 0.2)
Hallux	CA [cm²]	9.5 (2.3)	9.7 (2.2)	0.655	−0.2 (−1.2 to 0.8)	10.0 (2.2)	10.9 (2.2)	0.073	−0.9 (−1.6 to 0.08)
	MF [%BW]	11.9 (7.4)	12.2 (5.8)	0.789	−0.3 (−2.6 to 1.9)	16.9 (9.4)	15.1 (8.7)	0.511	1.8 (−2.3 to 4.3)
	PP [kPa]	297 (246)	291 (232)	0.859	6.1 (−66.8 to 7.9)	415 (274)	424 (273)	0.766	−9.0 (−118.7 to 89.8)
	CT [ms]	512 (201)	493 (182)	0.587	19.1 (−55.5 to 93.7)	526 (141)	571 (151)	0.371	−45.2 (−159.6 to 64.6)
	PTI [(kPa)*s]	90.8 (92.1)	86.2 (91.2)	0.624	4.6 (−15.3 to 24.6)	112.5 (96.3)	122.5 (83.0)	0.456	−10.0 (−60.6 to 29.1)
	FTI [%BW*s]	3.5 (3.1)	3.4 (2.8)	0.786	0.1 (−0.7 to 0.9)	3.8 (2.5)	4.1 (2.3)	0.331	−0.3 (−1.5 to 0.5)
Forefoot	CA [cm²]	52.9 (9.9)	53.5 (10.2)	0.302	−0.6 (−1.7 to 0.6)	48.6 (7.3)	49.0 (7.0)	0.485	−0.3 (−1.4 to 0.7)
	MF [%BW]	103.3 (7.3)	106.7 (9.5)	0.070	−3.4 (−7.2 to 0.4)	98.2 (11.6)	102.2 (6.3)	0.194	−4.0 (−10.2 to 2.3)
	PP [kPa]	709 (202)	771 (254)	0.090	−62.5 (−136.6 to 11.6)	790 (273)	959 (244)	**0.001***	−169.1 (−225.2 to −82.7)
	CT [ms]	736 (92)	704 (110)	0.134	31.3 (−11.2 to 73.7)	698 (131)	711 (94)	0.589	−12.8 (−63.1 to 37.5)
	PTI [(kPa)*s]	255.2 (74.2)	262.8 (104.8)	0.652	−7.6 (−43.6 to 28.3)	302.1 (146.3)	365.4 (160.0)	**0.006***	−63.3 (−105.5 to −21.2)
	FTI [%BW*s]	41.6 (6.2)	40.7 (6.4)	0.482	0.9 (−1.8 to 3.7)	37.0 (7.9)	40.2 (6.9)	0.056	−3.2 (−6.5 to 1.1)
Midfoot	CA [cm²]	30.3 (8.2)	30.2 (8.1)	0.987	−0.0 (−0.9 to 0.8)	26.7 (9.3)	27.4 (9.9)	0.404	−0.7 (−2.5 to 1.1)
	MF [%BW]	27.0 (8.2)	26.1 (7.5)	0.393	0.9 (−1.4 to 3.3)	25.1 (15.2)	26.8 (17.0)	0.269	−1.7 (−4.9 to 1.5)
	PP [kPa]	167 (63)	166 (54)	0.863	0.9 (−10.9 to 12.9)	233 (155)	291 (229)	0.231	−57.6 (−156.8 to 41.7)
	CT [ms]	577 (105)	561 (122)	0.448	16.1 (−28.5 to 60.5)	594 (100)	569 (111)	0.464	25.2 (−47.3 to 97.5)
	PTI [(kPa)*s]	68.6 (28.5)	62.2 (24.8)	**0.047***	6.4 (0.1 to 12.7)	80.4 (56.8)	90.7 (53.4)	0.430	−10.3 (−37.8 to 17.2)
	FTI [%BW*s]	9.3 (3.2)	8.2 (2.7)	0.052	1.1 (−0.0 to 2.2)	8.9 (6.9)	9.0 (6.0)	0.773	−0.1 (−1.6 to 1.2)
Heel	CA [cm²]	34.6 (5.1)	35.0 (4.5)	0.248	−0.4 (−1.1 to 0.3)	34.0 (5.1)	33.8 (5.4)	0.684	0.2 (−0.7 to 1.0)
	MF [%BW]	63.1 (10.7)	68.5 (8.7)	**0.049***	−5.4 (−11.2 to 0.3)	71.0 (19.3)	66.7 (17.2)	0.271	4.3 (−3.8 to 12.4)
	PP [kPa]	392 (193)	459 (261)	**0.049***	−66.7 (−133.2 to −0.3)	441 (165)	455 (146)	0.551	−14.2 (−64.7 to 36.2)
	CT [ms]	513 (83)	500 (137)	0.640	12.6 (−44.5 to 69.7)	467 (194)	482 (105)	0.704	−15.4 (−101.7 to 70.9)
	PTI [(kPa)*s]	103.7 (40.9)	118.5 (78.6)	0.294	−14.8 (−44.2 to 14.6)	110.3 (39.0)	111.7 (41.4)	0.828	−1.4(−14.8 to 12.1)
	FTI [%BW*s]	17.5 (3.9)	18.6 (4.3)	0.362	−1.1 (−3.4 to 1.3)	19.1 (5.6)	17.6 (5.9)	0.288	1.5 (−1.4 to 4.4)

Data are presented as mean (SD) and mean differences with 95% confidence intervals (CI). * and bold p values represents difference between baseline and T12 within the group. p values related to paired t-test. CA—contact area; MF—maximum normalized force; PP—peak pressure; CT—contact time; PTI—peak-time integral; FTI—force-time integral.

Discussion

Researchers have recognized that research on the efficacy of interventions can be accelerated if careful feasibility and pilot studies assessing the preliminary efficacy of certain interventions are conducted prior to conducting large RCTs [50]. We therefore report on the feasibility and preliminary efficacy of an ongoing RCT on the effect of a therapeutic foot-ankle exercise program for the biomechanical and clinical outcomes in people with DPN. The results confirmed that this study is feasible based on the 12-week adherence to the assessments and to the intervention protocol at 100% and 80%, respectively; in addition, the participants in the intervention group reported a high satisfaction rate toward the intervention (mean score of 4.57 out of 5). However, the recruitment rate was low at 0.9 patients/week compared with the 10 patients/week rate that was possible considering the availability of a laboratory. This low recruitment was mainly due to the rigorous eligibility criteria, and new strategies for improving recruitment must be employed to reduce the recruitment time for RCT completion. As regards the preliminary efficacy, among all the functional, biomechanical and clinical outcomes, a few were significantly improved in the intervention group when the baseline and T12 were compared; these outcomes were toe strength, DPN symptoms and specific plantar pressure parameters. This finding may help in the study design or in the analysis of the efficacy of foot-ankle exercise programs in large RCTs.

Feasibility

The recruitment rate was low (0.9 patients/week) mainly because many patients did not meet the eligibility criterion "severe and moderate DPN" according to their fuzzy scores. Thus, new recruitment strategies were developed to improve the recruitment

rate and to guarantee the success of the RCT recruitment. A partnership with the largest hospital in Latin America (Hospital das Clínicas da Faculdade de Medicina da USP) was entered into, providing us access to a database of approximately 4000 people with diabetes whom we could recruit for our RCT. Based on the recruitment success rate of 66%, 119 initially eligible subjects are needed to include 78 participants for the RCT, which is achievable using the new database. Although 66% is a moderate rate, the achieved recruitment success rate is compatible with several other operational factors that influence the flow of assessments and intervention; such factors include the period the biomechanics laboratory facilities were operational, the time spent on each biomechanical assessment, and the strategy employed to avoid scheduling follow-up assessments and baseline assessments within the same week.

The participants were satisfied with the exercise therapeutic program as shown by the mean score of 4.57 based on a 5-point scale. In general, foot-ankle exercise programs are well-accepted [51]. This outcome seems directly related to adherence; an 80% adherence can be considered high and it falls within the range that indicates feasibility [52]. Moreover, the high satisfaction with the training program was apparently reflected in the 0% dropout from the 12-week study, suggesting that the chosen exercise protocol is appropriate for further investigation in the RCT. A previous trial [53] did not observe any effect of a 24-week intervention that combined lower limb strengthening and gait and balance training, probably due to lack of motivation and a high dropout rate (42%), which may have been influenced by the lack of an exercise progression that was not tailored according to the progression made by the participant, different to what we implemented in the present RCT.

Program efficacy

The signs and symptoms of DPN had changed after the intervention (MNSI score). The intervention group reported fewer symptoms after the intervention compared with their baseline condition. In the control group, the MNSI score slightly improved after 12 weeks. There are some possible explanations for the improvement of symptoms in both groups. First, there could be a placebo effect resulting from the interaction of the physiotherapist with the participants, which may bring about a positive response independent of any specific treatment [54]. Second, the usual care orientations given by the physiotherapist to both groups would lead to changes in the participant´s health care habits that could result in a better control of diabetes and thus of the DPN symptoms. Lastly, within 12 weeks, there could be a natural variation in the DPN symptoms not related to any intervention effect [10].

After 12 weeks of the foot-ankle exercises, only the toe strength of all the functional outcomes significantly increased with a mean of 1.6% BW, representing a 27% increase in isometric strength. The exercise protocol focused on strengthening several flexor muscles of the interphalangeal and metatarsalphalangeal joints, including the flexor digitorum brevis and longus, flexor digiti minimi brevis, quadratus plantae, lumbricals, plantar and dorsal interossei muscles of the toes. We presume that this result is directly related to the foot-ankle exercise program. Our result was slightly lower than that reported by Mickle et al. (2016) wherein the increase in toe flexor strength in older adults after 12 weeks of exercise was 36% [55]. Another study showed that exercises promoting the foot muscle strength in young runners significantly increased the toe-flexor muscle strength by 16% after 5 weeks of exercise and by 27% after 10

weeks [56]. Unfortunately, in clinical contexts, a certain degree of unwillingness to accept the prescription of foot-ankle exercises in DPN patients has been observed because it is widely believed that muscle weakness and joint limitations are irreversible in DPN. Our results suggest that this is not the case, consistent with other findings showing that, despite the low level of evidence [23], foot-ankle exercises improve the muscle function and joint mobility in people with DPN [10,12−15,21,22]. A larger RCT should confirm whether this finding establishes a foundation for the implementation of physical therapy intervention for neuromuscular diseases, including DPN.

The intervention did not yield many changes in plantar pressure distribution after 12 weeks: the toe contact time was prolonged and the forefoot peak pressure and pressure-time integral were increased. The former suggests that the intervention might have increased the contribution of the toes during a foot rollover, mainly during body propulsion, leading to a prolonged contact and higher/prolonged pressures applied to the ground. This finding is important as the contribution of the toes is reduced during locomotor tasks in patients with DPN [6], and this phenomenon is usually attributed to restrictions in foot-ankle joint mobility [57,58] and to intrinsic muscle weakness [59].

The increased forefoot pressures may have been due to the changing role of the forefoot in gait propulsion given that the intervention focused on improving the intrinsic foot muscle strength and function. These findings suggest that while attention must be devoted in keeping plantar pressures below the risk threshold for ulceration in people with DPN [60], this should not be the sole aim of physiotherapeutic interventions, as the results showed that the foot-ankle exercise programs demonstrated several beneficial effects in the investigated population. Within 12 weeks, the control group showed an

increased mean force and peak pressure in the heel, worsening the distribution of pressure over the foot and probably the foot rollover over time in the absence of any specific intervention. The strengthening exercises and walk training demonstrated a preliminary efficacy in improving toe function as reflected in foot rollover changes, which we believe is a promising path toward maintaining the residual biomechanical capability of propelling the body forward during walking; however, a larger RCT should provide more sound evidence to support these preliminary effects.

The biomechanical sensor−pressure plate that was used to measure the effect of the intervention on foot isometric strength and plantar pressure distribution during gait has shown its potential to identify changes over time in the studied population and could be an indicator of great value of the improvement of DPN due to a therapeutic foot-ankle exercise program. Data from pressure sensors were the primary outcome in another trial focusing on the effectiveness of foot-ankle exercises in individuals with DPN, and the authors observed a change in the foot rollover towards a more physiological process, supported by the improved plantar pressure distribution measured [10]. Although data derived from pressure plates have been recognized as an important parameter to determine the onset of diabetic foot ulcers, the information from plantar pressure sensors is not used on a regular basis in clinical settings to diagnose and manage impairments associated with various musculoskeletal, integumentary, and neurological disorders [61], such as DPN. Our results showed that pressure data could potentially contribute to tailoring therapeutic strategies for people with diabetes and DPN and monitoring the short- and long-term effects of exercises intervention on gait biomechanics.

Although wearable sensors (accelerometers) similar to those selected to assess the level of physical activity in our study have long been recognized to be one of the most effective ways to objectively measure physical activity, they have been widely used in controlled conditions [62]. In our feasibility study, we used this sensor in real life, aiming to quantify the physical activity by counting the number of steps during a regular week of the participant. We believe that this measure is a strong indicator of physical heath, especially in DPN individuals. For instance, average daily steps count in people with diabetes and DPN was found to be inversely related to intermuscular adipose tissue volume [63].

The strengths of this study include the rigorous RCT methodology, that is, a supervised physiotherapeutic approach combined with remote intervention, which we think has increased the participant satisfaction and adherence and contributed to the low dropout rate. For these reasons, the intervention was considered feasible and no further amendments will be made in the trial registry and protocol. We are the first to evaluate the musculoskeletal outcomes in people with DPN through a specialized foot training protocol that focuses on improving the strength and functionality of the foot-ankle complex. A limitation of this study has to do with recruitment. Despite the high prevalence of diabetes in the Brazilian population [64], the recruitment rate for this RCT was low due to the rather strict eligibility criteria. In addition, the two study groups did not experience the same degree of on-site interaction; the control participants had an interaction with the physiotherapist and received feedback only during the baseline and 12-week assessments, whereas the intervention group participants had weekly interactions with the physiotherapist. This difference might have led to a greater degree

of dissatisfaction toward the study, and it may result in a greater dropout rate among control subjects in a larger trial. Furthermore, other usual parameters related to the clinical control of diabetes, such as hemoglobin glycade and glycaemia, were not assessed and might have influenced the investigated functional and clinical outcomes. Other aspects of the training, such as nocebo or placebo effects, might also be relevant factors that may have obscured the genuine effects of the training program.

Conclusion

We conclude that this study is feasible based on moderate recruitment and on the adherent and satisfied study population; thus, no further amendments in the protocol and trial are needed. The foot-ankle exercise program showed some positive preliminary clinical, functional and biomechanical effects over time, such as an improvement in strength and mobility of people with DPN, which justifies the further assessment of outcomes in a larger RCT.

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Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical Statement: This study was registered at ClinicalTrials.gov as NCT02790931 (June 6, 2016) under the name “Effects of foot muscle strengthening in daily activity in diabetic neuropathic patients”, and approved by the Ethics Committee in Research of the School of Medicine of the University of Sao Paulo (24/03/2016, Protocol 1.464.870).

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CAPÍTULO 4 - RESULTADOS DO ENSAIO CLÍNICO RANDOMIZADO

4.1 Foot-ankle therapeutic exercise program can improve gait speed in people with diabetic neuropathy: a randomized controlled trial

Abstract

This study sought to determine whether a foot-ankle therapeutic exercise program can improve daily physical activity (i.e. number of steps) and fast and self-selected gait speed in people with diabetic peripheral neuropathy (DPN). In this single-blind randomized controlled trial and intention-to-treat analysis**,** 78 volunteers with DPN were allocated into a control group, which received usual care, and an intervention group (IG), which received usual care plus a 12-week foot-ankle exercise program. The adherence at 12 weeks rate in the IG was 92.3% (36 participants) and the dropout was 5.1% in the control group (2 participants). The number of steps and self-selected gait speed did not change significantly in either group, although a 1,365-step difference between groups were observed at 1-year followup. The 12-week foot-ankle therapeutic exercises improved significantly fast-gait speed (primary outcome), ankle range of motion, and vibration perception (secondary outcomes) compared with usual-care at 12 weeks**.** At 24 weeks, the IG showed better quality of life than controls. At 1-year, fast-gait speed and vibration perception remained higher in the IG versus controls. Overall, the findings suggest that program may be a complementary treatment strategy for improving musculoskeletal and functional deficits related to DPN.

MeSH Keywords: Physiotherapy, Exercise, Foot, Diabetic neuropathy, Diabetic foot, Clinical trial

Trial registration

ClinicalTrials.gov NCT02790931 (June 6, 2016) under the name “Effects of foot muscle strengthening in daily activity in diabetic neuropathic patients”, https://clinicaltrials.gov/ct2/show/NCT02790931

Introduction

Diabetic peripheral neuropathy (DPN), an important risk factor for amputation and reduced physical mobility, occurs in more than 50% of people with diabetes [1]. DPN is associated with decreased muscle strength and physical activity level, as measured by steps per day [2] and reduced gait speed [3]. Daily steps in persons with DPN (PWDPN) are inversely proportional to the amount of intramuscular adipose tissue [4], suggesting that muscle impairment is a factor underlying decreased physical activity. Other studies suggest that motor and sensory deficits [2,5] and reduced foot-ankle range of motion (ROM) [3,6] are directly related to decreased physical activity levels, as are the reduced quality of life (QoL) and decreased gait speed associated with DPN [5].

Physical functionality, a third WHO health indicator alongside mortality and morbidity, requires prioritizing rehabilitation and prevention of musculoskeletal disorders [7]. Compiled data from *Global Burden of Diseases, Injuries and Risk Factors* (1990 and 2019), considering 25 health conditions that could benefit from rehabilitation, indicated that, in terms of prevalence and years of life lived with disability, the top condition for almost 30 years has been musculoskeletal disorders [7]; one in every three

people worldwide would benefit from rehabilitation. Diabetes progression and DPN compromise musculoskeletal function, leading to limitations in everyday physical functioning. Furthermore, according to the WHO (2021), diabetes prevalence has been rising more rapidly in low- and middle-income countries, in Brazil for instance, than in high-income countries, and this unequal advance is coupled with a scarcity of studies that focus on rehabilitation in this population. Thus, there is a strong need for further investigations of rehabilitation strategies for musculoskeletal conditions worldwide, especially related to motor dysfunctions resulting from diabetes and DPN progression.

Controlled and non-controlled studies have sought to assess the effects of different exercise therapy strategies, including foot-related exercises, balance training, and weightbearing and resistance exercises, on different DPN-related outcomes [8]. These findings provided the foundation for the International Working Group on Diabetic Foot (IWGDF; 2020) rehabilitation strategy recommendations, such as foot- and mobility-targeted exercises, to mitigate risk factors for foot ulceration. However, while they showed that these exercises may improve DPN symptoms and increase ankle-joint ROM, it is still unclear whether they could improve foot-ankle muscle strength and functionality in people with a low or moderate risk of foot ulceration [8]. In addition, the evidence is still weak because the majority of randomized controlled trials (RCTs) addressing this are of low quality, present small effect sizes, and do not involve exercises that specifically target the main musculoskeletal dysfunction in PWDPN. Further, the variety of described foot-related exercises preclude definitive conclusions about their effectiveness [8].

The primary aim of this RCT was to investigate the effects of a 12-week foot-ankle therapeutic exercise program on daily physical activity level and self-selected and fast-gait speeds in PWDPN. The secondary aims were to investigate the effectiveness of this intervention at 6, 12, and 24 weeks on ankle-joint ROM, tactile and vibration sensitivity, DPN symptoms, QoL, foot health and functionality, hallux and toe muscle strength, and foot ulcer incidence at 1-year followup. Originally, all primary and secondary outcomes were planned to be assessed at 1-year followup; however, due to the COVID-19 pandemic, these aims were modified [9].

Results and discussion

Baseline assessment data are described in Table 7. In the IG, 36 participants (92.3%) completed the 12-week exercise program (Figure 6). The dropout rate at 12 weeks was 5.1% in the CG (2 participants); reasons for dropout in both groups are described in Figure 6. The dropout at 24 weeks included an additional participant in each group (2.6%). After 1 year, only one participant, in the CG, dropped out (2.6%). Absence was high for the 6-, 12- and 24-week and 1-year followup visits due to the COVID-19 pandemic (Figure 6). Therefore, mitigating strategies to improve internal and external study validity were adopted to alter the originally planned methods and statistical analysis.

Table 7 - Control and intervention group characteristics at baseline.

Variables	Intervention group (n=39) Mean (SD)	Control group (n=39) Mean (SD)	p-value	95% (CI) for mean estimated difference
Age (years)	61.5 (11.7)	60.1 (8.9)	.259	
Height (m)	1.6 (0.08)	1.6 (0.09)	.490	
Body mass (kg)	77.3 (14.0)	80.8 (16.4)	.145	

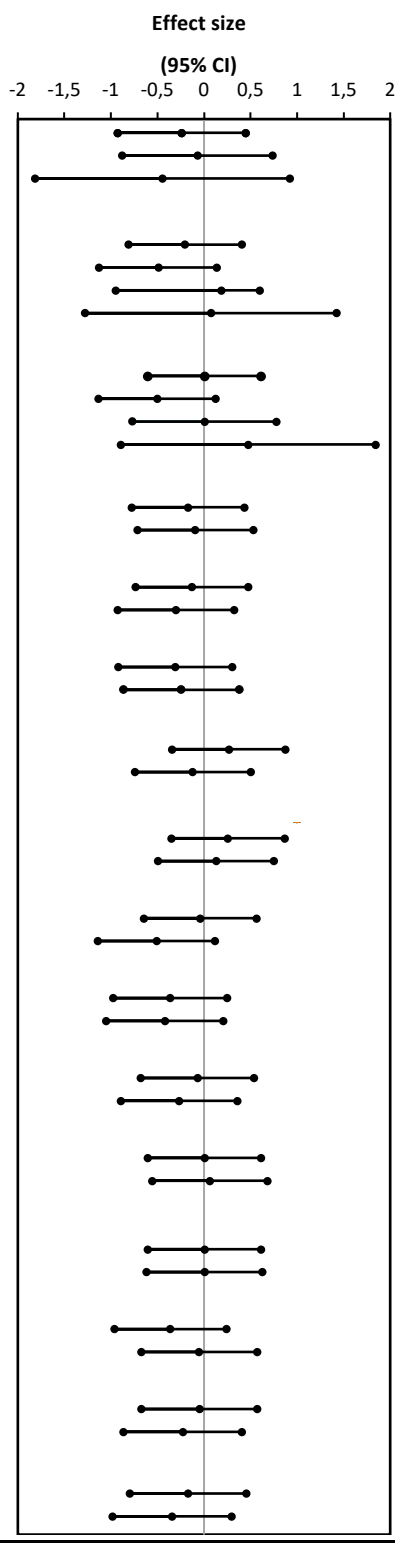
Daily physical activity (number of steps)	8.092 (4.230)	7.641 (4.087)	.599	[-1.321, 2.300]
Fast gait speed (m/s)	1.5 (0.2)	1.5 (0.3)	.881	[-0.08, 0.19]
Self-selected gait speed (m/s)	1.1 (0.2)	1.0 (0.1)	.264	[-0.04, -0.14]
MNSI (score)	6.3 (2.9)	6.3 (1.9)	.779	[-0.7, 1.2]
FHSQ – Foot pain (score)	55.8 (28.3)	55.3 (26.0)	.930	[-11.6, 12.1]
FHSQ – Foot function (score)	70.3 (26.5)	64.2 (26.9)	.320	[-0.5, 22.8]
FHSQ – Shoes (score)	49.3 (37.0)	44.4 (35.6)	.546	[-10.8, 21.4]
FHSQ – Foot health (score)	26.7 (23.3)	33.2 (27.8)	.274	[-15.2, 8.4]
Ankle plantaflexion ROM L (◦)	31.8 (7.2)	31.8 (7.9)	.989	[-4.5, 1.5]
Ankle plantaflexion ROM R (◦)	28.7 (8.8)	29.6 (8.3)	.598	[-4.9, 1.8]
Ankle dorsiflexion ROM L (◦)	18.4 (6.7)	19.3 (7.4)	.207	[-4.85, -0.01]
Ankle dorsiflexion ROM R (◦)	17.2 (6.5)	17.8 (6.2)	.589	[-4.4, 0.8]
Tactile sensitivity (number of areas)	2.2 (2.3)	2.5 (2.5)	.130	[-2.0, 0.2]
Tactile -Threshold- L	3.8 (1.4)	4.0 (1.7)	.596	[-0.9, 0.5]
Tactile -Threshold- R	3.9 (1.4)	3.5 (1.5)	.422	[-0.4, 0.9]
Vibration – L	1.6 (0.8)	1.5 (0.7)	.662	[-0.2, 0.4]
Vibration – R	1.5 (0.8)	1.4 (0.7)	.394	[-0.1, 0.6]
Quality of life (score)	0.59 (0.1)	0.59 (0.2)	.905	[-0.05, 0.10]
Hallux strength – (%BW)	12.1 (6.3)	12.2 (4.9)	.911	[-2.6, 2.3]
Toe strength – (%BW)	7.9 (5.1)	8.3 (4.4)	.676	[-2.1, 2.1]

Abbreviation: MNSI – Michigan Neuropathy Screening Instrument; FHSQ – Foot Health Status Questionnaire; ROM – Range of Motion; L – Left; R – right; BW – Body Weight.

According to the IWGDF, a major focus in the prevention of plantar ulcers is treatment of modifiable risk factors [8]. Our study aimed to evaluate the effectiveness of foot-ankle exercise training on lower limb function and on modifiable risk-factor outcomes in PWDPN. The results (Table 8, Figure 5, and Table 9 in the Supplementary material) and discussion presentations are organized and structured as patient, intervention, comparison, outcome (PICO) questions for each modifiable risk factor evaluated in this RCT.

Table 8 - Secondary and primary outcomes from intervention group and control groups.

	Intervention Group	Control Group	p-value	95% CI for Estimated Mean Difference
	Means ± SD	Means ± SD		
Daily physical activity (steps)				
12 weeks	8.367 ± 4.418	7.385 ± 3.137	0.294	1.371 [-1.204, 3.946]
24 weeks	7.446 ± 3.525	7.072 ± 3.898	0.222	1.677 [-1.029, 4.383]
1 year	8.458 ± 4.206	7.093 ± 2.532	0.109	3.402 [-0.777, 7.580]
Fast gait speed (m/s)				
6 weeks	1.56 ± 0.27	1.44 ± 0.32	0.073	0.15 [-0.01, 0.31]
12 weeks	1.65 ± 0.36	1.47 ± 0.37	0.020*	0.19 [0.31, 0.36]
24 weeks	1.59 ± 0.26	1.53 ± 0.44	0.873	0.02 [-0.16, 0.19]
1 year	1.43 ± 0.19	1.45 ± 0.31	0.027*	0.31 [0.35, 0.57]
Self selected gait speed (m/s)				
6 weeks	1.04 ± 0.24	1.04 ± 0.18	0.797	-0.01 [-0.13, 0.10]
12 weeks	1.07 ± 0.15	0.98 ± 0.21	0.383	0.06 [-0.06, 0.17]
24 weeks	1.04 ± 0.14	1.04 ± 0.26	0.599	-0.04 [-0.18, 0.10]
1 year	0.99 ± 0.12	1.05 ± 0.13	0.464	-0.09 [-0.33, 0.15]
MNSI (score)				
6 weeks	6.5 ± 2.2	6.1 ± 2.4	0.711	0.3 [-1.0, 1.4]
12 weeks	5.9 ± 1.9	5.7 ± 2.2	0.945	-0.1 [-1.2, 1.2]
FHSQ - foot pain (score)				
6 weeks	62.5 ± 24.7	59.1 ± 26.0	0.470	5.2 [-9.0, 19.5]
12 weeks	69.2 ± 20.8	62.2 ± 25.4	0.132	11.2 [-3.4, 25.7]
FHSQ - foot function (score)				
6 weeks	75.6 ± 23.6	68.0 ± 25.4	0.361	6.2 [-7.2, 19.8]
12 weeks	80.9 ± 21.9	75.3 ± 23.9	0.196	9.2 [-4.7, 23.1]
FHSQ – shoes (score)				
6 weeks	39.8 ± 30.8	48.0 ± 32.2	0.245	-10.9 [-29.4, 7.5]
12 weeks	46.5 ± 35.4	42.2 ± 31.5	0.807	2.3 [-16.7, 21.5]
FHSQ - Foot Health (score)				
6 weeks	36.2 ± 22.5	42.6 ± 29.0	0.723	2.5 [-11.4, 16.4]
12 weeks	41.3 ± 19.3	44.4 ± 30.6	0.787	1.9 [-12.2, 16.1]
Ankle plantaflexion ROM L (°)				
6 weeks	32.4 ± 6.5	32.1 ± 6.8	0.933	-0.1 [-3.9, 3.6]
12 weeks	33.6 ± 6.8	30.3 ± 5.8	0.337	2.0 [-2.0, 5.8]
Ankle dorsiflexion ROM L (°)				
6 weeks	19.4 ± 4.9	17.5 ± 5.6	0.414	1.3 [-1.8, 4.3]
12 weeks	20.0 ± 5.4	17.8 ± 4.8	0.349	1.5 [-1.7, 4.8]
Tactile				
6 weeks	2.1 ± 2.5	1.9 ± 2.9	0.514	-0.4 [-1.6, 0.8]
12 weeks	2.7 ± 2.5	2.0 ± 2.7	0.884	-0.1 [-1.3, 1.1]
Tactile - threshold - L				
6 weeks	3.7 ± 1.6	3.7 ± 1.6	0.781	0.1 [-0.7, 0.9]
12 weeks	3.7 ± 1.7	3.8 ± 1.8	0.960	0.0 [-0.8, 0.8]
Vibration – L				
6 weeks	1.3 ± 0.7	1.3 ± 0.7	0.865	0.0 [-0.4, 0.4]
12 weeks	1.5 ± 0.8	1.5 ± 0.8	0.030*	-0.1 [-0.9, -.05]
Quality of life (score)				
6 weeks	0.68 ± 0.14	0.63 ± 0.13	0.393	0.04 [-0.05, 0.13]
12 weeks	0.70 ± 0.18	0.69 ± 0.17	0.312	0.05 [-0.04, 0.15]
Hallux strength (%BW)				
6 weeks	12.6 ± 6.1	12.3 ± 4.9	0.971	-0.1 [-2.9, 2.8]
12 weeks	12.7 ± 5.9	11.5 ± 3.8	0.301	1.6 [-1.3, 4.4]
Toes strength (%BW)				
6 weeks	9.7 ± 5.0	8.8 ± 5.2	0.985	0.0 [-2.3, 2.4]
12 weeks	10.1 ± 5.8	8.3 ± 4.7	0.349	1.0 [-1.2, 3.6]



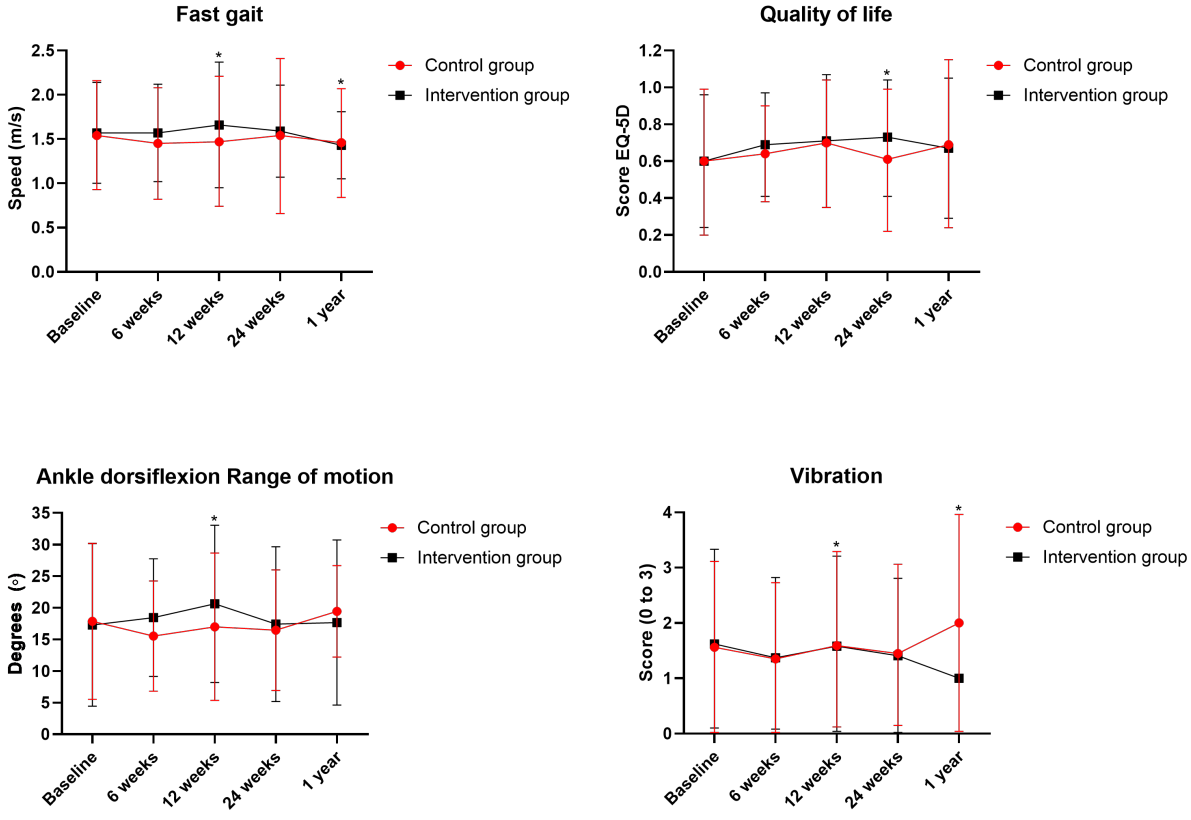


Figure 5 - Different between intervention group and control group on fast gait speed, quality of life, ankle range of motion and vibration outcomes.

In PWDPN, can the addition of a foot-ankle therapeutic exercise program improve gait speed?

Fast-gait speed, but not self-selected gait speed, was significantly affected by the foot-ankle exercise program compared with usual care alone (table 8, figure 5). After 12 weeks, IG participants walked faster than CG participants (p=0.020; interaction effect), and after 24 weeks and 1 year, the IG still maintained significantly greater fast-gait speed (Table 8, p=0.027; interaction effect).

DPN leads to a deterioration of lower limb motor function, with rapid decrements of ankle strength [25] and intrinsic foot muscle strength and size [26,27].

Decreased muscle strength is directly related to worsening of functional abilities such as balance, walking, and gait speed [28]. Slower gait speed is related to increased stride time variability, which increases the risk of falls in the elderly [29], and reduced gait speed is also independently associated with greater risk of mortality in older adults [30]. Moreover, White et al. (2012) [31] reported an association between decreased gait speed and increased risk of death among older adults. Thus, it is clear that gait speed is closely linked to general health-related outcomes in older adults, as the participants of this RCT. Furthermore, reduced gait speed in PWDPN is related to low levels of physical activity [3], and thereby increases the risk of developing ulcers [32]. The exercise program did not affect self-selected gait speed, another relevant outcome for PWDPN, perhaps due to its lower sensitivity to change. Taveggia et al. (2014) [33]also observed significant improvement in fast but not self-selected gait speed after exercise-based multimodal treatment in PWDPN.

IG participants not only increased their fast-gait speed after 12 weeks of the program; they also maintained this greater speed, even after 1 year. An improvement of 0.10 m/s in usual walking speed predicts a substantial reduction in mortality in older adults [34] and an increase of 0.11 m/s in fast-gait speed in persons with musculoskeletal dysfunctions, such as DPN, is considered clinically important [35]. In our study, IG participants showed a mean difference of 0.18 m/s compared with CG participants, a greater increase than that recommended for clinical improvement and mortality reduction. Thus, our foot-ankle exercise program potentially promotes an indirect protective effect against mortality risk.

Melese et al. (2020) [36] reviewed the effectiveness of different exercise modalities on gait speed in DPN subjects, including five studies on various exercise modalities, such as gait and balance training, proprioceptive training, ROM exercises, and lower limb strengthening. Only two studies included foot-ankle specific training resembling ours in their protocols [36]; both observed an increase in self-selected speed over time in the experimental group. To date, we are not aware of any previous study investigating the effectiveness of foot-ankle training on fast-gait speed.

Although our program focused mainly on gaining muscle strength and ROM, the functional exercises in the protocol could have also induced faster walking speed. The gains in fast-gait speed achieved could improve lifestyle via metabolic control and health benefits, especially in participants with poor aerobic resistance and overweight, who might find it difficult to engage in moderate to intense daily-living activities [37,38]. Faster gait speed ability may help improve functional capacity for aerobic activity, including daily living activities involving motor challenges, such as rushing to catch a bus, cross a street, or be on time for an appointment.

In PWDPN, can the addition of a foot-ankle therapeutic exercise program improve daily physical activity levels?

Considering that foot exercises were able to improve outcomes related to daily performance, we hypothesized that the number of steps participants take in their daily living activities would also be improved after the intervention. The number of steps taken over a 6-day period did not differ between groups after 12 weeks of foot-ankle exercises (table 8 and figure 5). This may be due to step count not being sensitive

enough; a search for other outcomes that represent daily activity may be needed. A closer look at this negative result, however, revealed that while all participants started the study at a moderate activity level (7,641 and 8,092 steps in the CG and IG, respectively), the CG showed steadily decreasing activity, to a low activity level (7,093 steps) by the 1-year followup, according to Tudor-Locke and Bassett (2004) classification. The IG, in contrast, remained at a moderate activity level at the 1-year followup (8,458 steps).

Steps are a fundamental unit of human locomotion, and thus are a preferred metric for quantifying physical activity [39]. The status of being moderately active represented a health advantage for people in the IG, because in addition to helping with lifestyle and daily living activity, more steps could improve musculoskeletal capacity, especially foot-ankle muscle strength [40]. This could improve the performance of daily locomotor tasks, and also benefit metabolic and glycemic control [41].

Some bias may have been introduced in that steps per week, although measured with an accelerometer, are to a certain extent self-reported, because participants themselves read and recorded the number of daily steps displayed on the accelerometer. Some participants reported that they occasionally forgot to write down their steps, a possible bias also noted and discussed by other authors [42]. A systematic review concluded that self-report measures of physical activity can be both higher and lower than directly measured physical activity levels [43], suggesting variability in self-report measures.

The IWGDF [16], recommends informing persons with diabetes at low or moderate risk for foot ulceration (IWGDF risk 1 or 2) that a moderate increase in daily

walking-related weightbearing activity (eg, an extra 1,000 steps/day) is safe and does not increase ulcer risk. Although neither group increased step number by 1,000 during the study, the IG increased step number by approximately 400 after 1 year, which is still within a safe increase according to the IWGDF. The CG decreased step number by approximately 600 after 1 year. This difference, while not significant, is notable; a larger sample size may shed more light on this.

IWGDF guidelines also focus on risk factors for ulceration, and recommend foot-related exercises as a prevention strategy [16], but RCTs on foot-ankle exercises for PWDPN are still scarce. To date, we are not aware of any study investigating the effects of exercises targeted specifically to the foot-ankle complex on daily physical activity. Grewal et al. (2015) [14] and Mueller et al. (2013) [44] showed increases in step number in PWDPN after foot-related exercise; however, their programs included general balance or weightbearing exercises, rather than foot-ankle specific exercises, as in our program. Therefore, although they are recommended, evidence regarding foot-ankle exercises and physical activity levels in PWDPN is still weak.

In PWDPN, can the addition of a foot-ankle therapeutic exercise program improve toe strength and ankle-joint ROM?

As outcomes related to musculoskeletal function, such as muscle strength and joint ROM, are of paramount importance for PWDPN, we sought to also assess the effectiveness of our foot-ankle exercise program on ankle ROM and muscle strength of the toes (including hallux) in PWDPN. After 12 weeks of foot-ankle training, the IG showed increased ankle dorsiflexion ROM compared with the CG ($p=0.048$; interaction

effect, table 9 in the supplementary material, and figure 5). In the 24-week and 1-year followups, there were no differences between groups in the ROM (table 9 in the supplementary material). In addition, there were no significant differences between foot-ankle training and usual care on toe muscle strength (table 8, and table 9 in the supplementary material).

A systematic review assessing the effects of foot- and mobility-related exercises on foot-ankle muscle strength in PWDPN concluded that their efficacy is still unclear [8]. Out of the three studies included in the systematic review [40,45,46], two showed increased foot-ankle strength and one found no effect [47]. It is important to highlight the heterogeneity of the methods used to assess foot-ankle muscle strength, which hinders the ability to analyze the efficacy of foot-related exercises for this outcome.

Regarding foot-ankle ROM, a cross-sectional study of 281 individuals revealed that people with or without DPN experienced limited joint mobility in all foot joints [48]. According to a systematic review by Monteiro-Soares et al. (2012) [49], limited subtarsal and first metatarsophalangeal joint mobilities were associated with diabetic foot ulcer development. For this reason, this modifiable risk factor was targeted in our intervention, and has been a common target in other foot-related exercise interventions focusing on foot-health and musculoskeletal improvement in PWDPN[40,50,51]. Our study showed improved ankle dorsiflexion ROM in the IG compared with the CG after 12 weeks of foot-ankle training. Our results corroborate other investigations that found an increase in ankle dorsiflexion ROM after 4 weeks of foot-targeted exercises [50] and an increase in ROM of the first metatarsophalangeal joint after an 8-week foot-targeted exercise program[51]. Only one RCT found no differences in ROM of the ankle and first

metatarsophalangeal joints after a 12-week foot-targeted exercise program [40]. A noteworthy difference between the studies was that Cerrahoglu et al. (2016) [50] and Kanchanasamut et al. (2017) [51] applied general and balance exercises in their protocols in addition to the foot-targeted exercises, unlike Sartor et al. (2014) [40], who focused specifically on foot-ankle exercises. The addition of these general and balance exercises probably helped to improve foot-ankle ROM in the PWDPN. Our protocol included functional exercises as well, which may also have contributed to the improvement in ankle dorsiflexion ROM after 12 weeks of exercise.

Improvements in foot-ankle ROM should indirectly lead to better locomotor performance and more independence and autonomy for PWDPN regarding daily-living activities. Therefore, our findings and the positive results from other cited RCTs and non-controlled studies [45,52,53] reinforce the importance of exercising the foot-ankle to gain this clinically relevant outcome [49]. Furthermore, foot- and mobility-related exercises may be beneficial for improving other modifiable risk factors for foot ulceration, such as foot sensitivity and DPN symptoms [8].

In PWDPN, can the addition of a foot-ankle therapeutic exercise program improve DPN symptoms and tactile and vibration sensitivities?

The foot-ankle intervention did not affect DPN symptoms and tactile sensitivities (table 8, and table 9 in the supplementary material). According to van Netten et al (2020) [8], evidence that foot and mobility-targeted exercises may improve DPN symptoms is low-quality due to inconsistency and imprecision of study design, with small effect sizes and large confidence intervals.

The clinical importance of vibration sensitivity for the development of diabetic foot ulcers has been demonstrated by research associating current or past diabetic foot ulcers with altered tuning fork vibration perception [49]. In addition, Zippenfennig et al. (2021) [54] reported worse vibration perception thresholds in PWDPN compared with controls and people without DPN. In our study, after 12 weeks of foot-ankle training, the IG presented better vibration sensitivity compared with the CG (p=0.030; interaction effect, table 8, and figure 5), and that difference was maintained at the 1-year followup assessment (p=0.023; interaction effect, table 9 in the supplementary material).

Aerobic exercise may activate increased Schwann cell proliferation, a phenomenon that may play an important role in stimulating axonal regeneration [55]. It is possible that our foot-ankle exercise protocol provided sufficient stimulation to achieve such a cellular effect. This exercise-induced increase in peripheral nerve regeneration has been shown to promote improvements in both functional and morphological markers of nerve and motor function in mice [56]. Furthermore, a supervised aerobic exercise program performed 4 h per week (brisk walking on a treadmill) was able to significantly improve vibration perception thresholds in people with diabetes over a 4-year period [57]. These axonal responses and sensory and motor improvements might be the reason for the benefits in vibration perception and functional performance, such as the increase in fast-gait speed, that we observed in the IG participants. Whereas most studies on peripheral sensory function have evaluated the effects of aerobic exercise, our results revealed that exercise focusing on the foot-ankle joints can also be beneficial, indicating the promise of such exercise as a complementary treatment for prevention of complications from DPN.

In PWDPN, can the addition of a foot-ankle therapeutic exercise program improve QoL, foot health, and functionality?

Because we observed changes in locomotor function (fast-gait speed), joint ROM, and vibration sensitivity, we speculated that these gains together would also improve QoL and functionality in PWDPN. The foot-ankle exercise program yielded a positive effect on QoL at the 24-week followup compared with CG (p=0.048; interaction effect, table 9 in the supplementary material). Compared with baseline, the IG showed a significantly improved QoL score at 12 (p=0.006, time effect, table 8 and figure 5) and 24 (p=0.006, time effect, table 9 in the supplementary material) weeks.

Exercise can improve QoL through improving DPN symptoms[40], foot-ankle ROM [46,50,51], functionality [40], muscle strength [45,46], and foot rollover [40]. Aerobic exercise, resistance exercise, combined exercise, and yoga all have a positive effect on QoL compared with usual care in people with type 2 Diabetes [58]. A pretest–posttest study with a nonequivalent control group assessing the effects of a Tai Chi Chuan program in diabetic patients [59] found improvement in different domains of the Korean SF-36 questionnaire. Although few studies have evaluated the effect of specific foot-ankle exercises on the QoL of PWDPN, self-care associated with exercise practice has been shown to lead to a better QoL in people with diabetes [60]. Our program resulted in improved QoL in the IG that was manifested after 12 and 24 weeks.

Also, after 12 and 24 weeks, the IG participants improved their foot pain scores compared with baseline assessment (p=0.044 and p=0.026; time effect, respectively). The CG also showed improvements in foot health after 1 year, compared with baseline

and 6 weeks (p= 0.001 and p= 0.025; time effect, respectively). The foot-health improvement in the CG might be due to the usual-care guidance offered to the patient during the orientation session. This could have been sufficient to improve foot functionality, as revealed by the FHSQ scores. The placebo effect is an important factor to be considered, especially in physical therapy trials. The patient-physiotherapist relationship involves warmth, confidence, friendliness, support, sympathy, language reciprocity, use of psychosocial talk, eye contact, smiling and caring expressions of support and interest, and interpretation of the patient's nonverbal cues and expressions, and this relationship is established alongside a treatment regimen. All of these serve to potentiate placebo effects [61].

In PWDPN, can the addition of a foot-ankle therapeutic exercise program better prevent foot ulceration?

Over a 1-year followup, only two participants developed a plantar foot ulcer, one from the IG and one from the CG. The IG participant was diagnosed approximately 13 weeks after randomization, whereas the CG participant was diagnosed approximately 5 weeks after randomization. Due to an insufficient number of participants with foot ulcers, we cannot say whether the later time to develop an ulcer in the IG participant was linked to the intervention.

Strengths and Limitations

The strengths of this study include the rigorous RCT methodology and adoption of a robust statistical model (GMM), a larger sample size than other studies in the same

field [40,50,51], and a group intervention approach with individual progression that integrates incremental gains. One limitation was a relatively high dropout rate during followup visits, mainly due to the COVID-19 pandemic. Furthermore, other parameters related to the clinical control of diabetes, such as glycated hemoglobin and glycaemia, were not assessed, and might have influenced our functional and clinical outcomes.

We believe that the improvements seen in the IG participants in several functional outcomes, such as foot-ankle ROM and fast-gait speed, as well as clinical outcomes such as vibration sensitivity, had a direct impact on general clinical improvement in the IG, as evidenced by increased QoL and foot-health measures. We suggest future mediation analysis of our clinical trial data to further understand which outcomes indirectly influenced the changes observed in QoL in intervention participants. We planned and conducted an interim analysis that was published as a feasibility study [62], but its outcomes did not drive our choices of mitigating strategies for responding to extenuating circumstances. The main purpose of the planned interim data analysis was to analyze recruitment and adherence rates and potential changes in the outcomes, and not to plan for mitigating strategy implementations.

Conclusion

We conclude that the 12 weeks of the foot-ankle therapeutic exercise program showed positive effects compared with usual care on the primary outcome of fast-gait speed, and on the secondary outcomes of foot-ankle ROM, vibration sensitivity, and QoL. However, no effects were seen on the two other primary outcomes after 12 weeks (self-selected gait speed and number of steps), although a 1,365-step difference

between groups were observed at 1-year followup. Improvements in vibration sensitivity and ROM may indicate an improvement in modifiable risk factors for foot ulceration, whereas an increase in gait speed may be an indicator related to mortality reduction in this population. Taken together, the findings of our study suggest that foot-ankle exercises may be an effective complementary treatment strategy for improving some musculoskeletal and functional deficits related to DPN. For other outcomes, larger trials are needed to further investigate the effects of such an exercise program.

Methods

Design

A 12-month, single-blind, parallel-group, two-armed superiority randomized controlled trial was designed to investigate the benefits of a foot-ankle exercise protocol on clinical and biomechanical outcomes in individuals with DPN. A detailed description of this protocol, following CONSORT (Consolidated Standards of Reporting Trials) recommendations, has been published elsewhere (15). It was prospectively registered at ClinicalTrials.gov (NCT02790931; June 6, 2016) under the name ‘‘Effects of Foot Muscle Strengthening in Daily Activity in Diabetic Neuropathic Patients.’’

Participants and Recruitment

Sample size calculation was conducted using GPower v. 3.1 (16) based on the following outcomes: daily physical activity level (number of steps), and self-selected and fast gait speeds. These three outcomes were chosen because they reflect important functional gains for patients with DPN. The following parameters were applied in the sample size calculation: a statistical design of F-test repeated measures and interaction between and within factors with 3 repeated measures (baseline, 12 weeks and 1 year follow-up) and two study groups (control and intervention); a statistical power of 0.80; an alpha of 0.05; and an effect size of 0.175, 0.170, and 0.154 for fast gait speed (17), self-selected gait speed (18) and number of steps (19), respectively. The minimum sample sizes were 54, 58 and 70 individuals, respectively. Thus, the sample size was based on the number of steps, which resulted in the largest number of participants (n= 70). Assuming a 10% total dropout rate, we recruited 78 patients between December

2017 and December 2019 using digital social media advertising, outpatient clinic databases and via direct contact with people with diabetes during health campaigns at the university campus. Eligibility criteria included both sexes, age between 18 and 75 years; type 1 or 2 diabetes mellitus with moderate DPN as diagnosed by a fuzzy decision support system (20); ability to walk independently for at least 10 m; a maximum of one amputated toe, which could not be the hallux; access to electronic devices with internet that allow usage of the web software. The exclusion criteria were: presence of an active plantar ulcer; history of surgical procedure at the hip, knee or ankle, or indication of surgery throughout the intervention period; history of arthroplasty, and/or current use of orthosis for the lower limbs, or indication of lower limb arthroplasty throughout the intervention period; diagnosis of neurological diseases; dementia or inability to give consistent information; be under any physiotherapy care during the intervention period; major vascular complications and/or severe retinopathy.

The trial was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the School of Medicine of the University of São Paulo (Resolution 196/96 of the National Health Council; Research protocol No. 1.464.870).

An independent researcher, blinded to group-code correspondence, prepared a randomization schedule using the Clinstat software (University of York, York, UK), determining a sequence of numerical codes that was used to allocate the participants to an intervention group (IG) or control group (CG) after baseline assessment. The allocation sequence was kept in opaque envelopes that were sequentially numbered. Two other physiotherapists, both blinded to the treatment allocation, were responsible

for all clinical, functional, and biomechanical outcome assessments. The participants were instructed not to reveal their treatment allocation to the physiotherapist who conducted the assessments. All participants' data were kept confidential before, during, and after the study by encoding their names. A flowchart summarizing the clinical trial procedures is shown in Figure 6.

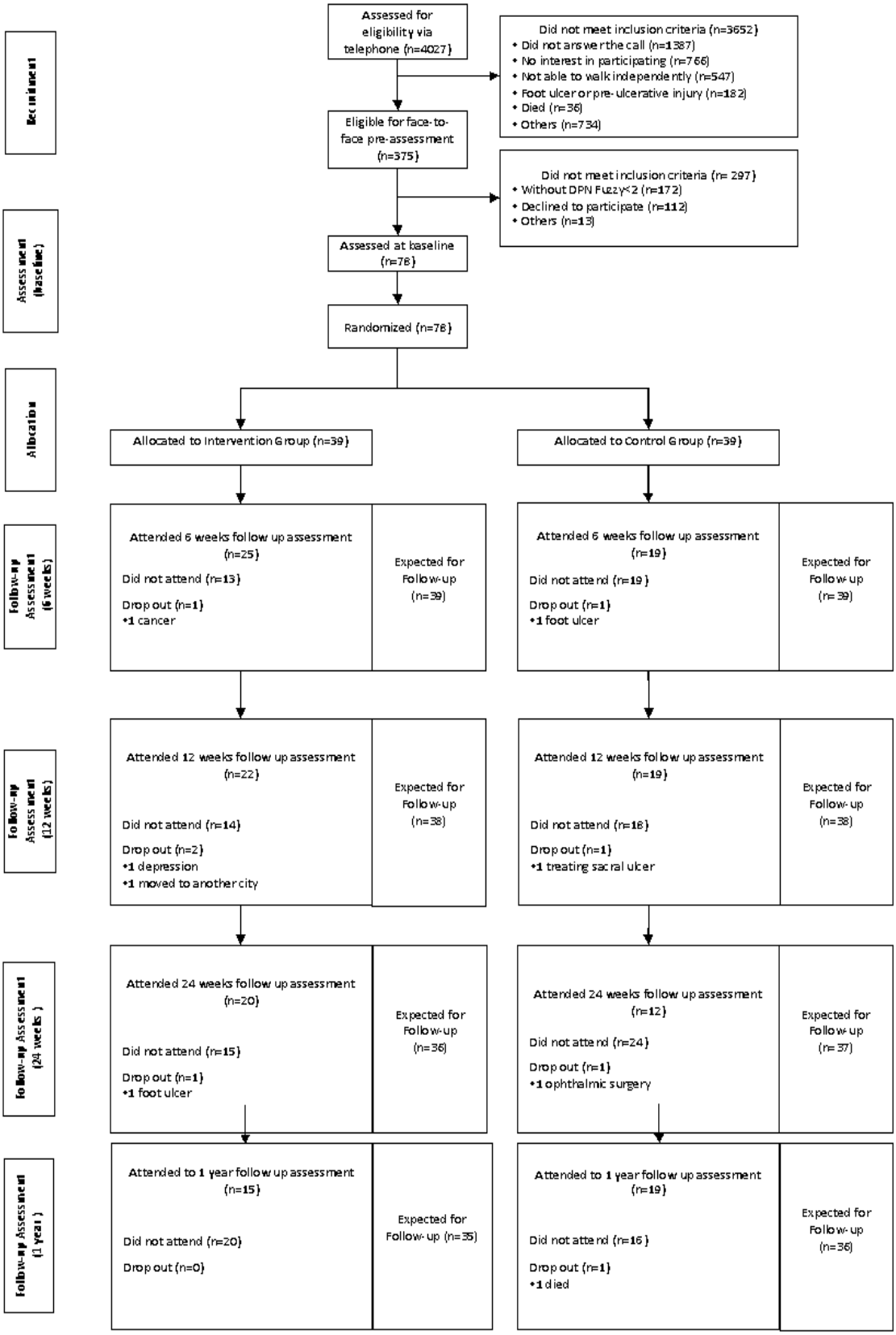


Figure 6 - Flowchart of recruitment, assessment, and follow-up process.

Treatment Arms

The control group participants received the usual care recommended by medical staff and by the guidelines of the International Working Group on the Diabetic Foot (IWGDF) (13), as follows: (1) screening for a history of foot ulceration or lower-extremity amputation, peripheral artery disease, foot deformity, pre-ulcerative signs on the foot, poor foot hygiene, and ill-fitting or inadequate footwear; (2) inspecting the feet and the insides of shoes daily, washing the feet daily (with careful drying, particularly between the toes), avoiding the use of chemical agents or plasters to remove calluses or corns, using emollients to lubricate dry skin, and cutting toe nails straight across; (3) providing education aimed to improve foot care knowledge and behavior, as well as encouraging the participants to adhere to this foot care advice. All of these usual care orientations were given in the baseline session.

The intervention group participants received the usual care, along with a 12-week foot-ankle exercise program. A part of the exercise protocol was performed twice a week under the supervision of a physiotherapist, and a sequence of foot-ankle exercises was performed twice a week by the participant at home, who was remotely supervised through the Educational Diabetic Foot Software (SOPeD, www.soped.com.br). The exercise protocol was designed to be as simple and practical as possible to effectively manage the musculoskeletal complications related to diabetes. Both protocols (SOPeD and supervised foot-ankle exercises) were designed to consist of the same set of modules: (a) warm-up exercises, (b) intrinsic foot muscle strengthening, (c) extrinsic foot-ankle muscle strengthening, and (d) functional exercises, such as balance and gait training. To promote long-term participation, each supervised session

was conducted in groups of five to eight participants (11). The exercise progression was based on the difficulty of its execution and such progression was made through the increase of intensity and/or difficulty of the exercise to each patient as the supervised exercises were performed during a face-to-face intervention. The whole exercise program is published elsewhere (15).

Assessments

The assessments consisted of 5 evaluations: at baseline, 6 weeks (T6), 12 weeks (T12), 24 weeks (T24) and 1 year follow-up (T1y). The daily physical activity level was measured for 6 consecutive days by counting the number of steps using a 3D accelerometer (Power Walker-610, Yamax, Japan). Each participant was instructed to use the accelerometer daily, except during bathing and rest.

For self-selected and fast gait speeds, two trials for each were conducted, and the average speed was calculated and used for analysis. Two photocells (CEFISE, Speed Test Fit Model, Nova Odessa, Brazil) located in the middle (at the 6 m mark) of the 10-meter walkway were used to measure the walking time and to calculate the gait speed.

Tactile sensitivity was assessed using a 10g monofilament in four plantar areas (plantar surface of the hallux and heads of the 1st, 3rd, and 5th metatarsal bones) in both feet (21). The number of areas in which the participant did not feel the pressure applied by the monofilament was recorded (22). The tactile sensory threshold was assessed on the dorsal surface of the hallux on both feet using six monofilaments (0.05g, 0.2g, 2g, 4g, 10g, 300g). Monofilaments were applied in order of increasing stiffness. A

positive threshold was recorded when the subject could feel the pressure applied by the monofilament (23).

Vibration sensitivity was assessed by the timed method using a 128 Hz tuning fork applied to the dorsal surface of the distal phalanx of the hallux on both feet. The time difference (in seconds) between the instant at which vibration sensation diminishes beyond the participant and the examiner's perceptions was recorded on a standardized form (24). Values less than 10 s were classified as present vibratory sensitivity, greater than 10 s was classified as decreased vibratory sensitivity, and no perception was classified as absent vibratory sensitivity.

Passive ankle range of motion (ROM) was evaluated bilaterally by an ankle electrogoniometer (model SG110/A, Biometrics, Gwent, UK). After setting the zero angle (90 degrees of the ankle joint flexion angle while lying), the assessor measured the passive ROM of the participant in supine position.

Hallux and toe strength was assessed by an emed-q pressure platform (Novel, Munich, Germany) by pressing the hallux and toes against the plate, as described previously (25).

Originally, number of steps, gait speed, sensitivities, ankle ROM and foot strength were planned to be assessed at each of the 5 assessment moments, however, due to the COVID-19 pandemic, at 24-weeks and 1-year follow-up these assessments could not be performed (14).

DPN symptoms were evaluated by the Brazilian version of the Michigan Neuropathy Screening Instrument (MNSI) (26). This questionnaire includes 15 items and the total score ranged from 0 to 13 (higher scores representing a worse DPN condition).

Quality of life was assessed by EuroQoL 5-dimensions (EQ-5D) questionnaire (27). It is based on a classification system that describes health in five dimensions: mobility, personal care, usual activities, pain/discomfort and anxiety/depression. The EQ-5D associates a value between −0.59 and 1.00, which represents the health status of an individual (1.00 being the best possible health condition).

Foot health and functionality was evaluated by the Brazilian-Portuguese version of a foot health status questionnaire (FHSQ-BR) (28). This study used four domains of this questionnaire: foot pain, foot function, shoes, and general foot health. Each domain was scored from 0 to 100 points, where 100 represents the best possible condition and 0 represents the worst condition. The scores were calculated using FHSQ software, version 1.03 (Care Quest, Australia).

Originally, the MNSI, FHSQ-BR and EQ-5D were planned to be assessed at each evaluation moment locally at the laboratory, however, due to the COVID-19 pandemic, at 24-weeks and 1-year follow-up these assessments were made over the telephone (14).

The occurrence and moment of occurrence of plantar foot ulcers were also assessed throughout the entire study (12-months period). If an ulcer occurred either during the intervention or the follow-up periods, a nurse specialized in diabetic foot with 14 years of experience assessed photographs of the ulcer and defined if the occurrence was indeed an ulcer. A diabetic foot ulcer is defined as a “full thickness lesion of the skin distal to the malleoli in a person with diabetes mellitus” (29). When a participant developed a plantar foot ulcer, the intervention was discontinued, but the subject was still being included in the intention-to-treat analysis.

Statistical Analysis

Statistical analyses were performed using the *Statistical Package for the Social Science* (SPSS, IBM; v.23.0), adopting a 5% significance level. All analyses used the full set of randomly assigned participants under the intention-to-treat assumption. Originally, the statistical analysis was planned to be performed using ANOVAs, however, due to the COVID-19 pandemic and the consequent large amount of missing data, a Generalized Linear Mixed Model (GLMM) method was adopted (14). After analyzing the causes for missing data, they were considered to be missing completely at random (MCAR). Then, GLMM method was used for univariate analyses, considering the following as factors: groups (CG and IG), time of assessment (Baseline, T6, T12, T24 and T1y), and the interaction effect (time by group). Participants and time were considered as random effects and groups as fixed effects in the GLMM modeling. Q-Q graphs were plotted to verify the adequacy (normality) of each model. Univariate (main effects) and multivariate (interaction effect) comparisons of the estimated marginal means were adjusted with the Bonferroni correction. The comparisons between the pairs of estimated marginal means were made based on the original scale of each of the dependent variables of the study.

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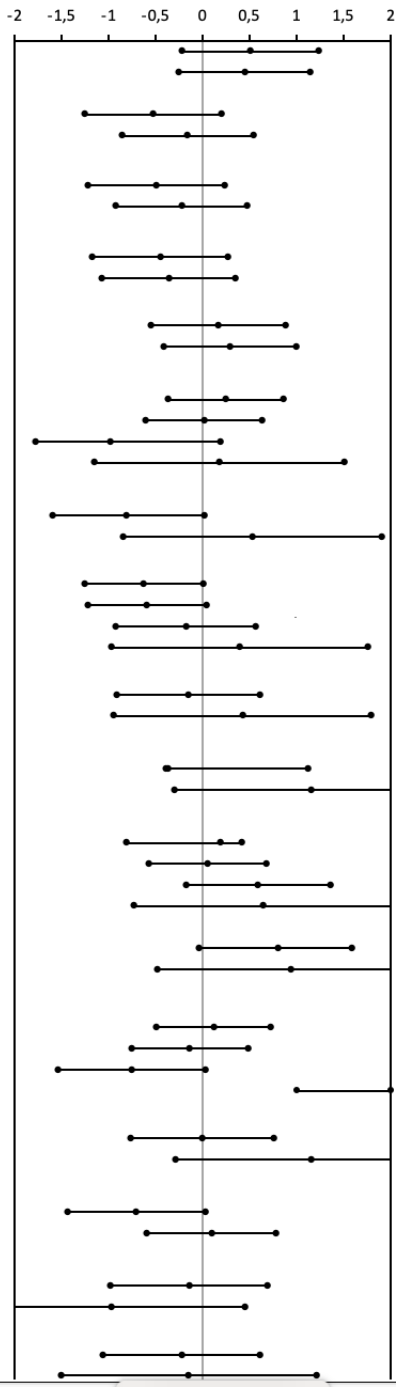
Supplementary Material

Table 9 - Secondary outcomes results from the intervention group and control groups in the 24-week and 1-year followup

	Intervention Group	Control Group	P-value	95% CI for estimated means difference
	Estimated marginal means	Estimated marginal means		
MNSI (score)				
24 weeks	5.3 ± 1.7	6.3 ± 2.3	0.331	-0.7 (-2.0 to 0.6)
1 year	5.5 ± 2.1	6.5 ± 2.4	0.086	-1.2 (-2.5 to 0.1)
FHSQ – FOOT PAIN (score)				
24 weeks	73.8 ± 23.9	58.5 ± 36.4	0.119	12.6 (-3.2 to 28.3)
1 year	64.3 ±27.7	59.6 ±32.3	0.760	2.4 (-13.3 to 18.2)
FHSQ – FOOT FUNCTION (score)				
24 weeks	83.7 ± 18.2	70.3 ± 37.7	0.465	5.6 (-9.4 to 20.6)
1 year	77.0 ± 25.5	70.5 ± 35.2	0.647	3.5 (-11.6 to 18.6)
FHSQ – SHOES (score)				
24 weeks	50.8 ± 32.7	36.1 ± 33.0	0.105	17.1 (-3.6 to 37.8)
1 year	53.2 ± 40.3	38.6 ± 40.5	0.836	2.2 (-18.7 to 23.1)
FHSQ – FOOT HEALTH (score)				
24 weeks	39.8 ± 20.6	44.1 ± 32.4	0.177	-10.5 (-25.7 to 4.7)
1 year	40.5 ± 33.3	50.5 ± 35.4	0.079	-13.7 (-28.9 to 1.5)
ANKLE PLANTAFLEXION ROM R (°)				
6 weeks	30.1 ± 7.6	33.0 ± 7.9	0.114	-3.4 (-7.6 to 0.8)
12 weeks	30.4 ± 6.8	30.5 ± 7.5	0.233	-2.7 (6.9 to 1.7)
24 weeks	33.0 ± 5.2	28.0 ± 4.9	0.543	1.6 (-3.4 to 6.5)
1 year	26.0 ± 2.0	27.0 ± 6.1	0.767	-1.2 (-9.1 to 6.7)
ANKLE PLANTAFLEXION ROM – L (°)				
24 weeks	34.4 ± 5.1	30.2 ± 5.4	0.135	3.5 (-1.1 to 8.1)
1 year	24.6 ± 8.9	28.5 ± 6.8	0.514	2.5 (-5.0 to 10.1)
ANKLE DORSIFLEXION ROM R (°)				
6 weeks	18.4 ± 4.7	15.5 ± 4.4	0.158	2.4 (-0.9 to 5.7)
12 weeks	20.6 ± 6.3	17.0 ± 5.9	0.048*	3.6 (0.3 to 7.1)
24 weeks	17.4 ± 6.2	16.4 ± 4.8	0.872	0.4 (-3.8 to 4.4)
1 year	17.6 ± 6.6	19.4 ± 3.6	0.988	0.0 (-7.3 to 7.3)
ANKLE DORSIFLEXION ROM L (°)				
24 weeks	18.5 ± 4.1	17.9 ± 3.8	0.710	-0.7 (-4.6 to 3.1)
1 year	18.0 ± 1.7	20.1 ± 5.6	0.399	-2.9 (-9.6 to 3.8)
TACTILE				
24 weeks	1.6 ± 2.5	2.6 ± 3.1	0.126	-1.0 (-2.4 to 0.3)
1 year	0.3 ± 0.5	3.0 ± 2.7	0.366	0.1 (-2.9 to 1.0)
TACTILE – THRESHOLD – R				
6 weeks	4.1 ± 1.5	3.8 ± 1.6	0.465	0.3 (-0.5 to 1.1)
12 weeks	3.9 ± 1.4	4.0 ± 2.1	0.911	0.0 (-0.9 to 0.9)
24 weeks	3.8 ± 1.6	4.8 ± 1.8	0.256	-0.6 (-1.5 to 0.4)
1 year	3.3 ± 0.5	4.1 ± 1.4	0.595	-0.4 (-1.9 to 1.1)
TACTILE – THRESHOLD – L				
24 weeks	3.4 ± 1.3	4.8 ± 2.3	0.073	-0.9 (-1.8 to 0.08)
1 year	3.3 ± 0.5	4.7 ± 1.7	0.402	-0.6 (-2.0 to 0.8)
VIBRATION – R				
6 weeks	1.4 ± 0.8	1.5 ± 0.9	0.677	-0.1 (-0.5 to 0.3)
12 weeks	1.5 ± 0.8	1.4 ± 0.7	0.758	0.1 (-0.3 to 0.5)
24 weeks	1.7 ± 0.9	1.1 ± 0.6	0.061	0.5 (-0.02 to 1.0)
1 year	1.3 ± 0.5	1.8 ± 1.0	0.312	-0.4 (-1.2 to 0.4)
VIBRATION – L				
24 weeks	1.4 ± 0.7	1.4 ± 0.8	0.910	0.1 (-0.4 to 0.6)
1 year	1.0 ± 0.0	2.0 ± 1.0	0.023*	-1.0 (-1.8 to -0.1)
QUALITY OF LIFE (score)				
24 weeks	0.72 ± 0.16	0.60 ± 0.19	0.048*	0.11 (0.001 to 0.21)
1 year	0.67 ± 0.19	0.69 ± 0.23	0.886	-0.01 (-0.11 to 0.09)
HALLUX STRENGTH (%BW)				
24 weeks	13.2 ± 6.8	12.3 ± 5.3	0.669	-0.7 (-4.1 to 2.6)
1 year	15.1 ± 4.9	11.7 ± 4.0	0.512	1.6 (-3.1 to 6.3)
TOES STRENGTH (%BW)				
24 weeks	8.8 ± 5.4	7.7 ± 3.6	0.983	-0.1 (-2.8 to 2.7)
1 year	7.0 ± 3.8	6.6 ± 2.2	0.256	2.2 (-1.6 to 6.0)



CAPÍTULO 5 - CONSIDERAÇÕES FINAIS

5.1 Discussão geral

Esta tese buscou propor, testar a viabilidade e a eficácia de um programa de exercícios terapêuticos para os pés de pessoas com NPD nos níveis de atividade física e velocidade da marcha, bem como seus efeitos em desfechos clínicos e funcionais relacionados à NPD, tais como amplitude de movimento do tornozelo, sensibilidade tátil e vibratória, sintomas da NPD, qualidade de vida, saúdes dos pés, força muscular e incidência de úlceras.

A primeira etapa deste projeto foi propor um protocolo de exercícios para os pés e tornozelos e outros funcionais para pessoas com NPD que apresentam um comprometimento musculoesquelético em membros inferiores progressivo e importante que levam a uma cascata de complicações físicas e sistêmicas (1,2). Descrevemos em detalhes todo o procedimento metodológico do ensaio clínico randomizado de grupo paralelo, simples-cego e controlado que incluiu 78 pessoas com NPD alocadas aleatoriamente para cuidados com os pés usuais (grupo controle) ou cuidados usuais e exercícios terapêuticos para os pés supervisionados duas vezes por semana durante 12 semanas (3). Os participantes foram avaliados 5 vezes em um período de 1 ano em relação aos desfechos primários (nível de atividade física diária, velocidades de marcha rápida e auto-selecionada) e secundários (incidência de úlcera

no pé, sintomas da neuropatia, amplitude de movimento passiva do tornozelo, qualidade de vida, saúde e funcionalidade do pé e força muscular do pé).

Na literatura, encontramos estudos que buscaram avaliar os efeitos de exercícios relacionados à mobilidade e fortalecimento em pessoas com NPD em diversos desfechos, porém a grande maioria deles utilizou exercícios globais para membros inferiores (treinamento de equilíbrio, fortalecimento com e sem sustentação de peso, exercícios aeróbicos e tratamento manual multimodal) que não enfocaram especificamente os déficits musculoesqueléticos relacionados a diabetes e NPD (4–11). Alguns dos estudos que utilizaram um treinamento específico para os pés e tornozelos focando déficits oriundos da NPD apresentaram vieses metodológicos que necessitavam ser superados, tais como falta de um grupo controle (12), baixo número de participantes (13) e avaliação dos efeitos em curto prazo (14,15). Assim, o protocolo proposto buscou sanar algumas dessas limitações metodológicas ao propor um ensaio clínico com um período mais longo de acompanhamento (12 meses), incluindo desfechos relacionados à NPD, um tamanho amostral calculado que tenha um poder suficiente para responder os desfechos primários e um programa de exercícios específicos para o fortalecimento dos músculos intrínsecos e extrínsecos do tornozelo e pé a ser implementado em pequenos grupos e que estimule a autonomia dos participantes (3).

Como esta abordagem terapêutica de exercícios para os pés em pequenos grupos é relativamente nova para esta população alvo, a segunda etapa desta tese buscou testar a viabilidade desse protocolo e do ensaio clínico que avaliaria sua eficácia. Foi publicado um estudo em que examinamos a viabilidade e eficácia preliminar de 12 semanas do programa de exercícios terapêuticos para os pés em pessoas com NPD (16).

Foram alocados aleatoriamente 30 participantes no grupo de cuidados com os pés usuais (controle - n=15) ou cuidados usuais e exercícios terapêuticos para os pés supervisionados (intervenção - n=15). Para viabilidade, avaliamos a taxa de recrutamento e a adesão e satisfação dos participantes. Para a eficácia do programa, avaliamos as mudanças da linha de base para 12 semanas no nível de atividade física diária, velocidade de marcha, sensibilidade tátil, amplitude de movimento do tornozelo, sintomas de NPD, qualidade de vida, saúde e funcionalidade do pé, força do pé e pressão plantar durante a marcha.

Em 52 semanas, recrutamos 45 participantes elegíveis (1 participante/semana), mas enfrentamos diversas dificuldades no recrutamento, a maioria relacionada aos critérios de inclusão do estudo, como por exemplo NPD moderada e grave. Infelizmente muitos casos de NPD não são diagnosticados e há uma grande falta de informação por parte dos pacientes a respeito dessa complicação oriunda da diabetes, o que leva os pacientes a não buscarem tratamento. A adesão ao programa foi de 80% e a satisfação dos participantes teve uma média (DP) de 4,57 (0,70) de 5 pontos. Grande parte da adesão e satisfação ao tratamento se deu pelo trabalho feito em pequenos grupos, o que motivava os participantes. Outro fator para a alta adesão foi a progressão dos exercícios de forma individual, respeitando a evolução de cada participante. O grupo intervenção melhorou significativamente a força dos dedos dos pés, o tempo de contato durante a marcha, os sintomas da NPD e os picos de pressão no antepé durante a marcha aumentaram. Já os participantes do grupo controle, mostraram um aumento significativo dos picos de pressão e força no calcanhar durante a marcha.

Assim, concluiu-se que o programa de exercícios foi viável, com base em uma taxa moderada de recrutamento e uma população aderente e satisfeita, e a intervenção mostrou vários efeitos preliminares positivos ao longo do tempo em comparação com o tratamento usual (16).

A terceira e última etapa desta tese foi de fato implementar o programa na amostra calculada e testar a eficácia do programa de exercícios na população alvo. Os principais resultados mostraram melhora na velocidade da marcha rápida, na amplitude de movimento passiva do tornozelo e na sensibilidade vibratória em relação aos controles em 12 semanas do programa de exercícios. Em 24 semanas, o grupo intervenção melhorou ainda a qualidade de vida em relação aos controles. Em 1 ano, a velocidade da marcha rápida e a sensibilidade vibratória foram melhores no grupo intervenção em relação aos controles.

Esses resultados parecem ser muito promissores no tratamento e prevenção de complicações oriundas da NPD. É reconhecido que a NPD leva a uma deterioração da função motora dos membros inferiores, com decréscimos rápidos da força do tornozelo e força muscular intrínseca do pé (1). A diminuição da força muscular está diretamente relacionada à piora das habilidades funcionais, como equilíbrio, caminhada e velocidade da marcha (17). A velocidade de marcha mais lenta está relacionada ao aumento da variabilidade da passada, o que aumenta o risco de quedas em idosos (18), e a velocidade de marcha reduzida também está independentemente associada a maior risco de mortalidade em idosos (19). Assim, fica claro que a melhora na velocidade da marcha pode estar intimamente ligada à saúde dos participantes incluídos neste estudo

e intervenções terapêuticas que possam aumentá-la, tais como o programa desenvolvido nesta tese, podem beneficiar pessoas com NPD.

Os Guidelines para o tratamento e a prevenção de complicações crônicas da NPD (pé diabético) são desenvolvidos e implementados internacionalmente desde 1996 pelo International Working Group on Diabetic Foot (IWGDF), principal órgão científico que determina as melhores condutas para o manejo da NPD, já tendo até 2019 publicado seis guidelines. Importante destacar que até 2019, o IWGDF nunca tinha incluído nenhuma abordagem terapêutica ou preventiva ativa com foco nos déficits musculoesqueléticos oriundos da Diabetes e da NPD, tal como a proposição de exercícios terapêuticos (https://iwgdfguidelines.org/guidelines/guidelines/). Entretanto, em 2019, quando estávamos desenvolvendo este estudo, pela primeira vez, o IWGDF incluiu nos guidelines a recomendação de exercícios de mobilidade e força para os pés nas diretrizes para o tratamento e prevenção das complicações da NPD, todavia com uma recomendação ainda fraca e uma evidência científica baixa (20).

Desta forma, pode-se concluir que esta tese e os artigos oriundos dela contribuirão sobremaneira para melhorar a qualidade da evidência científica e, futuramente, a recomendação desse tipo de abordagem preventiva para as complicações musculoesqueléticas da diabetes e da NPD, bem como para a prevenção dos fatores de risco modificáveis relacionados à úlcera plantar (21). Acreditamos que os resultados desta tese contribuirão de forma substancial na disseminação de exercícios para os pés como conduta terapêutica para pessoas com NPD.

5.2 Implicações clínicas

Os resultados do ensaio clínico sugerem diversas implicações clínicas para pessoas com NPD. A primeira a ser citada é o aumento da velocidade da marcha, pois como informado em outros capítulos, a diminuição da velocidade da marcha parece estar associada a outras complicações, incluindo a morte. Então, clinicamente, a pessoa que aumenta a velocidade do andar pode ter inúmeros benefícios relacionados, principalmente a sua funcionalidade. Talvez exercícios terapêuticos como o programa de exercícios para os pés desenvolvido neste estudo seja o passo inicial para que a pessoa com diabetes consiga sair do sedentarismo, pois a partir de uma melhora funcional, como a locomoção, ajude e encoraje-a a ser mais ativa, e assim, busque outras atividades físicas que a façam sair do sedentarismo, o que provavelmente a levou ao desenvolvimento da diabetes.

Outra contribuição clínica relevante é a melhora da amplitude de movimento do tornozelo e melhora da sensibilidade vibratória. Estas variáveis já são conhecidas como fatores de risco para úlceras plantares e sabe-se que grande parte das pessoas que desenvolvem estas úlceras aumentam significativamente o risco de amputação do membro e o risco de morte (22). Dessa forma, melhorar tais condições são imprescindíveis para a saúde geral de pessoas com NPD também como forma de modificar fatores de risco para ulcerações.

Por fim, ainda que a pessoa não tenha percebido que está andando mais rápido, sentindo melhor os pés e com uma maior amplitude de movimento de tornozelo, ela conseguiu perceber que sua qualidade de vida melhorou, como sugerem os resultados

do estudo após 24 semanas. Tal resultado também tem sua contribuição na saúde da pessoa com diabetes e NPD, pois essa melhora de percepção da qualidade de vida pode encorajá-la a aderir melhor ao tratamento proposto.

Além de todos esses benefícios clínicos, outra implicação positiva desse tipo de abordagem terapêutica, é a relativa facilidade de implementação no sistema de saúde brasileiro, pois não é oneroso, principalmente se o serviço de saúde já tiver instalado o setor de reabilitação, além do treinamento da equipe ser fácil e prático. Esperamos que haja uma mudança de paradigma a respeito do processo de reabilitação de pessoas com NPD com a disseminação desses resultados e com a implementação desta abordagem terapêutica nacionalmente.

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ANEXO 1 – APROVAÇÃO COMITÊ ÉTICA

USP - FACULDADE DE MEDICINA DA UNIVERSIDADE DE SÃO PAULO - FMUSP

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: EFEITOS DE UMA INTERVENÇÃO PERSONALIZADA VIA SOFTWARE NA VELOCIDADE DA MARCHA, BIOMECÂNICA E FUNCIONALIDADE DE TORNOZELO E PÉ DE PESSOAS COM POLINEUROPATIA DIABÉTICA: UM ENSAIO CLÍNICO CONTROLADO RANDOMIZADO

Pesquisador: Isabel C. N. Sacco

Área Temática:

Versão: 5

CAAE: 54283516.3.0000.0065

Instituição Proponente: Faculdade de Medicina da Universidade de São Paulo

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.554.572

Apresentação do Projeto:

Trata-se de retirada de instituição co-participante no projeto, sem escalreicimento dos motivos.

Objetivo da Pesquisa:

EFEITOS DE UMA INTERVENÇÃO PERSONALIZADA VIA SOFTWARE NA VELOCIDADE DA MARCHA, BIOMECÂNICA E FUNCIONALIDADE DE TORNOZELO E PÉ DE PESSOAS COM POLINEUROPATIA DIABÉTICA: UM ENSAIO CLÍNICO CONTROLADO RANDOMIZADO

Avaliação dos Riscos e Benefícios:

Inalterados

Comentários e Considerações sobre a Pesquisa:

Adequada

Considerações sobre os Termos de apresentação obrigatória:

Inalterados

Recomendações:

Nenhuma

Conclusões ou Pendências e Lista de Inadequações:

Nenhuma

Endereço: DOUTOR ARNALDO 251 21º andar sala 36
Bairro: PACAEMBU **CEP:** 01.246-903
UF: SP **Município:** SAO PAULO
Telefone: (11)3893-4401 **E-mail:** cep.fm@usp.br

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1078125_E4.pdf	15/03/2018 11:05:31		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE.pdf	13/11/2017 16:39:59	Renan Lima Monteiro	Aceito
Declaração de Instituição e Infraestrutura	Anuencia.pdf	26/07/2017 17:36:17	Renan Lima Monteiro	Aceito
Projeto Detalhado / Brochura Investigador	Projeto.pdf	26/07/2017 17:35:37	Renan Lima Monteiro	Aceito
Cronograma	cronograma.docx	09/03/2016 12:27:15	Isabel C. N. Sacco	Aceito
Folha de Rosto	plataformabrasil.pdf	09/03/2016 12:25:01	Isabel C. N. Sacco	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SAO PAULO, 21 de Março de 2018

Assinado por:
Maria Aparecida Azevedo Koike Folgueira
(Coordenador)

APÊNDICE 1– TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Projeto de pesquisa: ***"Efeitos de uma intervenção personalizada via software na velocidade da marcha, biomecânica e funcionalidade de tornozelo e pé de pessoas com polineuropatia diabética: um ensaio clínico controlado randomizado".*** Eu,_____, concordo em participar da pesquisa conduzida pela Profa. Dra. Isabel de Camargo Neves Sacco, pelo MSc. Fisioterapeuta Renan Lima Monteiro e pela Fisioterapeutas Cristina Dallemole Sartor e Jane Suelen Silva Pires Ferreira do Laboratório de Biomecânica do Movimento e Postura Humana do Departamento de Fisioterapia, Fonoaudiologia e Terapia Ocupacional, da Faculdade de Medicina, da Universidade de São Paulo. Os resultados, guardadas as devidas identificações e mantida a confidencialidade, serão analisados e utilizados única e exclusivamente para fins científicos.

Este projeto tem como objetivo **estudar os efeitos da fisioterapia para os pés associado ao uso de um *software* na velocidade do andar, na ocorrência de úlceras nos pés, na funcionalidade do dia a dia e na marcha de pacientes diabéticos com neuropatia periférica.**

Explicação dos procedimentos:

- Etapa 1:

Esta etapa ocorrerá no Laboratório de Biomecânica do Movimento e Postura Humana da USP, localizado na Cidade Universitária e contará com questionários, uma avaliação da sua caminhada e da força e saúde dos seus pés. O(a) senhor(a) será submetido a uma anamnese para avaliar os sinais e sintomas da polineuropatia diabética. Responderá a um questionário que avaliará o estado de saúde dos seus pés. Para a avaliação da marcha, colocaremos marcadores (bolinhas prateadas de isopor) em determinados pontos do seu corpo e o(a) senhor(a) caminhará algumas vezes pelo laboratório. Além disso, a velocidade do seu andar também será avaliada, de modo que o(a) senhor (a) caminhará no laboratório sem os marcadores, e na velocidade de sua escolha. A força dos seus pés será avaliada com o(a) senhor(a) sentado numa cadeira movimentando seus pés, tornozelos e joelhos e de pé pisando sobre uma plataforma. Um goniômetro manual será utilizado para medir a amplitude de movimento do seu tornozelo e pé. Para verificar se há presença de doença vascular, será mensurada a pressão arterial no seu tornozelo e braço. Além disso, a temperatura dos seus pés será mensurada com a utilização de um termômetro digital e de câmera térmica, com o(a) senhor (a) deitada. Por fim, lhe informaremos se o(a) senhor(a) fará parte do Grupo que receberá um tratamento fisioterapêutico presencial e via software ou se fará parte do grupo que não receberá o tratamento.

- Etapa 2:

O tratamento fisioterapêutico presencial terá duração de 12 semanas e será realizado simultaneamente ao uso do *software*. Após as 12 semanas de intervenção presencialmente supervisionada, os pacientes continuarão realizando exercícios de forma independente em domicílio utilizando o mesmo *software* com progressões programadas individualmente, 2 vezes por semana até o final do estudo (após um ano da avaliação inicial). O uso do *software* em domicílio será monitorado pelo seu acesso ao *software* e também segundo o preenchimento dos formulários de realização dos exercícios.

- Etapa 3:

O(a) senhor(a) deverá retornar ao laboratório de biomecânica do departamento de Fisioterapia (Cidade Universitária – USP) após 6 semanas, 12 semanas, 24 semanas e 1 ano da data de início do estudo para reavaliarmos sua força, velocidade da ,marcha, risco de úlcera, e aplicação dos mesmos questionários da primeira visita.

Desconforto e risco: o experimento não envolverá qualquer desconforto ou risco à sua saúde física e mental, além dos riscos encontrados nas atividades normais que o(a) senhor(a) realiza diariamente.

Benefícios: Caso o/a senhor(a) seja sorteado para o grupo de exercícios, o(a) senhor(a) receberá gratuitamente um tratamento fisioterapêutico de 12 semanas, sendo remotamente supervisionado via *software* durante os 12 meses do estudo (2 vezes por semana-). Caso o(a) senhor(a) seja sorteada para o grupo controle (sem o tratamento, o(a) senhor(a) irá contribuir para o entendimento da importância dos pés e tornozelos nas saúde de pacientes neuropatas).

Garantia de acesso: Em qualquer etapa do estudo você terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas. O principal investigador é a profª. Drª Isabel de Camargo Neves Sacco que pode ser encontrado no Laboratório de Biomecânica do Movimento e Postura Humana, Departamento de Fisioterapia, Fonoaudiologia e Terapia Ocupacional, na rua Cipotânea, 51, Cidade Universitária (telefone 3091-9426) Se você tiver alguma consideração ou dúvida sobre a ética da pesquisa, entre em contato com o Comitê de Ética em Pesquisa (CEP) – Rua Ovídio Pires de Campos, 225 – 5º andar – tel: 3069-6442 ramais 16, 17, 18 ou 20, FAX: 3069-6442 ramal 26 – E-mail: cappesq@hcnet.usp.br

É garantida a liberdade da retirada de consentimento a qualquer momento e deixar de participar do estudo, sem qualquer prejuízo à continuidade de seu tratamento na Instituição.

É seu direito ser mantido atualizado sobre os resultados parciais das pesquisas, quando em estudos abertos, ou de resultados que sejam do conhecimento dos pesquisadores.

Despesas e compensações: não há despesas pessoais para o participante em qualquer fase do estudo, incluindo consultas e avaliações. Também não há compensação financeira relacionada à sua participação. Se existir qualquer despesa adicional, ela será absorvida pelo orçamento da pesquisa.

Os resultados verificados serão guardados com suas devidas identificações e mantidos em confidencialidade, os quais serão utilizados única e exclusivamente para fins científicos.

Acredito ter sido suficientemente informado a respeito das informações que li ou que foram lidas para mim, descrevendo o estudo que busca **investigar os efeitos da intervenção fisioterapêutica presencial e via *web software*, na velocidade do andar, na incidência de úlceras plantares, na funcionalidade e biomecânica de tornozelo e pé na marcha de pacientes com polineuropatia diabética.**

Eu discuti com os responsáveis: Profª Drª. Isabel de Camargo Neves Sacco e/ou MSc Renan Lima monteiro ou Jane Suelen Silva Pires Ferreira sobre a minha decisão em participar nesse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos e riscos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que minha participação é isenta de despesas e que tenho garantia do acesso a tratamento hospitalar quando necessário. Concordo voluntariamente em participar deste estudo e poderei retirar o meu consentimento a qualquer momento, antes ou durante o mesmo, sem penalidades ou prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou no meu atendimento neste Serviço.

Assinatura do paciente/representante legal Data ___/___/___

Assinatura da testemunha Data ___/___/___

(Somente para o responsável do projeto)

Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido deste paciente ou representante legal para a participação neste estudo.

Data ___/___/___

Assinatura do responsável pelo estudo

APÊNDICE 2 – PROGRAMA DE INTERVENÇÃO FISIOTERAPÊUTICA

Objetivo		Exercício	Progressão
AQUECIMENTO	Nível 1	1. Alongamento da planta do pé	2x 30 seg → 2 x 1 min → 3 x 1 min
		2. Massagem com a bolinha	1 x 1 min → 2 x 1 min → 3 x 1 min
		3. Movimentar os pés para cima, para baixo e em círculos	1 x 10 rep → 2 x 10 rep → 3 x 10 rep → 4 x 10 rep
		4. Alongamento da Panturrilha	1 x 20 seg
	Nível 2	5. Escrever palavras com os pés	palavras curtas → palavras longas
		6. Entrelaçar os dedos das mãos nos dedos dos pés e realizar movimentos circulares	1 x 20 rep em cada pé
		7. Manipulação em cada dedo (parafuso das falanges)	1 x 20 rep em cada pé
		8. Massagem com a bolinha sem contato com o calcanhar	pressionar a bolinha por 1 min em cada pé
		9. Auto massagem	1 x 20 seg
EXERCÍCIOS PARA A MUSCULATURA INTRÍNSECA DOS PÉS	Nível 1	1. Alternar o apoio dos dedos (1º E 5º DEDOS)	1 x 10 rep → 1 x 10 rep (em pé)
		2. Pegar objetos com os dedos	Algodão 1 x 10 repetições; 2 x 10 repetições. Bolinha 1 x 10 repetições; 2 x 10 repetições Lápis 1 x 10 repetições; 2 x 10 repetições.
		3. Enrugar toalha com os pés	1 x 5 rep → 1 x 10 rep
		4. Abrir e fechar dos dedos (do segundo ao quinto dedo)	1 x 10 rep → 1 x 20 rep → 1x 10 rep (com elástico) → 1 x 20 rep (com elástico)
		5. Apertar os dedos contra o separador	1 x 10 rep → 2 x 10 rep → 3 x 10 rep (em cada pé)
	Nível 2	6. Dedilhar dos dedos	1 x 10 rep → 1 x 10 rep (em pé) → 1 x 20 rep (em pé)
		7. Flexão dos dedos com theraband	1 x 10 rep → 2 x 10 rep → 2 x 10 rep (em pé)
		8. Abaular o pé com arco	1 x 10 rep → 2 x 10 rep → 3 x 10 rep
		9. Andar apertando os dedos no chão	1 x 10 passos, pressionando por 1 seg → 2 x 10 passos → 3 x 10 passos
		10. Abaular o pé sem o arco	1 x 10 rep → 2 x 10 rep → 3 x 10 rep
EXERCÍCIOS PARA A MUSCULATURA EXTRÍNSECA DOS PÉS	Nível 1	1. Subir na ponta dos pés	1 x 5 rep → 1 x 10 rep → 1 x 15 rep
		2. Bater o ante pé no chão	1 x 30 rep → 2 x 30 rep → 2 x 40 rep
		3. Apertar a bolinha	1 x 10 rep → 1 x 15 rep → 1 x 20 rep
		4. Passo para frente e para trás	2 x 15 rep → 2 x 20 rep → 2 x 30 rep
	Nível 2	5. Equilíbrio em um único pé	1 x 10 seg → 2 x 10 seg → 1 x 20 seg → 2 x 20 seg
		6. Fortalecimento da musculatura medial do pé	1x10 rep (Faixa elástica amarela) → 1x10 rep (Faixa elástica vermelha)
		7. Fortalecimento da musculatura lateral do pé	1x10 rep (Faixa elástica amarela) → 1x10 rep (Faixa elástica vermelha)
CIRCUITOS FUNCIONAIS	Nível 1	1. Andar cruzando os passos (Andar lateralmente)	1 x 5 rep → 1 x 10 rep → 1 x 15 rep
		2. Mudança de direção	Direita, esquerda, frente e atrás → Frente, direita, esquerda, atrás, frente, atrás → Atrás, esquerda, frente, atrás, direita, esquerda, frente.
		3. Mudança de direção (Diagonal)	1 x 10 rep
	Nível 2	4. Marcha com obstáculos	2 x 15 rep → 2 x 20 rep → 2 x 30 rep
		5. Marcha com obstáculos em terreno instável	1 x 10 rep → 1 x 15 rep → 1 x 20 rep