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The role of supervised exercise therapy in intermittent claudication

Egon Ferreira Rodrigues

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INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR, UNIVERSIDADE DO PORTO

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Porto, Junho de 2019

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RESUMO

Introdução: A prevalência mundial da Doença Arterial Periférica está a crescer, estando inevitavelmente associada a uma diminuição da capacidade funcional e da qualidade de vida. A fisiopatologia base resulta da redução do fluxo sanguíneo e da entrega de oxigénio aos músculos envolvidos, entre outros mecanismos envolvidos. O exercício físico é um dos pilares no tratamento da claudicação intermitente, sendo que as *guidelines* recomendam o exercício físico supervisionado como 1ª linha.

Objetivo: O objetivo primário desta revisão foi analisar os efeitos do exercício físico supervisionado em três áreas: fisiologia, distâncias percorridas e qualidade de vida. Os objetivos secundários foram rever as limitações deste programa e a viabilidade de outros programas.

Métodos: Foi realizada uma pesquisa no PubMed com as seguintes palavras-chave do Medical Subject Headings: "*Peripheral Arterial Disease*", "*Intermittent Claudication*", "*Exercise Therapy*", e "*Supervised*". As *guidelines* também foram consultadas.

Desenvolvimento: As alterações fisiológicas associadas ao exercício físico supervisionado não estão totalmente esclarecidas. Por um lado, o exercício induz fenómenos de isquemia que aumentam os níveis inflamatórios e o *stress* oxidativo. Por outro, a participação nestes programas demonstrou trazer benefícios nas distâncias percorridas e na qualidade de vida, associados a mudanças na função endotelial, no estado inflamatório, nas fibras musculares e na angiogénese. Apesar disto, o exercício físico supervisionado está pouco implementado devido às suas limitações e alternativas como o exercício na comunidade e no domicílio estão a surgir com resultados promissores.

Conclusão: O exercício físico supervisionado está associado a adaptações fisiológicas locais e sistémicas. A sua ineficaz implementação permite que programas alternativos comecem a ganhar relevância como tratamento nestes doentes.

Palavras-chave: *Peripheral Arterial Disease, Intermittent Claudication, Exercise Therapy, Supervised*

ABSTRACT

Background: The global prevalence of Peripheral Arterial Disease is growing. This condition is associated with serious hallmarks, such as impaired functional capacity and decreased quality of life. Reduced blood flow and oxygen delivery are its dominant mechanisms, although additional ones contribute to it. Exercise therapy is a cornerstone in the management of intermittent claudication and current guidelines recommend supervised exercise therapy as first-line treatment.

Objective: The primary aim of review was to analyse the impact of supervised exercise therapy on three levels: physiological, walking distances (objective outcomes) and quality of life (subjective outcomes). The secondary objectives were to review its limitations and the feasibility of other programs.

Methods: A search was conducted on PubMed database with the following key words of Medical Subject Headings: "*Peripheral Arterial Disease*", "*Intermittent Claudication*", "*Exercise Therapy*", and "*Supervised*". Main guidelines were also consulted.

Development: Physiological changes associated with supervised exercise therapy are not fully understood. Repetitive ischemia-induced phenomena by exercise can lead to an increase of inflammatory levels and oxidative stress. However, the participation in these programs demonstrates benefits in walking distances and quality of life, associated with changes in endothelial function, inflammatory state, muscle composition and angiogenesis. In contrast, ankle-brachial index does not change. Despite the good outcomes, supervised exercise is poorly widespread due to its limitations and emerging alternatives such as structured community-based or home-based therapies are surging with promising results.

Conclusions: Supervised exercise therapy is associated with local and systemic physiological changes. However, it remains an underutilized tool and alternative programs for claudicant patients are emerging.

Key words: Peripheral Arterial Disease, Intermittent Claudication, Exercise Therapy, Supervised

ABBREVIATIONS

ABI – Ankle-Brachial Index

ADMA – Asymmetric Dimethylarginine

CAC – Circulating Angiogenic Cells

CBET – Community-Based Exercise Therapy

COR – Class of Recommendation

CRP – C-Reactive Protein

EPC – Endothelial Progenitor Cells

FGF2 – Fibroblast Growth Factor-2

FMD – Flow-mediated Vasodilation

HBET – Home-Based Exercise Therapy

HGF – Hepatocyte Growth Factor

HMOX1 – Heme Oxygenase 1

HMOX2 – Heme Oxygenase 2

HsCRP – High-sensitivity C-Reactive Protein

IC – Intermittent Claudication

ICAM-1 – Intercellular Cell Adhesion Molecule-1

IL – Interleukin

LM – Lean Mass

LOE – Level of Evidence

MHC – Myosin Heavy Chain

NO – Nitric Oxide

NOS – Nitric Oxide Synthetase

PAD – Peripheral Arterial Disease

QoL – Quality of Life

ROS – Reactive Oxygen Species

SET – Supervised Exercise Therapy

SF-36 – Short Form 36-Item Questionnaire

SMM – Skeletal Muscle Mass

SOD1 – Superoxide Dismutase 1

SPPB – Short Physical Performance Battery

VCAM-1 – Vascular Cell Adhesion Molecule-1

VEGF-A – Vascular Endothelial Growth Factor

VEGF-R1 – Vascular Endothelial Growth Factor

WIQ – Walking Impairment Questionnaire

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FIGURE LIST

1. BACKGROUND

Peripheral arterial disease (PAD) continues to grow in global prevalence associated with the population ageing. Prevalence of lower extremity PAD is approximately 202 million people worldwide, of whom almost 40 million are living in Europe.[1] The major risk factors for lower extremity PAD are similar to those for coronary and cerebrovascular disease, with some differences in the relative importance of factors, such smoking and diabetes mellitus as strong risk factors.[2]

Patients with PAD are rather a heterogeneous population. Symptoms are categorized according to the Fontaine or Rutherford classifications. While the majority of patients are asymptomatic, intermittent claudication (IC) is the most common presentation in symptomatic patients.[3] It´s defined by fatigue, discomfort, cramping, or pain of vascular origin in the muscles of the lower extremities that is consistently induced by exercise and relieved by rest within 10 minutes.[4] Although the calf muscles are most often affected, any leg muscle group may be affected.[2]

Peripheral arterial disease is a component of systemic atherosclerosis that leads to a reduced functional capacity, walking ability,[5] and reduced quality of life (QoL).[6] The underlying mechanisms responsible for limitations in this population are dominantly the reduction in exercise blood flow and oxygen delivery to exercising skeletal muscle, but additional pathophysiologic mechanisms can contribute. Prior to the development of structural changes and clinical symptoms, endothelial dysfunction is the earliest marker of vascular dysfunction. Therefore patients with IC have an impaired endothelial function characterized by a decrease in flow-mediated vasodilation (FMD).[7] In addition, these patients present a higher endothelial apoptosis and reactive oxygen species (ROS) production.[8]

An increased pro-inflammatory state as measured by levels of high-sensitivity C-reactive protein (HsCRP),[8] interleukin(IL)-6,[9] IL-8,[8] and endothelial-derived adhesion cells, such vascular cell adhesion molecule-1 (VCAM-1) and intercellular cell adhesion molecule-1 (ICAM-1), is present when compared with healthy controls.[9] Endothelial cell inflammation and circulating biomarkers of inflammation, as well as antioxidant capacity, are all impaired,[8] and were associated with reduced exercise performance and microcirculation of the ischemic calf musculature during exercise.[10]

The reduced capillary density in calf muscles[11] and the lower levels of angiogenic growth factors, like vascular endothelial growth factor (VEGF-A) and hepatocyte growth factor (HCF), suggest that patients with IC have lower levels of angiogenesis.[8] Impaired microcirculation plus exercise-induced ischemia that exacerbate inflammatory response and ROS production may be deleterious for skeletal muscle, with reduced muscle mass, shift toward greater proportion of type II fibres and fewer type I fibres, and changed mitochondrial function, as possible consequences.[12] In fact, lower ankle-brachial index (ABI) values are associated with lower calf muscle mass, supporting the hypothesis that lower extremity ischemia has a direct adverse effect.[13]

Beyond the impact on functional capacity and QoL, PAD is linked strongly and independently associated to cardiac and cerebrovascular disease morbidity and mortality. A large proportion of those with PAD have concomitant cardiovascular and/or cerebrovascular disease, thereby contributing to their elevated rates of cardiovascular mortality.[14]

Taking these patient's specificities into account, the current guidelines defend that treatment must be individualized and based on a careful assessment of risk factors, compliance, and subjective values of the patients. All patients with IC should receive multi-component therapy with the goals focused on reducing cardiovascular events rates, improving performance, and preventing functional decline.[2-4]

Exercise therapy has been a cornerstone in the management of IC for more than 40 years. Exercise programs may be self-directed, supervised, of varying intensity and may be institution- or home-based.[2] *ESC/ESVS 2017*[3] and *AHA/ACC 2016*[4] *Guidelines* recommend supervised exercise therapy (SET) as first-line treatment of subjects with IC to improve symptoms and reduce concomitant cardiovascular risk. Supervised exercise therapy can be safely prescribed in these patients,[15] with a reduce of overall cardiovascular mortality by 52% and morbidity by 30%.[16]

Supervised exercise therapy is defined by the *AHA/ACC 2016 Guideline* as a program that takes place in a hospital or outpatient facility in which intermittent walking exercise is used as the treatment modality and is directly supervised by qualified healthcare provider(s). Alternatively, when SET is unavailable, structured community- (CBET) or home-based (HBET) exercise programs that takes place in the personal setting of the patients with the guidance of healthcare providers who prescribe an exercise regimen similar to that of a supervised program, can be beneficial (COR IIa, LOE A).[4] This alternative may incorporate behavioural changes techniques, such as health coaching and/or use of activity monitors.[4]

Exercise programs for IC potentially consist of various forms of lower extremity exercise alone, in combination (walking, running, cycling, etc), upper extremity exercise, or both, and vary with respect to intervals of training, duration of training, intensity of training, and claudication end points.[2] Typically, SET is based on treadmill and track walking, which are the most effective. Sessions are performed at least 3 times per week for a minimum of 12 weeks (3 months). Each session is performed for a minimum of 30-45 minutes, involving intermittent bouts of walking to moderate-to-maximum claudication, alternating with periods of rest, and a warm-up and cool-down period of 5–10 minutes each. Over time, pain-free and maximal walking distance increase such that periodic adjustments in speed and grade are required by rehabilitation personnel in order to elicit claudication symptoms.[4]

However, even though these programs are well structured, they will always depend on patient compliance. Higher exercise compliance was strongly associated with an improvement in claudication.[17]

2. METHODS

The review was performed using PubMed databases. The search strategy aimed to identify articles which included SET as therapy of patients with IC. This search was conducted using the following medical subject heading (MeSH) terms: “Peripheral Arterial Disease”, “Intermittent Claudication”, “Exercise Therapy”, and “Supervised”. It was limited from January 2000 to December 2018, in English language.

The inclusion criteria were: published data in English language and studies which analyse the outcomes of SET, its limitations and alternative programs. Single case reports, hybrid approaches or focus in other therapeutic techniques, and study populations not exclusively Fontaine grade II / Rutherford grade I were excluded (Figure 1).

4. PHYSIOLOGICAL CHANGES

The exercise training has effects beyond improvements in walking distance, such as systemic and local biologic adaptations. Although the precise mechanisms are unknown,[2] several studies have tried to understand them.

a) Influence of exercise on blood flow and endothelial function

Parmenter *et al.* suggested in a systematic review of randomized controlled trials including 1237 patients that changes in lower limb haemodynamic measures of flow and pressure do not appear to explain clinical benefits of exercise in patients with IC.[18] No significantly changes were observed on resting ABI, post-exercise ABI or reactive hyperaemic calf blood flow after an exercise program.[18] Also a *Cochrane Database Systematic Review 2017* did not found improvements on ABI after exercise therapies.[19] A limitation of these studies is that SET was not the only exercise program performed. Januszek *et al.*[20, 21] showed an increase in ABI at the completion of 12 weeks long SET, although one of them lost statistical significance at follow-up.[20]

Endothelial dysfunction is the earliest event in the development of atherosclerosis, and is therefore present in patients with IC. This injury, manifested by impairment of the endothelial-dependent vasodilation, contributes to the increase peripheral resistance, decreased blood flow rate, and limited oxygenation. The brachial artery FMD, as a widely used method for assessing this function, is the per cent change in artery diameter during post-occlusive reactive hyperaemia.[20] It is an independent predictor of cardiovascular risk[22] and is reduced in these patients.[7] An improvement of endothelial function was achieved in some studies where FMD significantly increase after 12-weeks SET[20, 21, 23, 24] or 6-months SET[25], but not in all.[26]

Nitric oxide (NO), a potent vasodilator, which may be responsible for this improvement, has shown ambiguous results in different studies.[24, 26, 27] A decreased of NO, measured by levels of nitrite and nitrates (stable metabolites of NO), was observed in one study[26], and an increase of plasma nitrite levels post single exercise at the end of 12-weeks SET was observed in another study.[24] A third work did not found changes in the activity of nitric oxide synthetase (NOS).[27] The endogenous NOS inhibitor asymmetric dimethylarginine (ADMA) has shown a significant decrease upon SET with a sustained reduction at follow-up.[28] Delaney *et al.* randomized 35 patients with IC into 12-weeks of treadmill-only SET group or 12-weeks of a combination of treadmill and lower-limb resistance SET to observe NO and ADMA variations.[26] In the treadmill group, they obtained a decreased NO (as mentioned above) and no changes in ADMA, while in combination group no significant decrease of NO was noticed but an increase in ADMA was present.

Other vasoactive substances, such thromboxane A_2 and prostacyclin have been studied in response to exercise in patients with IC. However, authors concluded that improvement of walking abilities and endothelial function is not related to thromboxane A_2 and prostacyclin release.[21]

b) Influence of exercise on inflammation and oxidative stress

Associations between inflammation and functional measures have been assessed by some studies. McDermott *et al.* concluded that higher levels of C-reactive protein (CRP), IL-6, soluble ICAM-1, and soluble VCAM-1 are related to worse walking ability in PAD patients.[29]

Studies established an association between regular walking exercise in patients with IC and their inflammatory state. In fact, higher levels of physical activity have been associated with lower levels of inflammatory markers such HsCRP,[30] CRP, IL-6, soluble ICAM-1, and soluble VCAM-1.[31] Also homocysteine, which is pro-inflammatory and pro-atherogenic, showed a decrease with higher levels of walking.[31]

There seems to be a contradiction in the levels of circulation inflammatory markers related to exercise. While there is an increase in some markers due to acute treadmill exercise, the participation in a SET program induces a long-term “anti-inflammatory” effect.[32]

As shown in Table I, immediately after exercise, claudicants developed significant neutrophil activation and degranulation with free radical damage.[32, 33] However, at the end of SET this rise was not present anymore.[32, 33] The amelioration of inflammation status was corroborated by the decrease of IL-12 and interferon-γ following an acute bout of exercise in treadmill-training group.[33] Free radicals injury appeared to be curtailed after 3 months although this effect was not maintained at 6 months of follow-up.[32]

Several studies, using different markers, have sought to determine better the impact of an exercise program (mostly treadmill-based SET) on the patient’s inflammatory state. SET decreases non-specific markers of inflammation, such CRP[27, 34] or HsCRP[20] and fibrinogen[34], and levels of cytokines, such IL-6.[27]However, a randomized controlled trial that allocated 27 patients to a SET with 6 months of duration did not observe changes of markers of inflammation, measuring HsCRP, fibrinogen, and IL-6.[35] Plasma levels of the specific endothelium-derived inflammatory markers E-selectin and ICAM-1 were reduced after a 2-months SET program[36], but Nowak *et al.* did not reach these improvements although E-selectin had a tendency to decrease.[27] (Table I)

The oxygen imbalance and the phenomenon of ischemia-reperfusion are also associated with oxidative stress and spill-over of ROS, as observed by Turton.[32] To assess the antioxidant capacity, Nowak *et al.* evaluated expression of antioxidant genes Heme Oxygenase 1 (HMOX1), Heme Oxygenase 2 (HMOX2), and Superoxide Dismutase 1 (SOD1). At the beginning of SET, a single exercise increased levels of SOD1 and decreased levels of HMOX1. At the end of SET, exercise-induced upregulation of SOD1 was maintained, downregulation of HMOX1 disappeared, and it was observed a trend toward increased expression of HMOX2, suggesting that 12-weeks SET may improve the antioxidant response.[27]

c) *Influence of exercise on angiogenesis*

A reduced capillary density is found in the gastrocnemius muscle of patients with IC, and this alteration correlates significantly with several indicators of exercise tolerance such as peak oxygen consumption, peak walking time and claudication onset time.[11] Increase in capillary density should enhance the nutritional blood flow within the contracting muscle, resulting in a greater oxygen extraction and muscle performance.

A limited blood flow, as it occurs in PAD patients, leads to a difficulty in maintaining sufficient oxygen at the muscle, namely when the metabolic demands of the activity surpass what can be supported aerobically. Thus, exercise-induced ischemia is expected to increase the stimuli for angiogenesis due to hypoxia.[37] Investigators have analysed the presence of these stimuli in patients with IC after an acute treadmill test through measurement of plasma VEGF-A and others (Table I). While it was observed that calf muscle VEGF-A mRNA concentrations increased after exercise[38], it did not reflect changes in VEGF-A levels[38, 39] or in soluble VEGF-Receptor 1 (VEGFR-1)[39] in blood samples from 15 to 120 minutes post-exercise. Fibroblast growth factor-2 (FGF2), other pro-angiogenic molecule present in exercised muscle, showed a clear decrease in its plasma level.[38]

Gastrocnemius muscle biopsies to compare claudicants with healthy control subjects showed that IC patients had significantly fewer capillaries per area[11, 40] and significantly lower skeletal muscle VEGF-R1 concentrations. Both groups had similar skeletal muscle VEGF-A concentrations (pro-angiogenic) and $VEGF_{165b}$ concentrations (an anti-angiogenic form).[40] When submitted to SET programs, patients had an increase in capillary density[37, 40] and a decrease in skeletal muscle VEGF-A concentrations. No statistically significant changes were observed in $VEGF_{165b}$ concentrations, which trended to increase, neither in VEGF-R1 concentrations. Furthermore, there is a strong positive relationship between skeletal muscle VEGF-A concentrations and the capillary density after 12 weeks of SET.[40] Plasma VEGF-A values after SET training appeared to be unchanged in two studies,[27, 28] while another study has shown a significant increase.[34]

Circulating angiogenic cells (CAC) have been assessed by some authors that had contradictory findings.[27, 28, 34] Although Nowak *et al.*[27] tested the impact of single treadmill exercise on these cells and observed the increased number of a CAC subtype before, but not after 12-weeks training SET, the other two authors compared baseline values with post 6-months SET values. CAC levels had a significant increase in Schlager's study[28] but it had a significant decrease in Dopheide's study.[34] The last author also described a rise in levels of proangiogenic Tie-2 expressing monocytes.[34] However, none of these studies determined late outgrowth endothelial progenitor cells (EPC) which were shown to have distinct growth characteristics, morphological appearance and more endothelial-specific properties compared to early EPC (CAC, CFU-Hill).[28]

d) Influence of exercise on muscle morphology and muscle metabolism

Even if the literature's evidence does not clarify what exact measure of "strength" is impaired in population with IC due to an array of muscle groups assessed with various methods[12], a study by Wang *et al.* demonstrated that treadmill-based SET significantly increased calf-muscle strength and endurance. It also showed a moderate correlation between the improved muscle endurance and walking capacity.[41] Nevertheless, it did not provide direct evidence to explain the underlying mechanism.

Such improvements may be due to the increase in skeletal muscle mass (SMM), but it has been demonstrated that patients with increasing severity of lower limb PAD have reduced calf muscle area suggesting a negative relationship between ischemia and muscle mass.[13] Thus, repetitive ischemia-reperfusion caused by treadmill-based SET may be deleterious to muscle function. A recent randomized controlled trial in which standard treadmill SET was compared to combination walking and resistance exercises showed an increase in activity of muscle calpain, a protease implicated in myocyte damage and apoptosis only in treadmill-based SET. In addition, change in SMM in symptomatic legs after 12-weeks SET showed a tendency to decline.[42] On the other hand, combination group demonstrated increased of SMM in symptomatic legs and a tendency to decreased calpain activity.[42] This goes according to the results of Pilz *et al.*, which showed that strength parameters such "pushing", "pulling", and "tiptoe standing" significantly increased after SET combining endurance and strength training.[43] Vun's findings showed that completion of standard treadmill SET with 12 weeks of duration is not accompanied by a loss of lean mass (LM) in the symptomatic calves, but it resulted in a significant decrease in bilateral thigh LM.[44]

An interesting finding by McDermott revealed that muscle characteristics in the leg with higher ABI were significantly associated with walking performance, suggesting that the leg with higher ABI compensates the impairments.[13]

Muscle mass alone may be not the only determinant of strength and function. In support of this, changes in muscle fibre composition have been observed after SET. Thirty-eight patients with IC submitted to 12 weeks long SET obtained an increase in the proportion of myosin heavy chain (MHC) type I expression within the symptomatic gastrocnemius muscle. In addition, this finding was correlated with improved walking performance.[45] A rise in the proportion of MHC type I is potentially beneficial for claudicants, increasing oxidative capacity and reducing the rapid switch to anaerobic glycolysis associated with the faster glycolytic fibers.[45]

5. OUTCOMES OF SET

The walking impairment, the QoL and the outcomes of SET are usually measured by validated tests. Based on these tests, researchers can establish and compare objective measures of walking ability and also subjective measures related to QoL in patients with IC.[46]

a) *Objective outcomes* (Table II and Table III)

The objective outcomes are represented by the walking distance or time to onset of claudication pain (also called pain-free walking distance or time) and maximal walking distance or time during a test. These measures are commonly obtained by the treadmill walking test or the 6-minute walking test.[46] Treadmill test is conducted in a tightly controlled setting, while the 6-minute walk simulates walking in the community, since it is performed in a hall corridor.[46]

A *Cochrane 2017 review* that compares any exercise program used for treatment of IC with no exercise group showed the effectiveness of exercise on the improvement of walking times and distances.[19] *Cochrane 2013 review* demonstrated that the increase in maximal treadmill distance and pain-free walking distance by SET were statistically significant once compared to non-supervised exercise.[47]

Fakhry *et al.* published a meta-analysis comparing SET versus a non-interventional group. Results demonstrated that SET was associated with a 180 meters and 128 meters greater increase in maximal treadmill walking distance and pain-free treadmill walking distance, respectively.[48]

Although a number of clinical trials had examined short-term impact of SET in IC (up to 1 year of follow-up[47, 48]), few studies have reported long-term outcomes in these patients. At long-term follow-up, two studies which applied 12 weeks of SET showed that maximum walking distance or time had no sustained improvement after 4 years (1,66 to 6,66)[49] or 4,8 years (3,9 to 5,5).[50] Indeed this value and pain-free walking distance or time value returned to baseline values (no significant difference for initial values observed before SET). Menard *et al.* recognized that this was present in patients who were no longer exercising at follow-up and become sedentary. Those patients who reported exercising a minimum of 60 minutes per week after the end of supervision maintained a superior pain-free walking time (121% above baseline) and maximum walking time (109% above baseline).[49] Fakhry *et al.* demonstrated a relative maintained walking distances after 7 years of follow-up (+975 meters for maximum walking distance and +700 meters for pain-free walking distance). However, there was no information from participants on regular exercise performance after the trial, and SET lasted 24 weeks.[51] Similar results were obtained on another study that followed patients with IC 3 years after completing SET (for 10 weeks in this case). After the initial improvement in walking ability at 3 months up to 1 year, there was no further significant improvement at 2 and 3 years, although the increase was sustained.[52]

b) *Subjective outcomes* (Table II and Table III)

The large number of scales to assess the QoL makes it difficult to aggregate and to compare results. This review focused on the questionnaires more frequently applied: Walking Impairment Questionnaire (WIQ) and Short Form 36-Item Questionnaire (SF-36).

The WIQ (scoring range 0-100) provides a well-validated measure of functional ability assessing: limitation in walking are analysed in 4 domains (pain, distance, speed, and stair climbing), while the SF-36 (scoring range 0-100) provides a comprehensive assessment of health-related quality of life. It measures 8 domains (physical, role and social functioning, mental health, patient health perceptions, vitality, body pain, and change in health) and results can be separated into physical and mental component summary score.[46]

Findings of a meta-analysis which included randomized controlled trials of any exercise training versus usual medical care in patients with PAD suggested that exercise training improves their physical component of the SF-36 as well as perceived walking distance, speed and stair-climbing as measured by the WIQ. However, the mental component of the SF-36 was not improved.[53] Similar meta-analysis which included any exercise program revealed improvement in physical component and mental component of the SF-36 at six-months, but the last one no longer showed improvement when a random-effects model was applied.[19]

About SET, no study demonstrated a significant effect on QoL parameters when compared with non-supervised exercise therapy. Only the role general health of SF-36 at 3 months and the role of pain at 6 months showed significant improvement with SET.[47] A 7 year study demonstrated significant improvement in SF-36 physical functioning, SF-36 body pain, and SF-36 general health at 1 year, but not after 7 years. Despite that, the Vascular Quality of Life Questionnaire score increased significantly after 7 years.[51] Menard *et al.*, who separated patients into two groups during the follow-up (4 years), concluded that those who reported regular exercise exhibited significantly higher physical function, role-physical function, body pain, and physical component summary score of SF-36 when compared with the sedentary group. This difference was also verified for WIQ distance score, speed, and stair-climbing ability.[49]

c) Other outcomes (Table II)

Patients with IC, in which the main symptom is reduced walking ability, can have difficulty to do activities of daily living which require lower extremity function as the major component.

The Short Physical Performance Battery (SPPB) is a global measure of lower-limb physical function that scores between 0 and 12. Patients are submitted to 3 tests: 1) 4-meters walk test to assess the walking velocity in a line straight line; 2) Chair stand test, patients were asked to stand up and sit down five times; and 3) Semi-tandem and full-tandem stance to assess their ability to maintain a tandem or semi-tandem for 10 seconds.[54] After 12 weeks of SET, patients with a score of 7.5 at baseline improved to 11. This improvement of physical function was maintained at 12-months follow-up[54], although a longer follow-up (≥1-4 years) demonstrated a significant decline in this score.[55] Mockford's findings also suggested that SET can improve balance in patients with IC.[54] These changes can be important on improving the quality of performing functional tasks, such walking with less risk of falls, climb stairs and complete activities of daily living.

On the other hand, the gait of claudicants does not appear to change with SET. In fact, two studies concluded that SET does not have impact on lower limb mobility[56] and does not improve gait parameters in patients with IC.[57]

6. LIMITATIONS OF SUPERVISED EXERCISE THERAPY

In several randomized controlled trials and systematic reviews, SET is compared with usual care, placebo, walking advice and endovascular revascularization. The evidence supporting the efficacy of SET programs to alleviate IC's symptoms is robust. Based on contemporary guidelines, SET should be offered to all patients with IC.[2-4] Nevertheless, only few of all newly diagnosed IC patients worldwide receive this treatment.[58] Harwood *et al.* showed that approximately 1 in 3 screened patients with IC was suitable for and willing to undertake SET.[59]

In 2012, an European survey on SET availability among vascular surgeons showed that only 30.4% had access to SET. This availability seems to vary greatly depending on the country, with the Netherlands leading the list (100%), followed by France (66.7%).[60] In the Netherlands, more than three-quarters of new patients with IC are estimated to be referred for SET by vascular surgeons.[61] This superiority is explained by the launch of ClaudicatioNet concept in 2011.[58] While ClaudicatioNet includes more than 1700 specialized physiotherapists and fully coverage of SET by the basic health insurance[58], the limited availability of qualified therapists[61] and the lack of reimbursement[58] on other countries are barriers to the implementation of SET.

SET takes place in a hospital or health care clinic setting. Training is performed for a minimum of 12 weeks, at least 3 times weekly with a minimum of 30 to 45 minutes per session. Intermittent bouts of walking to moderate-to-maximum claudication, alternating with periods of rest are used as the treatment modality. Programs entail adequate coaching and direct supervising by qualified healthcare provider(s).[4]

Some of the barriers are due to these program specificities: the capacity of a single department in a hospital is limited and not sufficient to provide SET to all patients with IC of the adherent community. Attending a hospital three times weekly is time consuming and expensive for patients.[58] Inability to attend classes, due to location or timing, represented 11.7% of the reasons to exclude a patient form being submitted to SET and 3.8% of the reasons for having poor adherence.[59] These transportation issues were mentioned by 13.46% of the patients who reported SET's subjective barriers.[17]

Other major reason for poor uptake and adherence is patient's lack of motivation. This lack of interest was a subjective barrier to exercise compliance for 25% of 98 patients.[17] Similar results were obtained by a meta-analysis that found this barrier in 30.6% of the patients who did not accept SET and in 29.2% of the patients who dropped out.[59]

Comorbidities were the reason why a significant proportion of patients were not enrolled in or failed to complete SET.[17, 59] Concomitant health problems, such as arthritis or cardiopulmonary disease, can be responsible for an inability to exercise on an appropriate level. A Dutch survey revealed that the criteria to not refer for SET are largely based on existence of major comorbidity.[61]

Other reasons given were social factors such family or work commitments and the feeling that training was not beneficial.[17, 59]

7. ALTERNATIVES

Supervised exercise therapy offered at medical facilities for patients with IC, although effective, are often unatainnable due to a number of implementation barriers, including lack of reimbursement and the need to travel to specialized locations for the training intervention.[58] A systematic review summarized refusal rates by potential participants in 23 clinical trials of SET and demonstrated that even when SET was available without cost to the participant with IC, approximately two-thirds of people declined participation.[59]

The difficulty of implementing such programs provides a rationale for the use of alternatives such as walking programs in community settings or home-based walking programs, considering that these may be less costly and more feasible for patients to participate in. Even though CBET and HBET have the potential to be more accepted and accessible, these alternatives without supervision were considered not effective for patients with IC.[62] However, some adjustments in these programs, such as incorporating more intensive monitoring and coaching by staff, may change this lack of effectiveness.

In fact, when SET is not feasible or available, *ESC/ESVS 2017* recommended non-supervised exercise training (COR I, LOE C)[3], and *AHA/ACC 2016 Guideline* recommended structured Community-based Exercise Therapy or Home-based Exercise Therapy with behavioral change techniques (COR IIa, LOE A).[4]

a) Home-based walking programs

An HBET program is cheap and comfortable. As a matter of fact, home-based exercises take place in an environment of the patients choosing, such walking around neighbourhoods similar to walking in daily life. To enhance the effectiveness of HBET, researchers had used similar exercise instructions to those used for SET. Moreover, group-mediated cognitive behavioural intervention and/or an observation component (e.g. exercise logbooks, pedometers) were added to the simple walking advice.[63] These supplements transform the “go home and walk” advice into a structured program.[4] In support of this adaptations, a recent questionnaire has shown that patients with IC are interested in technology-delivered exercise which permit a HBET receiving health advice and activity remote monitoring.[64]

Therapeutic educational workshops and personalized phone coaching, with the aim of empowering patients, were tested as supplements of HBET.[65] Significant improvements in functional and QoL parameters were observed. The program also led to an improvement in autonomy of patients and cardiovascular risk control. Patients showed significant persistence of these changes during the 12-months follow-up.[65]

Several studies have compared structured HBET with SET and/or with non-exercising group (Table IV). Three studies used identical approaches (wored a step activity monitor technology during each exercise session and discussed their progress with a professional periodically) had high adherence rates.[66-68] Though Gardner *et al.*[66, 67] had promising outcomes, Mays *et al.*[68] did not improve maximum walking time compared with non-exercising group. Additional fiding were that HBET had a superior improve in 6-minute walking distance[67] and it appears to be more efficacious in increasing daily ambulatory activity than SET.[66]

A recent Cochrane review compared outcomes of SET versus structured HBET versus "go home and walk" advice.[69] Investigators of 12 trials designed HBET programs to be similar to SET programs supplemented with an observation component and/or an education component. Overall, adherence to HBET was 81% to 83% (SET: 82% to 85%) and data showed no significant difference between SET and HBET in QoL parameters. About walking distances there were no clear differences between HBET and walking advice group. However, authors alert for the considerably smaller sample size of the HBET that may have contributed to an indistinct effect assessment and may also explain the absence of a difference between HBET and walking advice groups.[69]

These programs have great variability and, in many cases, intervention components were poorly described and unjustified. In conclusion, there was "low-level" evidence that HBET can improve walking distances and QoL when compared with base line or usual care. Nevertheless, successful HBET programs typically included self-monitoring, goal-setting, and identification of barriers to walking and solutions towards overcoming them.[70]

Advantages of HBET include less burdensome and more convenience for patients, since walking in their neighbourhood or even within their home environment is more accessible than travelling to a supervised exercise center. In spite of that, HBET has its limitations. For example, the quality of sidewalks or the availability of adequate seating to rest when patient experiences IC may not be adequate or safe, difficulting the exercise practicing[62] and enhancing dropouts.

b) Community-based exercise therapy

The limitations of SET hospital-based or clinic-based programs led to the idea of taking a community approach for SET. Implementation of CBET with supervision was first described by Willigendael *et al.*[71] To improve the care for patients with IC, a regional network of physiotherapists was able to provide supervised exercise training close to the patient's home address.[71]

Based on this approach, regional[72, 73] and multicenter[74] studies investigated the effectiveness of supervised CBET. Similar results were obtained in the regional studies. Supervised CBET seems as efficacious as SET at hospital or clinic in improving walking distances. However, they both had high dropout rates (39,8%[72] and 52,6%[73]). The main reasons for patients to stop their therapy were emerging disease due to comorbidities, lack of motivation, and unsatisfying results.

A multicenter randomized clinical trial with 304 patients was able to demonstrate a beneficial effect of supervised CBET on walking distance, WIQ scores, and physical summary score of SF-36.[74] This study had a higher adherence compared with regional network studies. The drop-out rate was approximately 15%. Similar reasons of non-attendance were found.[74]

ClaudicatioNet, a supervised CBET based on the mentioned studies and the EXITPAD-trial, was launched in the Netherlands in 2011. This nationwide network of specialized physiotherapists provides supervised exercise therapy and lifestyle counselling for patients with PAD. It bridges the gap between the various healthcare professionals such as physiotherapists, vascular surgeons, and general practitioners. This care intervention has resulted in optimized quality of care for all patients with IC.[58]

8. DISCUSSION

Impairment of walking ability is the most obvious consequence of IC[5] that obligates patients to stop their walking due to onset of pain. Associated to this symptom, patients may have their daily life activities affected by either limiting pain or fear that this pain arises, justifying a reduced quality of life in this group.[6]

Supervised exercise therapy is a cornerstone in the treatment of patients with IC. This fact is corroborated by recommendations of the most important guidelines[2-4] and numerous randomized clinical trials. SET is associated with not fully understood local and systemic adaptations, which lead to an increased walking capacity[47] and a consequent improvements in patient's QoL.

Although Januszek *et al.*[20, 21] showed an increase on ABI, an important value to PAD, the gross of literature did not found significantly changes in this parameter, either resting ABI or post-exercise ABI.[18, 19] These results make less likely that a change in macrocirculation was responsible for the improvement in walking performance.

The endothelial function, assessed by FMD, appears to have a positive change with SET. Only one study[26] did not describe improves in FMD. The authors defend their results based on techniques used, although, of mentioned studies[20, 21, 23-26], only Brendle *et al.*[25] have demonstrated improvement in FMD using a different technique (proximal cuff occlusion). In fact, it seems to be a systemic effect of SET in endothelial function which is not yet fully explained. If on one hand studies about vasoactive substances are not conclusive[24, 26, 27], on the other the amelioration in inflammatory markers[20, 27, 32, 34, 36] suggest that exists a long-term anti-inflammatory effect with SET. Given the many mechanisms involved and the complex pathophysiology of endothelial dysfunction, this reduce of inflammatory state can be an important factor to improve of other regulators of endothelial function.

At a local level, the majority of studies account with small sample sizes, which may limit results[37-40], but an increased expression of muscle VEGF-A mRNA is present after an acute bout exercise[38] and an increased capillary density of gastrocnemius muscle is present after participating in a SET program.[37, 40] Although these findings are suggestive of angiogenesis due to training, studies about circulating angiogenic cells are not conclusive[27, 28, 34] and changes in plasma VEGF-A values[27, 28, 38, 39] or in muscle VEGF-A[40] do no support this hypothesis. Nevertheless, other growth factors may be responsible for the observed angiogenesis and further work is needed. SET, mostly treadmill-based, showed that does not exist a gain in skeletal muscle mass with this program.[42, 44] Actually, it was associated with an enhanced calpain activity[42], which can be deleterious for muscle. Despite the absent changes in muscle mass, SET increases the proportion of MHC type I[45], which benefices the oxidative capacity of symptomatic leg.

It is evident that exercise training, such as SET, has two important sides on patients with IC. First, SET is constituted by acute exercises with repetitive ischemia-reperfusion phenomena. These aggressions appear to be associated with an increase of inflammatory response and oxidative stress that can aggravate the endothelial function, reduce muscle mass and impair mitochondrial function. Second, SET confers a long-term effect that, ultimately, is responsible for benefits in walking capacity and in cardiovascular morbimortality. This effect seems to be related with an amelioration of inflammatory state, an improvement of endothelial function, an increased angiogenesis and a change of muscle fibres.

Improvement of walking distances is a general conclusion in the majority of studies. However, findings of Gardner *et al.*[67], such as SET having the greatest changes in times measured by treadmill test and HBET having superior distance measured by 6-minute walking test, reflect that the most used test, the treadmill test, may not reflect daily walking performance of patients due to its characteristics and a possible learning effect. In this context, 6-minute walking test may be more related with community settings.

Despite the benefits of SET in patients with IC, this is a poorly accessible and widespread therapy.[58] Issues such attending classes at the hospital or health care clinic are established barriers to implementation of SET. Without reimbursement, these constant travels are an important expense and represent a time burden for patients.[17, 59] Alternative programs have been studied to achieve SET results, overcoming its limitations.

ClaudicatioNet, a Netherlands' program, is the greatest example of SET applied in community settings.[58] The difference between the standard SET and supervised CBET is training's location. The first one takes place in a hospital or health care clinic, the second one takes place close to the patient's home address. As this is the only difference, this program is practically a supervised exercise therapy (SET). About outcomes, supervised CBET seems as efficacious as SET at hospital.[72-74] The large number of qualified therapists required may be a barrier to the implementation of a program of this size.

HBET with behavioural intervention and/or pedometers, for example offered by technology-delivered exercise, seems to be easily accepted by patients with IC.[64] Efficacious of HBET in improving claudication measures is questionable, with some important systematic reviews demonstrating no significant difference between HBET and usual care.[69, 70] Gardner *et al.*, in 2011[66] and 2014[67], demonstrated that patients at HBET with a monitor technology during each exercise session and periodical discussion with a professional of their progress, reach a significant improvement in walking distances. These programs have to be better studied in order to reduce their great variability[70] and to define a successful method.

Curiously, the QoL shows an improvement with training regardless the exercise program (SET, CBET or HBET)[47], suggesting that is the exercise itself, and not the context, that has the greatest impact on this parameter.

At long-term follow-up, studies had different findings. Two studies[49, 50] observed that objective outcomes of SET, such as maximal walking distance and pain-free walking distance, have no sustained improvement after the end of program, while other two[51, 52] observed a relative maintained walking distances. Only Menard *et al.*[49] distinguished between patients who became sedentary and who kept doing regular exercise, concluding that the sedentary group had a deterioration of their results after SET and the other group maintained the increased distances. Patients who reported regular exercise also exhibited higher values in QoL questionnaire. Interestingly, HBET appears to be more effective in increasing daily ambulatory activity in the community setting than SET, after the end of programs.[66]

HBET and CBET were studied as SET alternatives to counter its limitations. However patient-related barriers are common to all programs. Concomitant comorbidities, lack of motivation and unsatisfying results are main reasons for patients to stop CBET.[72-74] Also, in SET, these reasons have a great impact for poor uptake and adherence.[17, 59] Although patient-related barriers are difficult to manage, a cognitive behavioural intervention with professionals may be helpful in delineating goals, identifying individual barriers and how to overcome them, possibly resulting in greater motivation and patient compliance.

9. CONCLUSIONS

Supervised exercise therapy is first-line treatment of subjects with IC to improve symptoms and reduce concomitant cardiovascular risk. In addition to the improved walking distances, SET increases angiogenesis in gastrocnemius muscles, enhances endothelial function, reduces inflammatory state of patients and increases oxidative capacity due to changes in muscle fibres proportion.

However, SET is poorly accessible and widespread. Structured CBET and structured HBET are alternatives. ClaudicatioNet is a great example of structured CBET. This concept allows patients to get SET with physiotherapists near to their homes, with similar outcomes when compared with traditional SET. Structured HBET is a cheaper and more comfortable program for patients who have shown interest in technology-delivered exercise. Although there is “low-level” evidence that structured HBET improve walking distances, there are some promising studies that support this program.

Irrespective of the program used, there are barriers that appear to be universal. Comorbidities and lack of motivation are responsible for a large number of dropouts and poor adherences and patient compliance is central to achieve good results.

Lastly, the change in behaviour and adoption of regular practice of exercise after the end of SET seems to be associated with maintenance of the improvements.

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11. ATTACHMENTS

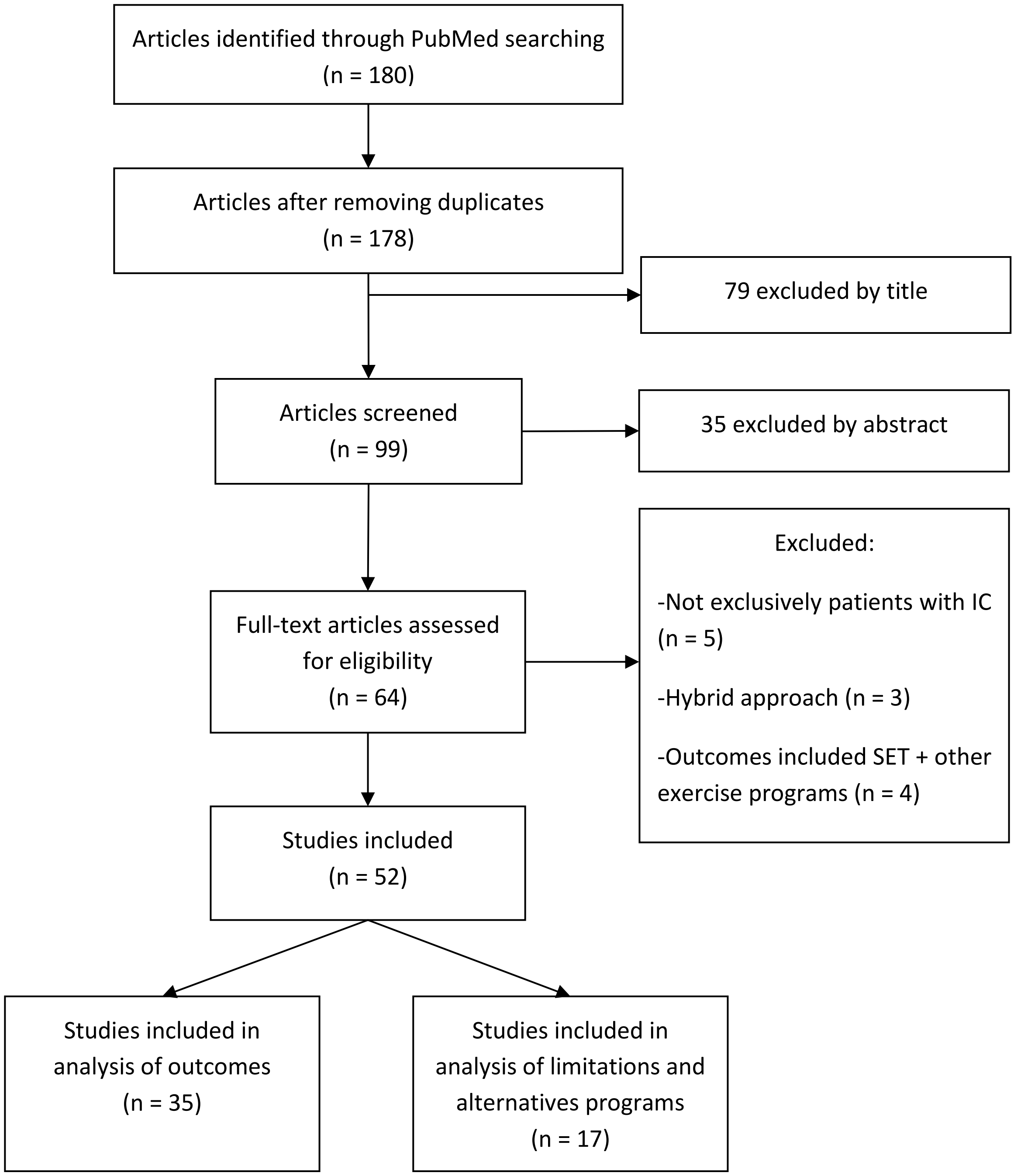

Figure 1 PRISMA driven flow chart of the selection of studies included in the review.

Table I Summary table of original articles included in the review of the physiological effects of SET.

Study	Patients (smokers and diabetics)	Program	Duration	Physiological effects of SET
Januszek *et al.*[20]	67 36 smokers 14 diabetics	SET	12 weeks	1. ABI values improved significantly with SET, such as FMD. 2. SET decreased HsCRP's concentration.
Januszek *et al.*[21]	59 28 smokers 11 diabetics	SET	12 weeks	1. ABI values improve significantly, such as FMD. 2. However, TXB2 and PGI2 were not directly correlated with these improvements.
Mika *et al.*[23]	60 27 smokers 8 diabetics	SET	12 weeks	1. SET increased FMD values. 2. No significant changes were found in HsCRP and fibrinogen.
Allen *et al.*[24]	35 11 smokers Ø diabetics	SET	12 weeks	1. SET increased FMD values that were accompanied by an increased plasma nitrite flux.
Brendle *et al.*[25]	19 8 smokers NR diabetics	SET	6 months	1. SET increased FMD values.
Delaney *et al.*[26]	35 13 smokers* 16 diabetics	SET	12 weeks	1. No significant changes were found in FMD. 2. In the treadmill-based SET, there was no change in ADMA values and there was a decrease in NO values.
Nowak *et al.*[27]	12 7 smokers 2 diabetics	SET	12 weeks	1. FMD tended to improve after SET, but no changes in the activity of nitric oxide synthetase were observed. 2. SET decreased CRP and IL-6. 3. SET improved the antioxidant response.
Schlager *et al.*[28]	40 17 smokers 16 diabetics	SET	6 months	1. SET increased levels of CAC. 2. SET decreased ADMA levels. 3. No significant changes were observed for VEGF-A and SDF-1 plasma levels.

Turton *et al.*[32]	46 19 smokers 8 diabetics	SET	12 weeks	1. Claudicants developed a significant neutrophil activation and degranulation after acute exercise. 2. SET abolished the increase seen in post-exercise neutrophil activation and reduced the rise in neutrophil degranulation. 3. Free radicals injury appeared to be curtailed after 3 months, but this effect was not maintained at follow-up.
Delaney *et al.*[33]	35 26 smokers* 16 diabetics	SET	12 weeks	1. Neutrophil elastase increased following acute exercise at the start of program. 2. At the end of SET, this rise in neutrophil elastase was not present. 3. The amelioration of inflammatory response was corroborated by the decrease of IL-12 and interferon-γ following an acute bout of exercise in treadmill-training group. Conversely, in the combination based exercise group, the pro-inflammatory cytokines IL-6 and IL-8 did increase following acute exercise at the end of the SET.
Dopheide *et al.*[34]	40 18 smokers 14 diabetics	SET	NR	1. SET led to decreased plasma CRP and fibrinogen. 2. SET led to increased plasma VEGF-A values. 3. CAC levels had a significant decrease after SET, while proangiogenic Tie-2 had an increase.
Schlager *et al.*[35]	53 33 smokers* 21 diabetics	SET	6 months	1. No significant changes were found in HsCRP, fibrinogen, and IL-6 after SET when compared with best medical therapy group.
Saetre *et al.*[36]	29 19 smokers 6 diabetics	SET	8 weeks	1. SET reduced plasma levels of specific endothelium-derived inflammatory markers (E-selectin and ICAM-I), but VCAM-I remained unchanged.
Duscha *et al.*[37]	35 5 smokers Ø diabetics	SET	12 weeks	1. SET increased capillary density in ischemic muscle. Those changes preceded the increase in peak oxygen uptake. 2. There were no changes in markers of oxidative capacity.
Wood *et al.*[39]	18 7 smokers 7 diabetics	SET	6 weeks	1. SET had no effect on plasma VEGF-A at rest or in response to acute exercise.
Jones *et al.*[40]	22 20 smokers* Ø diabetics	SET	36 sessions (max 16 weeks)	1. SET was associated with a significant reduction in VEGF-A levels. 2. An increase in capillary density in ischemic muscle was observed after SET.

Wang *et al.*[41]	22 3 smokers 2 diabetics	SET	12 weeks	1. SET increased calf-muscle strength and endurance.
Delaney *et al.*[42]	35 26 smokers* 16 diabetics	SET	12 weeks	1. In the treadmill-based SET, there was a increase in calpain activity.
Pilz *et al.*[43]	94 33 smokers 41 diabetics	SET	6 / 12 months	1. The combination of strength and endurance exercise significantly increased the walking speed, walking distance, and muscle strength (assessed by "pushing", "pulling" and "tip-toe standing").
Vun *et al.*[44]	36 10 smokers 7 diabetics	SET	12 weeks	1. SET was not accompanied by a loss of LM in the symptomatic calves. 2. However, a significant decrease in bilateral thigh LM was observed.
Beckitt *et al.*[45]	38 12 smokers 14 diabetics	SET	12 weeks	1. SET increased the proportion of MHC type I expression.
Versluis *et al.*[75]	10 NR smokers ᴓ diabetics	SET	6 months	1. No significant changes were found in ABI values. 2. No significant changes were found for number of arteries (angiogenesis) at the level of the arterial lesion.
Crowther *et al.*[76]	16 37 smokers 37 diabetics	SET	6 months	1. SET improved both submaximal walking economy and maximal walking performance (oxygen consume), without significant changes in maximal walking economy.

ABI: Ankle-brachial index; ADMA: Asymmetric dimethylarginine; CAC: Circulating angiogenic cells; CRP: C-reactive protein; FMD: Flow-mediated vasodilation; HsCRP: High-sensitivity C-reactive protein; ICAM-1: Intercellular cell adhesion molecule-1; IL: Interleukin; LM: Lean Mass; MHC: Myosin heavy chain; NO: Nitric oxide; NR: Not reported; PGI2: Prostacyclin; SDF-1: Stromal cell-derived factor-1; SET: Supervised exercise therapy; TXB2: Thromboxane A_2; VCAM-1: Vascular cell adhesion molecule-1; VEGF-A: Vascular endothelial growth factor; ᴓ diabetic excluded form study; * study does not differentiate previous smokers from current smokers

Table II Summary table of original articles included in the review of objective and subjective outcomes.

Study	Patients (smokers and diabetics)	Program(s)	Duration	Outcomes	Effects of SET in walking distances, quality of life and other parameters
Menard *et al.*[49]	34 NR smokers NR diabetics	SET	12 weeks	Treadmill test WIQ SF-36	1. Walking distances had no sustained improvement after 4 years. 2. Those patients who reported exercising a minimum of 60 minutes per week after the end of SET maintained a superior pain-free walking time (121% above baseline) and maximum walking time (109% above baseline). 3. Similar results were obtained in QoL parameters.
Mazari *et al.*[50]	60 9 smokers NR diabetics	SET	12 weeks	Treadmill test SF-36	1. Walking distances has no sustained improvement after 4,8 years.
Fakhry *et al.*[51]	75 17 smokers 15 diabetics	SET	24 weeks	Treadmill test SF-36	1. The walking distances after 7 years of follow-up were relatively maintained (+975 meters for maximal walking distance and +700 meters for pain-free walking distance), unlike the QoL parameters.
Ratliff *et al.*[52]	202 47 smokers 37 diabetics	SET	10 weeks	Treadmill test	1. Results seen at the end of SET were sustained at 3 years follow-up (+250 meters for pain-free walking distance and +372 meters for maximal walking distance).
Mockford *et al.*[54]	51 14 smokers 14 diabetics	SET	12 weeks	Treadmill test 6MWT SF-36 SPPB	1. SET improved the walking distances assessed by treadmill test and 6MWT. 2. SET improved physical function assessed by SPPB. 3. Significant improvements were noted in balance of IC patients.
Kirk *et al.*[55]	21 4 smokers 6 diabetics	SET	12 weeks	6MWT WIQ SF-36 SPPB	1. A decline in walking distances and physical function was observed after long-term follow-up (≥1-4 years). 2. Long-term follow-up was also accompanied by a decline in ABI measures.
Crowther *et al.*[56]	21 4 smokers 4 diabetics	SET	12 months	Gait parameters	1. SET had no significant effect on lower limb mobility, regardless of the increase in walking distances.
King *et al.*[57]	12 NR smokers NR diabetics	SET	12 weeks	Gait parameters	1. No significant differences were found in any of the gait parameters, such as pain-free walking speed, peak hip extension, peak ankle plantarflexion or first vertical ground reaction force peak.

Guidon *et al.*[77]	44 23 smokers 32 diabetics	SET	12 weeks	WIQ SF-36	1. Participation in SET resulted in improvements in functional capacity and QoL at 1 year post-participation, however these improvements were worse than those noted immediately following SET (12 weeks).

ABI: Ankle-brachial index; HBET: Home-based exercise therapy; IC: Intermittent claudication; NR: Not reported; QoL: Quality of life; SET: Supervised exercise therapy; SF-36: Short Form 36-Item Questionnaire; SPPB: Short Physical Performance Battery; WIQ: Walking Impairment Questionnaire; 6MWT: 6-minute walking test

Table III Summary table of meta-analysis included in the review of the objective and subjective outcomes of SET.

Study	Patients	Program(s)	Duration	Outcomes	Changes in walking distances and QoL with SET
Fokkenrood *et al.*[47]	1002	SET	Variable	Treadmill test SF-36	1. SET showed clear improvement in maximal walking distance compared with non-supervised group (approximately more 180 meters). 2. SET did not have a significant effect on QoL parameters.
Fakhry *et al.*[48]	1054	SET	Variable	Treadmill test	1. SET showed a difference of 180 meters in maximal walking distance and 128 meters in pain-free walking distance when compared with a non-interventional group.
Hageman *et al.*[69]	1400	SET HBET	Variable (>6 weeks)	Treadmill test WIQ SF-36	1. SET showed clear improvement in maximal walking distance compared with HBET group or non-exercise group (approximately 120 and 210 meters, respectively, in favour of SET). 2. No clear evidence of difference was observed in walking distances between HBET and non-exercise group. 3. SET and HBET had similar subjective outcomes (QoL parameters).

HBET: Home-based exercise therapy; QoL: Quality of life; SET: Supervised exercise therapy; SF-36: Short Form 36-Item Questionnaire; WIQ: Walking Impairment Questionnaire

Table IV Structured Home-based exercise therapy versus SET

			SET		Structured HBET			
Type	Study	Year	N.	Adherence	N.	Adherence	Objective outcomes	Subjective outcomes
Original	Gardner *et al.*[66]	2011	40	84,8%	40	82,5%	1. Changes in walking distance were significantly different from controls and were not different from changes in SET. 2. HBET appears to be more efficacious in increasing daily ambulatory activity.	1. Changes in QoL parameters were similar to changes in SET.
Original	Mays *et al.*[68]	2015	-	-	25	81,9%	1. HBET did not improve walking distances when compared with control group.	1. HBET improved QoL parameters when compared with control group.
Original	Gardner *et al.*[67]	2014	60	81,7%	60	80,6%	1. HBET was effective such SET in improving walking distances. 2. HBET was superior to the SET for improving 6MWT.	-
Meta-analysis	Hageman *et al.*[69]	2018	635	82-85%	320	81-83%	1. No clear evidence of difference was observed in walking distances between HBET and non-exercise group.	1. No significant difference between SET and HBET in QoL parameters.

HBET: Home-based exercise therapy; QoL: Quality of life; SET: Supervised exercise therapy; 6MWT: 6-minute walking test