Beneficial effects of dietary education, exercising and physical therapy on the quality of life of Peripheral Arterial Disease patients

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Abstract. In this clinical study we aimed to find an answer to the question ″What is the best approach that a medical team can have in front of a patient with chronic Peripheral Arterial Disease (PAD)″ so that we can minimize the evolution to stage IV. We randomized 111 patients (56 men and 55 women) diagnosed with PAD in the lower limbs into three groups: the control group, the exercise (kinetotherapy) group and the physical therapy group. Patients were evaluated using *Medical Outcomes Study (MOS) 36-Items Short Form Survey Instrument* (SF36) at baseline, 12 weeks after the start of the study and at the end of the study, after 24 weeks. The improvement in the physical function of patients with PAD was obvious from 12 weeks and even more so at 24 weeks for both the group of patients who exercised and the scores were statistically significant. The improvements in the mental component of SF36 are also significant, proving once again how important it is for the mental state of a subject to improve their fitness. The values for the vitality component are 40% higher for group 3 at 12 weeks and 30% higher at 24 weeks compared to group 2. Patients in groups 2 and 3, however, reported a significant improvement in general health since at 12 weeks, an improvement that was much better expressed at the end of the study.
Key words: *Peripheral Arterial Disease, kinetotherapy, physical therapy*.

Introduction

The classification of arterial diseases is somewhat arbitrary due to incomplete knowledge of the etiology, some forms being nosological entities well defined by certain clinical features, although they have multi etiology in which the main factor cannot always be highlighted. During the evolution of different forms of arteriopathy, mixed alterations can be associated. For example, in the evolution of obliterating thrombangiitis, lesions of atherosclerosis can also appear, in degenerative arteriopathies inflammatory processes can be entangled in certain phases. The progression of the lesions and their complications lead to ischemic changes or necrosis, depending on the location and severity of the impairment of blood flow. The most common manifestations of atherosclerosis are: ischemic heart disease, ischemia and stroke, peripheral or visceral ischemia syndromes.

A systematic study of 34 studies reported that globally, 202 million people were living with PAD, and during the preceding decade, the number of people with PAD increased by 28.7% in low- to middle-income countries and by 13.1% in high income countries (1). Only 10% of people with PAD have the classic symptom of intermittent claudication... Approximately 40% do not complain of leg pain, whereas the remaining 50% have a variety of leg symptoms different from classic claudication (2, 3).

Atherosclerosis is the most common cause of death in the world today, especially in developed countries.

PAD of the lower extremities affects 20%-30% of older patients, the prevalence increased dramatically with increasing age from less than 10% in those 55 through 59 years old to nearly 60% in those 85 years old or older (4).People with PAD have impaired function and quality of life, regardless of whether or not they report leg symptoms. Furthermore, patients with PAD, including those who are asymptomatic, experience a significant decline in lower-extremity function over time (5,6,7).

A few recent studies have demonstrated that even individuals with low-normal Ankle-brachial Index (ABI) (0.91–0.99) have reduced physical function compared with those with normal ABI (8).

Cardiovascular events are more frequent than ischemic limb events in any lower extremity PAD cohort, regardless of presentation. A lack of daily physical activity is an independent risk factor for cardiovascular disease that's why increased daily exercise training in PAD patients may improve their poor prognosis for long term. Clinical guides for PAD recommend supervised walking exercises, but evidence for the benefits

of the unsupervised walking exercise is minimal to absent. Meta-analyses of the functional improvement that resulted in PAD therapy studies whose duration ranged from 90 to 180 days showed that supervised exercise resulted in the greatest benefit, followed next by cilostazol, and then by pentoxifylline(9).
A 2011 systematic review evaluated lower extremity aerobic exercise against usual care and demonstrated a range of benefits, including the following: increased time to claudication by 71s (79%) to 918s (422%), increased distance before claudication by 15m (5.6%) to 232m (200%), increased walking distance/time by 67% to 101% after 40min of walking 2 to 3 times per week (10).
In a study that randomized patients with PAD to 3 groups (optimal medical care, supervised exercise training, and iliac artery stent placement), supervised exercise resulted in superior treadmill walking distance compared with stenting. Results in the exercise group and stent group were superior to optimal medical care alone (11).
Chronic peripheral vascular disease (PAD), usually with a long evolution over time, is one of the most common causes of disability, thus having a negative impact on the patient's quality of life. Injuries and complications of peripheral arterial disease, sometimes asymptomatic, for a long time, have extremely varied consequences, ranging from limb amputation or even death in neglected acute ischemia. Therapeutic methods applied correctly and in a timely manner, in peripheral vascular disease, yield results with a positive impact, including on these patients' quality of life.
In this clinical study we aimed to find an answer to the question *"What is the best approach that a medical team can have in front of a patient with chronic Peripheral Arterial Disease (PAD"* so that we can minimize the evolution to stage IV with the need for revascularization interventions or the onset of cardiovascular complications.

Material and Method
We randomized 111 patients, 56 men and 55 women, diagnosed with chronic occlusive peripheral arterial disease in the lower limbs. The patients in the group were treated in the Clinical Emergency County Hospital of Craiova, hospitalized in the Physical Medicine and Rehabilitation Clinic or in the specialized outpatient clinic, between February-December, 2019. This study was performed in accordance with the principles of Helsinki Declaration and Good Clinical Practice and was approved by Ethics Committee of the hospital. All patients provided written informed consent.
Once the diagnosis of peripheral arterial disease of the lower limbs was confirmed, the patients were included in the study after the consent to participate was obtained and after the inclusion in the inclusion and exclusion criteria have been analysed. The patients included in the study had to comply with the following *inclusion criteria*: diagnosis of PAD, with or without diabetes mellitus, positive Edinburgh Claudication Questionnaire, Fontaine stage IIa only (mild claudication, walking distance > 60 m),ambulatory without assistive devices, calf muscle claudication within 10 minutes of treadmill walking and calf muscle exercise. *Exclusion criteria*: PAD secondary to Buerger's disease, autoimmune arteritis, fibromuscular dysplasia, chronic and repetitive occupational trauma, venous stasis, hypercoagulability disorder, or arterial embolic disease, severe claudication, leg rest pain, skin ulceration, necrosis or gangrene, poorly controlled diabetes mellitus, poorly controlled hypertension, Raynaud's syndrome, exertional angina, dyspnea, fatigue, or dizziness, severe coronary artery disease, congestive heart failure, exercise intolerance limited by leg pain of nonvascular origin (e.g., arthritis, orthopedic pain), transmetatarsal or more proximal lower-extremity amputation, unstable claudication symptoms, inability of performing the exercise program or walking on the rolling carpet, revascularization or other major surgical interventions planned for the next 12 months, revascularization at lower limbs level, major orthopedic or surgical interventions three months before study inclusion, patient included in other current clinical studies, dementia.
Randomization was done in three groups in the order of inclusion. The control group, which throughout the study followed only the medication regimen along with hygienic and dietary recommendations (51 patients) (12, 13). To reduce adverse cardiovascular events associated with lower extremity PAD, our patient's treatment includes modification or elimination of atherosclerotic risk factors such as: cigarette smoking, diabetes mellitus, dyslipidemia, hypertension and promotion of daily exercise and use of a nonatherogenic diet. The patients with dyslipidemia (36%) take lipid-lowering drugs (statins or fibric acid derivative). Lifestyle interventions for PAD patients include smoking cessation, weight loss for obese patients, and intensive blood pressure and blood glucose control with antihypertensive drugs-ACE inhibitors (17%) and diabetes therapies (28%). We encourage proper foot care: appropriate footwear,

chiropody/podiatric medicine, daily foot inspection, skin cleansing, and topical moisturizing creams, urgently address skin lesions and ulcerations. Some patients take antiplatelet therapy for reducing the risk of MI, stroke, or vascular death, like Aspirin 75-325 mg per day (23% patients) or Clopidogrel 75mg per day (only 2%). Most patients take Pentoxifylline 400mg TID (71%) and 46% patients take ginkgo biloba 120 mg per day.

The exercise group (KT group), which followed a well-established, supervised, physical therapy programme for 12 weeks, then continued at home the exercise programme they had learnt for another 12 weeks (24 patients). The special kinesytherapy program was easy to understand, easy to learn and especially easy to repeat at home, without requiring any special equipment. The training starts with a 10 minutes warm-up, consisting of exercises for mobility and respiration, followed by exercises of analytical gymnastics, Buerger gymnastics, exercises for increasing the cardiac flow and codified walking (15-60 minutes daily), ending with relaxation exercises (5-10 minutes). Exercises were chosen according to the localization of the obliterations: exercises involving the muscles of the thigh and hip were chosen for upper obliterations, exercises involving the shank muscles were performed for middle obliterations (of femoral and popliteal arteries), and exercises involving the short muscles of the leg were preferred for distal obliterations. The number of exercise repetitions was established individually, according to the physical state of every patient, these being practiced up to the onset of moderate claudication, a moment followed by a short moment of rest in orthostatic or sitting position, until the symptoms diminished. Initially, the sessions lasted for approx. 30 minutes and the training time gradually increased with every session up to approx. 60 minutes. The kinesytherapy sessions took place 3 times a week. The group with exercise and procedures (KT +PT group), which during the first 12 weeks, in addition to the supervised physical therapy programme also followed a predetermined set of procedures of electrotherapy, hydrotherapy, thermotherapy, massage, and afterwards, during the next 12 weeks they were to continue at home the exercise programme they had learnt (36 patients).

Patients were evaluated using *Medical Outcomes Study (MOS) 36-Items Short Form Survey Instrument* (SF36), upon inclusion in the study, 12 weeks after the start of the study and at the end of the study, after 24 weeks.SF36 is probably the most commonly used Quality of life (QoL) questionnaire and is a generic instrument that includes the following 8 multi-item subscales that form the physical and mental health components: physical functioning (PF), role physical (RP), bodily pain (BP), social function (SF), role emotional (RE), mental health (MH), vitality (VT) and general health (GH). Each domain of these scales is scored from 0 (poorest health) to 100 (optimal health) (14).Its 36 questions allow for an assessment of the general state of health at that time for a subject. Repeating the administration of the questionnaire at different times in the history of a disease allows for both a global and a differentiated assessment on several components of the evolution of the disease.

Statistical analysis was performed using SPSS 16.0 for Windows software. Descriptive statistics including frequencies and means and correlation analysis were conducted. The Student's t-test was used to compare our scores against published norms and between different patient groups. ANOVA and Post Hoc tests were applied to compare the course of quality of life between patient groups. A p-value of <0.05 was considered statistically significant.

Results

The patients in the study group were between 57 and 82 years old, with a mean age of 69 years (SD=7.5). The distribution by age groups shows that 82% of patients with PAD, who are covered by this study, are over 60 years old, thus confirming the data in the literature, which indicates the age of over 60-70 years as a potential risk factor in development of peripheral ischemia (4).The groups were uniform in terms of age, with patients in all three groups having a similar mean age (67.7 years in the control group, 68 years in the exercise group, slightly higher in the exercise and procedure group - 70.8 years).

In the Edinburgh Artery study of 1592 men and women aged 55 to 74 years, the prevalence of arteriopathy, diagnosed using clinical criteria, was almost 17%, the number of those with an ankle-brachial index (ABI) below 0.9 was 9% and another indicator of arteriopathy, a reduction of more than 20% of systolic pressure in the ankle during reactive hyperaemia, was found in a percentage of 7.6% in those studied (14).ABI values and results of reactive hyperaemia correlated with an increase in the prevalence of the disease with age, and the prevalence of claudication, using the modified version of the Rose protocol (Edinburgh Claudication Questionnaire), was 4.5% (15). The determination of ABI in the patients from the studied group allowed the

calculation of an average of 0.655 (SD=0.094) with a minimum value of 0.469 and a maximum value of 0.827. Practically equal values of mean and median show a quasi-asymmetric distribution of values.

Table I. The ankle-brachial index (ABI) - descriptive statistics

ABI	
Mean	0.655
Standard Error	0.0089
Median	0.664
Standard Deviation	0.094
Sample Variance	0.0088
Kurtosis	-1.12
Skewness	-0.018
Range	0.358
Minimum	0.469
Maximum	0.827
Count	111
Confidence Level (95.0%)	0.0177

When quantifying the patients' risk of developing peripheral arteriopathy, it is essential to assess the risk factors involved. Thus, in an attempt to identify risk factors associated with peripheral arteriopathy, a number of 5084 patients, aged at least 65 years, were included in a large study conducted by Newman and colleagues (16). By exploring the relationship between the ankle-brachial index and cardiovascular disease, subjects were grouped according to the cardiovascular clinical status and this index whose values are included in the following groups of values (<0.8, ≥0.8- <0.9, ≥0.9- <1.0 and ≥1.0- <1.5). Patients with an ABI below 0.9 were diagnosed with peripheral arteriopathy. Risk factors associated with an ankle-brachial index below 1.0 were investigated and statistically assessed to determine relative risk. Newman and colleagues found that the four most important age-related factors in assessing the risk of developing peripheral arteriopathy are: diabetes mellitus - relative risk of 4.05, smoking - relative risk of 2.55, hypertension - relative risk of 1.51, total cholesterol (10mg/dl) - relative risk of 1.10.
In our patients, diabetes mellitus was most common, 35% in the control group, 30.4% in the exercise group and to a lesser extent, 28% in the group with exercises and procedures. The mean systolic blood pressure was approximately the same in the three groups, slightly higher in the exercise group (132.4 mmHg), which was also the case with the average value of the diastolic blood pressure (also slightly higher in the exercise group - 76 mmHg), however, within the limits of normal values.
We included in the study 68 smoking patients, of which 74% were men. Regarding the association of the strongest risk factors of arteriopathy, it can also be seen from the following table that the situation is different in the case of the two categories of patients. Thus, most frequently, smokers are diagnosed with hypertension (74%), in terms of comorbidities dyslipidaemia comes second with 54%, then chronic obstructive pulmonary disease (COPD) (38%) and diabetes mellitus (26%). Non-smokers are most commonly associated with hypertension and dyslipidaemia (59%), followed by diabetes mellitus and COPD (39%).

Table II. Initial characteristics in smokers and non-smokers

Parameters	**Non-smokers** (n=43)	**Smokers** (n=68)	**p**
Age (years)	70	68	0.27
The onset of claudication (yrs.)	3.6	4.2	0.87
Men (%)	14	74	0.57
Diabetes mellitus (%)	39	26	0.26
Arterial hypertension (%)	59	74	0.35
Hyperlipidaemia (%)	59	54	0.48
COPD (%)	39	38	0.93

The anamnesis conducted in patients upon inclusion in the study resulted in an average duration of 4 years elapsed since the onset of claudication. The average values of this duration for the three groups were all close to this value. In the patients in the control group, the mean was 3.9 years, in the patients included in the group that did only the exercises, the mean was 4 years and in those in the group with the exercises and the procedures, a mean of 4.1 years was found.
After measuring the eight variables that make up the SF36 questionnaire and recoding them, we calculated the scores for each of the scales and the means of these scores. The parameter we used in order to be able to assess the evolution under treatment of SF36 components was *the mean improvement scores* calculated at 12 and 24 weeks compared to the values upon inclusion in the study using the statistical calculation software SPSS 16.0. Figure 1 shows the evolution of the improvement scores for the physical component of SF36 in comparison for the three groups of patients studied.

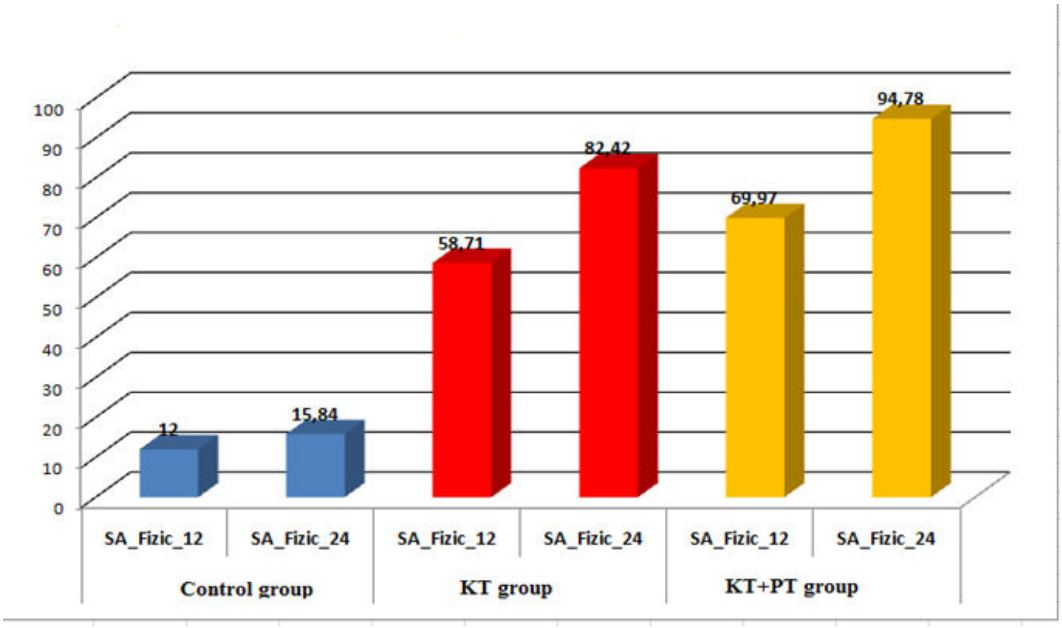

Figure 1. Improvement of scores for the physical component

All improvement scores were statistically significant. For the control group at 12 weeks, *p* was 0.003. For the other parameters, *p* was below 0.0005.The improvement in the physical function of patients with PAD was obvious from 12 weeks and even more so at 24 weeks for both the group of patients who exercised only and those who performed physical exercises along with the procedures. The mean score of improvement in the physical function increased in patients in the exercise group by 390% at 12 weeks and by 420% at 24 weeks. In patients in the group of exercise and procedures, the increase in improvement was 483% at 12 weeks and 498% at 24 weeks.
If we compare the increases of this parameter between the group with exercises and the group with exercises and procedures, we find that the application of the physical therapy programme and physical procedures allows an even more important improvement of the quality of life by improving fitness. The increase in the score for improvement of the physical function for those who performed procedures was 19% at 12 weeks and 15% at 24 weeks. Without being just as spectacular, the improvements in the mental component of SF36 are also significant, proving once again how important it is for the mental state of a subject to improve their fitness. Figure 2 shows the evolution of the score for the improvement in the mental component of SF36 in the three groups of patients with PAD.

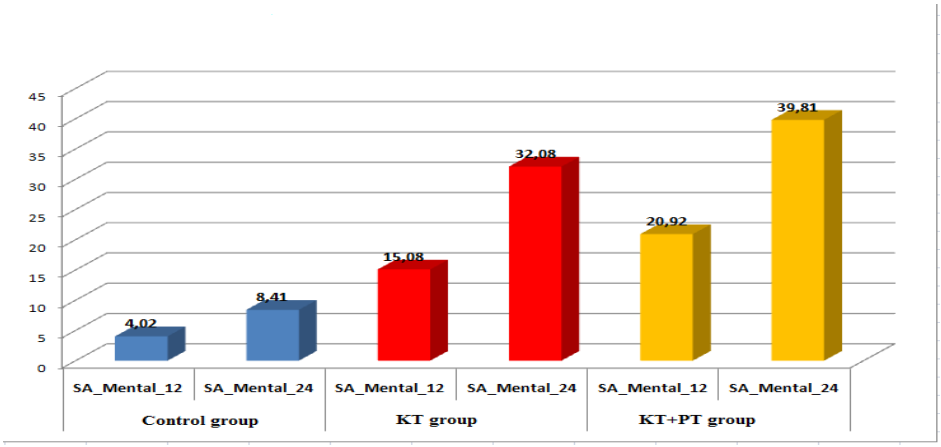

Figure 2. Improvement of scores for the mental component

At this point as well, as in the case of the physical component, we noticed that the improvement of the mental state expressed in the score of improvement in the mental component of SF36 occurs from the first 12 weeks of application of the physical therapy programme based on physical therapy.
In the group of patients who exercised, the improvement in the mental component at 12 weeks was 275% and at 24 weeks it was 281%.In the case of patients in group 3, who also underwent physical therapy in addition to the exercise programme, the favorable evolution of the score of improvement in the mental component of SF36 was even better with a gain of 420% at 12 weeks and 473% at 24 weeks.
The influence of physical procedures in the improvement of the mental status can be seen from the comparison of the scores for the improvement of the mental condition between groups 2 and 3. Both of them followed the physical exercise programme, but the physical procedures were added in group 3. At 12 weeks, an improvement in the mental component was obtained, 39% higher for group 3, and then, at 24 weeks the improvement was also 24% in favour of group 3.
If, for the physical component, by adding the physical procedures, we obtained a 19% increase in the improvement score at 12 weeks and a 15% increase at 24 weeks, we note that for the mental component, the favorable influence of physical procedures is much higher, 39% and 24%, respectively. This is another argument in favour of the fairness of the premise that the multidirectional approach of a patient with PAD can produce much better favorable effects and also that, contrary to the opinion of some, physical therapy has a first-hand role in the therapeutic plan.
We used the same calculation method for the Vitality Subscale and the General Health Subscale as for the Physical Component and Mental Component Subscales, calculating the *average improvement scores* for the two subscales at 12 and 24 weeks from the values upon inclusion in the study using the statistical calculation software SPSS 16.0. The evolution in the three groups for the Vitality component of SF36 at 12 and 24 weeks is described in figure 3.

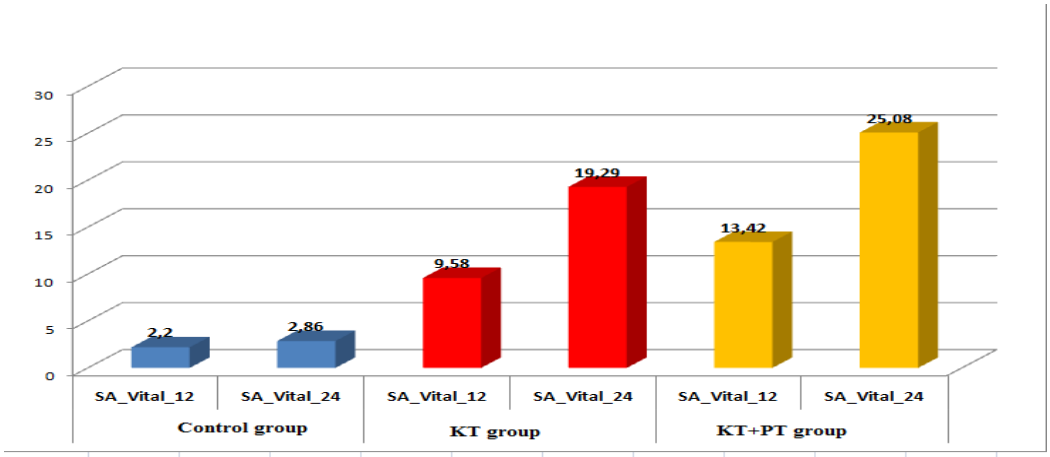

Figure 3. Improvement of scores for vitality

This component, which reflects quite accurately the influence of a therapeutic plan on the quality of life, has had an interesting evolution, as its improvement score has been steadily increasing throughout the 24 weeks in both group 2, which performed only the physical therapy programme, and in group 3, in which other physical therapeutic means were applied in addition to the physical therapy. Examining more closely the mean improvement scores, we find that they virtually doubled at 24 weeks compared to those at 12 weeks, 19.28 vs. 9.58 for group 2, and 25.08 vs. 13.42 for group 3.
The resonance of adding physical procedures to the physical therapy programme is even more interesting. The values for the vitality component are 40% higher for group 3 at 12 weeks and 30% higher at 24 weeks compared to group 2, which followed only the exercise programme.
The perception of the patients in the control group, who only continued the medication regimen without exercising and without the physical procedures, was that their general health condition did not deteriorate significantly and it did not improve at all at 12 weeks or at 24 weeks.
Patients in groups 2 and 3, however, reported a significant improvement in general health since the middle of the physical therapy period, an improvement that was much better expressed at 24 weeks, as can be seen from the following figure 4.
It should be noted that the main factor in improving general health was exercise, because we notice that the difference in improvement scores in favour of group 3 who also performed physical procedures, although significant, is quite low after both 3 months and 6 months.

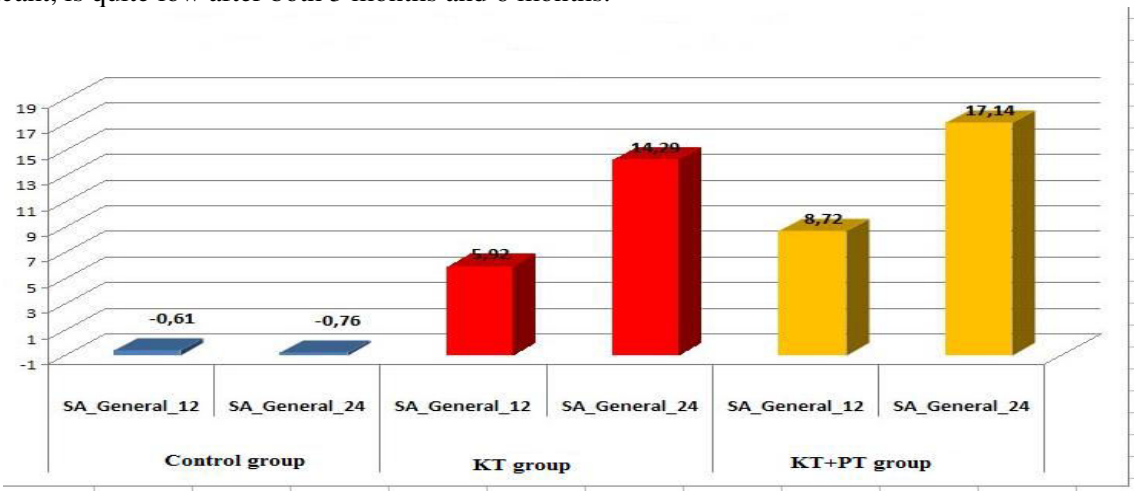

Figure 4. Improvement of scores for the general health condition component

Discussion and Conclusion

The results obtained from the statistical analysis of the parameters were compared with the results of studies in the literature. Other authors tried to quantify whether the HRQoL (health-related quality of life) is improved through exercise program in patients with PAD and also to clarify the optimal indication in order to maximize the quality of life compared to usual care (17,18). A systematic review of randomized clinical trials including a primary analysis of QoL via questionnaire was performed in 2017 by Harwood AE et al, in Gefässchirurgie, and concluded that the most commonly used tool was the Short Form 36 (SF-36) or variations of it, used in 23 out of the 31 studies included (74.19%) with a total of 3256 patients and 12 studies used the SF-36 in its English form (19).
In 2015, Prevost et al. studied in a clinical trial the effects of education and home based training on quality of life in forty-six patients diagnosed with peripheral artery disease (20). Initial and absolute claudication distance (ICD and ACD) as well as other functional parameters improved significantly and SF-36 scores improved significantly and remained stable. Ten patients did not show improvement in ICD or ACD within the first 3 months, but their SF-36 score did increase at subsequent visits.
Guidon et al. assess in a randomized clinical trial the one-year effects of participation in a 12-week supervised exercise programme on functional capacity and QoL for PAD patients (21). At 12 weeks, there was a trend towards improved QoL in both groups, control and exercises with a tendency for greater

improvement in the exercise group (p = 0.066). Participation in a supervised exercise programme results in improvements in functional capacity and QoL at 1 year post-participation.
In 2015, Vascular Medicine published a meta-analysis of 15 RCTs. 1257 participants were studied: 543 participated in supervised exercise, with only 61 undertaking resistance training and 316 unsupervised exercise (22). Walking significantly improved the Short-Form Physical Component Summary (SF-PCS) score when compared to controls [MD 1.24 (95% CI 0.48 to 2.01, p=0.001)], but not the Mental Component Summary (SF-MCS) score [MD –0.55 (95% CI –1.27 to 0.18, p=0.14)]. Exercise training improves the SF-PCS dimension, but not the SF-MCS score.
Sustained and persevering physical training can lead to significant improvement in quality of life parameters, and patients should be encouraged and supported in their exercise because the results of their effort may not come immediately, but they will certainly come during a correctly performed rehabilitation program under medical supervision.
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