Comparative study of evolution and survival of patients with intermittent claudication, with or without limitation for exercises, followed in a specific outpatient setting

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ABSTRACT

Background: Risk factors for atherosclerotic disease acting on natural history are well established, as well as the benefits of physical training in the treatment of intermittent claudication (IC). However, current data do not provide enough information about the relationship between clinical limitations and risk factors and the performance of physical training and its implications on the evolution and mortality of these patients.

Objective: To compare the claudication distance and survival of patients with IC throughout time in a specific outpatient setting, with or without limitation for exercises.

Methods: A retrospective cohort study was performed to review the protocols of 185 patients and 469 returns, from 1999 to 2005, evaluating demographic data, average claudication distance and death. The data were analyzed using the software Epi-Info, version 3.2, and SAS, version 8.2.

Results: Mean age was 60.9±11.1 years; 61.1% were males and 38.9% were females; 87% were Caucasians and 13% were non-Caucasians. Associated risk factors were hypertension (69.7%), smoking (44.3%), dyslipidemia (32.4%), and diabetes (28.6%). For the patients with claudicating distance lower than 500 m, mean initial distance was 154.0±107.6 m and final distance was 199.8±120.5 m. About 45% of the patients had some clinical limitation to perform the prescribed exercise program, such as angina (26.0%), stroke (4.3%), osteoarthrosis (3.8%), previous minor or major amputation (2.1%), or chronic obstructive pulmonary disease (1.6%). About 11.4% of the patients had previous myocardial infarction, and 5.4% of them were using cardiotonic drugs. Mean follow-up time was 16.0±14.4 months. Mean claudication distance increased 100% (418.47 to 817.74 m) throughout 2 years in the group without limitation ($p < 0.001$) and in nonsmokers ($p < 0.001$). Survival rate of patients with IC was significantly reduced in the group with limitation for exercises. Logistic regression analysis showed that limitation to exercises was the single factor significantly influencing mortality ($p < 0.001$).

Conclusion: Proper and regular exercises and quitting smoking improve claudication distance and reduce mortality rates of these patients, whether by the positive effects of exercises or by controlling risk factors and their adverse effects.

Keywords: Intermittent claudication, atherosclerosis, exercise therapy, risk factors.

RESUMO

Contexto: Os fatores de risco para doença aterosclerótica, que influenciam na evolução natural dessa doença, estão bem estabelecidos, assim como o benefício do programa de exercícios para pacientes claudicantes. Entretanto, faltam informações sobre a relação entres limitações clínicas e fatores de risco, com desempenho do programa de caminhadas e suas implicações na evolução e mortalidade destes pacientes.

Objetivo: Comparar, ao longo do tempo, a distância de claudicação e sobrevida de pacientes claudicantes em ambulatório específico, com ou sem limitação para exercícios.

Métodos: Foi feito um estudo tipo coorte retrospectivo de 185 pacientes e 469 retornos correspondentes, no período de 1999 a 2005, avaliando-se dados demográficos, distância média de claudicação (CI) e óbito. Os dados foram analisados nos programas Epi Info, versão 3.2, e SAS, versão 8.2.

Resultados: A idade média foi de 60,9±11,1 anos, sendo 61,1% do sexo masculino e 38,9% do sexo feminino. Oitenta e sete por cento eram brancos, e 13%, não-brancos. Os fatores de risco associados foram: hipertensão (69,7%), tabagismo (44,3%), dislipidemia (32,4%) e diabetes (28,6%). Nos claudicantes para menos de 500 m, a CI inicial em esteira foi de 154,0±107,6 m, e a CI final, de 199,8±120,5 m. Cerca de 45% dos pacientes tinham alguma limitação clínica para realizar o programa de exercícios preconizado, como: angina (26,0%), acidente vascular cerebral (4,3%), artropatia (3,8%), amputação menor ou maior com prótese (2,1%) ou doença pulmonar obstrutiva crônica (1,6%). Cerca de 11,4% dos pacientes tinham infarto do miocárdio prévio, e 5,4% deles usavam cardiotônico. O tempo de seguimento médio foi de 16,0±14,4 meses. A distância média de CI referida pelos pacientes aumentou 100% (de 418,47 m para 817,74 m) ao longo de 2 anos, nos grupos não-limitante ($p < 0,001$) e não-tabagista ($p < 0,001$). A sobrevida dos claudicantes foi significativamente menor no grupo com limitação. A análise de regressão logística mostrou que a limitação para realização de exercícios, isoladamente, influenciou significativamente na mortalidade ($p < 0,001$).

Conclusão: A realização correta e regular dos exercícios e o abandono do fumo melhoram a distância de claudicação, além de reduzir a mortalidade nesses casos, seja por meio de efeitos positivos próprios do exercício, seja por meio de controle dos fatores de risco e de seus efeitos adversos.

Palavras-chave: Claudicação intermitente, aterosclerose, terapia por exercício, fatores de risco.

Introduction

Atherosclerosis is a civilization disease, which grows with it and increasingly affects younger individuals.[1] It has a worldwide and apparently regular distribution, and is manifested in approximately 10% of this population.[1,2] It is one of the main causes of death in the Western world,[3] and despite being widely studied in its varied aspects, there is still no perfectly established etiopathology, presumed as multifactorial.[1] It accounts for 95% of coronary diseases, 85% of lower limb intermittent claudication, and 75% of strokes. The worldwide prevalence in the middle-aged population is 4% considering the limbs, but it is believed that it is underestimated because the atherosclerotic process remains subclinical and asymptomatic for a long time.[1]

Peripheral occlusive arterial disease (PAD), caused by atherosclerosis of arteries supplying the lower and upper limbs,[3,4] affects 20% of the population aged 70 years or older[1,5] and 3-6% of those aged less than 60 years.[1,3] Mean annual incidence of symptomatic PAD, according to a study by Framingham,[6] is 26/10,000 men and 12/10,000 women, increasing with age.[1,7] Prevalence of asymptomatic disease ranges between 0.9-22%, according to several studies; for each patient with intermittent claudication there are three with asymptomatic disease.[1]

Based on many epidemiological studies conducted over the past decades, risk factors for PAD influencing its natural course have been established, increasing its incidence and accelerating its progression. The main risk factors are age, gender, hyperlipoproteinemia, smoking, hypertension, diabetes mellitus (DM), obesity, hyperhomocysteinemia and genetic or family factors of atherosclerotic disease.[1,7]

In 5 years, 5-10% of patients with PAD develop non-fatal cardiovascular events (CAD), 30% die, and 55-60% survive, characterizing the natural course of this disease. Of those who survive, 25% have worsening of claudication, 5-10% need vascular restoring surgery, and 2-5% undergo major amputation.[7,8]

Clinical treatment of PAD should be started by primary prophylaxis of the disease, with changes in lifestyle to prevent its development. When the disease has already installed, secondary prophylaxis is performed. Its main goal is to control risk factors, using or not drug therapy, with the aim of delaying disease progression as an attempt to avoid CAD and cerebrovascular events (CVD); antiplatelet therapy should be given to all patients, except in case of contraindication. A program of daily walking should be implemented in this stage to develop collateral circulation, adapt the muscles to a low oxygen demand and, therefore, improve the patient's claudication distance and quality of life.[1,3,4,7, 9-13]

However, old age and coexistence of risk factors, especially smoking, hypertension, diabetes and dyslipidemia, considerably increase risk of PAD, CAD and CVD.[1,7] Such events may cause walking limitations, such as angina, stroke sequelae, chronic obstructive pulmonary disease, diabetic foot, minor or major amputations and prostheses; degenerative joint diseases, such as osteoarthropathy, can be added, making proper walking programs difficult and interfering with long-term evolution of these patients.

This article aims at comparing claudication evolution and the survival of claudicating patients in a specific outpatient setting, with or without limitation for exercises.

Methods

An observational, retrospective, cohort study of consecutive series of cases was performed in 185 claudicating patients receiving care at a specific outpatient clinic of vascular surgery in our institution from January 1999 through March 2005. This study was approved by the local Research Ethics Committee.

The patients with intermittent claudication were referred to the claudication clinic, where record protocols were filled with demographic data, risk factors, comorbidities, medications in use, previous surgeries, reported claudication distance (distance walked on the street), record of lower and upper limb pulses, ankle-brachial index (ABI) measurements, and intensity of pulses on palpation. In case there were no contraindications, the treadmill test was performed in patients with less than 500 m of reported claudication, using a standard constant speed of 3.2 km/h and fixed 10% inclination. This assessment was called treadmill claudication distance. This test recorded initial and final claudication distances, and a new ABI was measured after the test. Antiplatelet drugs were prescribed in the first appointment, usually acetylsalicylic acid (ASA) 200 mg/day for all patients who were not contraindicated. Laboratory tests were also requested (total cholesterol and cholesterol fractions, triglycerides, fasting glucose, uric acid, complete blood count, glutamic oxalacetic transaminase (GOT),

glutamic pyruvate transaminase (GPT), and glycosylated hemoglobin for diabetic patients) and recommendations on blood pressure control and on the importance of controlling other risk factors were given at the health center, encouraging the patient to quit smoking. In addition, the patient was advised to perform a daily walking program, at least for 1 hour, trying to improve claudication distance at every cycle.

In return visits (n = 469), usually at every 6 months, follow-up protocols were filled, containing information on medications in use, previous surgeries, reported claudication distance, patient adherence to clinical and drug therapy, maintenance or not of smoking, improvement or worsening of symptoms, record of limb pulses, measurement of higher ABI. In case there was no contraindication, the treadmill test was repeated using the same standardization. This test recorded initial and final claudication distances, and a new ABI was measured after the test. Laboratory tests were analyzed, and proper therapy was defined when necessary. All recommendations on control of risk factors and on the importance of a walking program were once again provided.

All the patients who had their first visit within the period described above were included in the study and classified into two groups:

-Non-limiting: patients who did not have clinical limitations to perform the exercise program (60-minute of uninterrupted walking, at least three times a week);

-Limiting: patients who did not perform the exercise program or performed it partially due to clinical limitations.

A retrospective survey of these cases was performed, adding the information on both protocols using the software Epi-Info version 3.2 and SAS version 8.2 (SAS System for Windows v.8.2, SAS Institute, North Carolina, USA), complementing the data with a review of medical charts, death registry of the Health Department of the State of São Paulo and record of surgeries performed at the operating theater of Hospital das Clínicas da Faculdade de Medicina de Botucatu (UNESP).

Using the resources of Epi-Info and SAS, descriptive and actuarial statistical analyses were performed on demographic data, risk factors, comorbidities, clinical or surgical treatment, drugs in use, evolution of claudication and claudicating patients' survival. In addition, a logistic regression study was conducted on risk factors in relation to mortality and claudication distance. All these analyses, including calculation of sample size, were statistically performed by the Research Support Group at our institution.

Results

The demographic data and comorbidities can be seen in Table 1. PAD accounted for 96% of cases, while arteritis accounted for 4%. Men were more affected than women. Eighty-seven percent were Caucasian, and 13% were non-Caucasian (Table 1).

Table 1 - Demographic data of the sample of patients with intermittent claudication

Characteristic (n = 185)	Limiting	Non-limiting	Total	Total (%)
Diagnosis				
POAD	81	96	177	96
Arteritis	1	6	7	4
Gender				
Male	44	69	113	61,1
Female	39	33	72	38,9
Race				
Caucasian	76	85	161	87
Non-Caucasian	7	17	24	13
Comorbidities				
CAD	48	8	56	30,3
Stroke	8	11	19	10,3
Arthropaty	7	0	7	3,8
Amputation	4	1	5	2,7
COPD	3	0	3	1,6
Deaths				
CAD	4	0	4	23,5
CVD	4	0	4	23,5
Other causes	7	2	9	53

CAD = coronary arterial disease; COPD = chronic obstructive pulmonary disease; CVD = cerebrovascular disease; POAD = peripheral occlusive arterial disease.

Mean age was 61.3±10.1 years (31-87 years); 25% were under 55 years and 75% were older than 67 years; 74.6% of patients had no previous surgeries until the first visit to the claudication clinic, and 25.4% had already undergone at least one vascular surgery. Clinical treatment was effective in 90.9% of all these patients, and in 9.1% a surgical intervention was required, of which 2.1% corresponded to amputations. Initial ABI of the right lower limb was 0.78±0.20, and 0.76±0.22 for the left lower limb.

There were many comorbid diseases and conditions with possible implication in exercise performance. CAD was present in 30.3%, of which 11.4% had previous myocardial infarction (MI), and 5.4% were using cardiotonic drugs. In addition, there were stroke sequelae, arthropathy, major amputation in patients with prostheses or minor amputation and chronic pulmonary obstructive disease (CPOD) (Table 1). However, of these patients, 26% had angina, 4.3% had stroke sequelae, 3.8% had arthropathy, 2.1% had major amputations and prostheses or minor amputations, and 1.6% with COPD reported limitations to perform the exercises (Figure 1). Thus, the group of patients considered as non-limiting comprehended 55.1% of the patients, whereas the limited patients accounted for 44.9%.

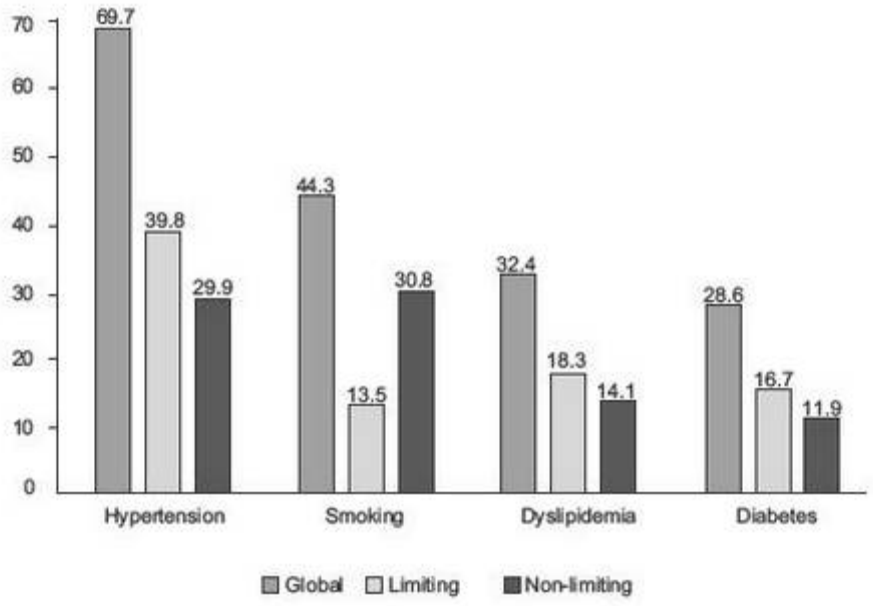
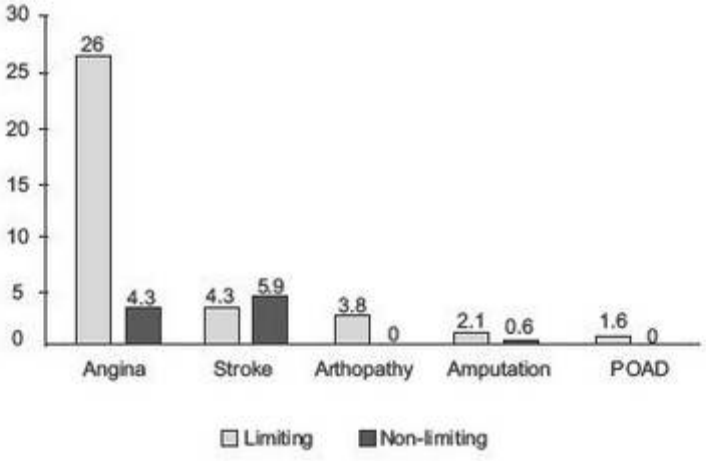


Figure 1 - Frequency of risk factors of the sample, according to groups

In average 69.5% of the patients were using antiplatelet drugs; 38% hypotensive drugs; 17.2% pentoxifylline; 12.1% statins; 9% cilostazol; and 8.4% anticoagulating drugs (Figure 2).



COPD = chronic obstructive pulmonary disease .

Figure 2 - Frequency of limitations to exercise

Mean follow-up time was 16.0±14.4 months; hence, after 24 months, the sample represented by the number of return visits was expressively reduced. Over this period, 16.4% were lost in the follow-up, and 9.2% died, mostly due to CAD and CVD (Table 1).

In claudicating patients for less than 500 m, mean initial claudication distance (IC) on the treadmill was 154.0±107.6 m, and final IC was 199.8±120.5 m in the 60-month follow-up period. Overall, mean reported IC distance increased throughout 5 years for the limiting ($p = 0.0021$) and non-limiting (0.0023) groups (Figure 3). Smokers and diabetic patients had no significant improvement ($p > 0.001$)

over the same period. After 24 months, specifically for the non-limiting and non-smoker groups (Figure 4), mean claudication distance reported by the patients increased from 418.47±621.09 to 817.74±1.084.17 m, representing an increase around 100% in walking distance ($p < 0.001$). In the group of limiting patients, there was mean nominal reduction of around 25% of this distance, but it was not significant ($p = 0.5657$). Risk factors hypertension, DM and dyslipidemia had no significant influence on reported claudication distance ($p > 0.001$).

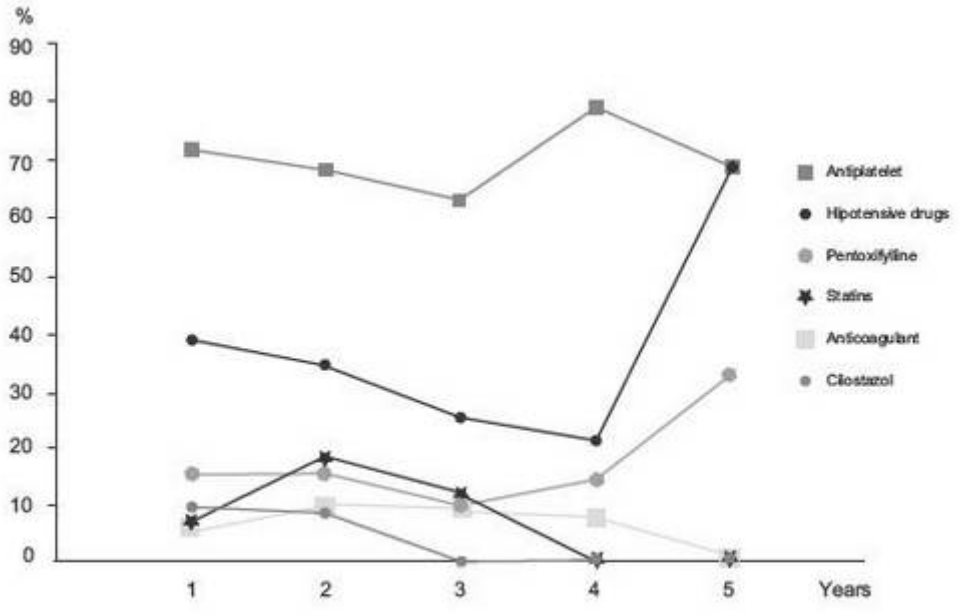


Figure 3 - Frequency of patients with respective drugs in use over a 5-year period

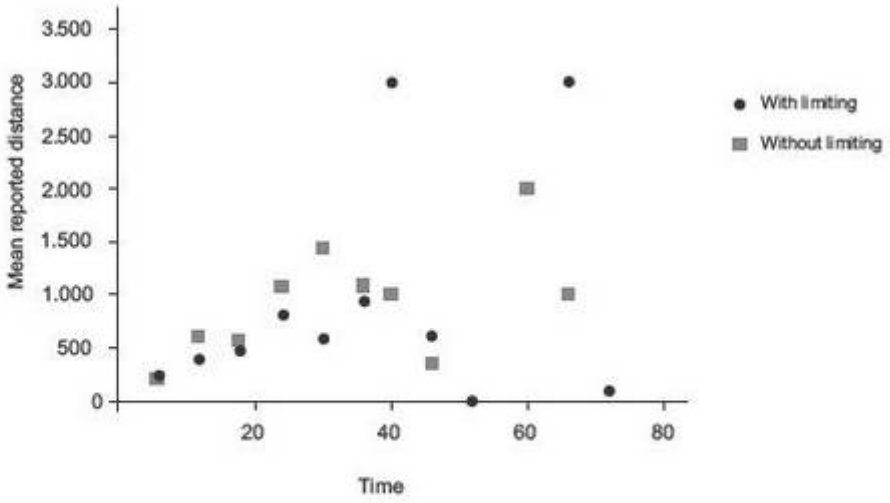


Figure 4 - Mean reported claudication distance according to groups

Actuarial and logistic regression analysis showed that survival was significantly lower in the group with limitation to perform exercises ($p < 0.001$) (Figure 4).

Survival analysis of subgroups with CAD (p = 0.857), stroke (p = 0.653), amputations (p = 0.352), arthropathy (p = 0.111) and COPD (p = 0.108) were similar, including comparison between the limiting and non-limiting groups.

The most frequent risk factors for PAD were hypertension, smoking, dyslipidemia and DM; hypertension and DM were even more frequent in patients in the limiting group. On the other hand, smoking was more frequent in patients of the non-limiting group (Figure 5).

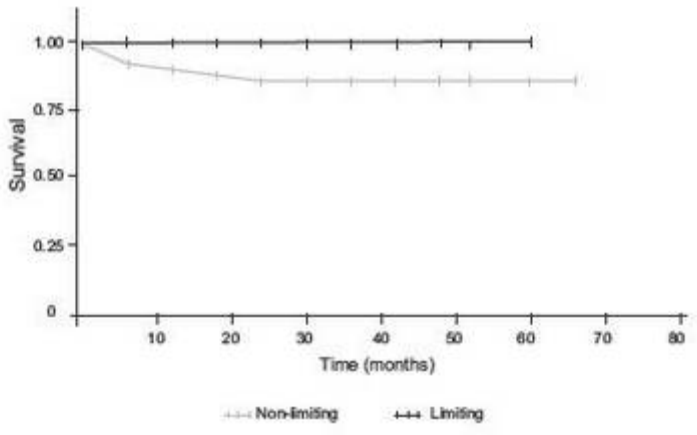


Figure 5 - Comparative survival between the limiting and non-limiting groups

There was no statistical difference in 5-year survival for smokers (p = 0.943), patients with dyslipidemia (p = 0.095), DM (p = 0.474) or hypertension (p = 0.200) compared with patients without these risk factors, both in the overall analysis and for each group alone (limiting and non-limiting). Analysis of the association of risk factors such as hypertension + DM (p = 0.185), hypertension + smoking (p = 0.142), DM + smoking (p = 0.485), hypertension + smoking + DM + dyslipidemia (p = 0.090) did not show statistical difference as to survival, both in the limiting and non-limiting patients.

Logistic regression having mortality as outcome showed that, of many risk factors (hypertension, DM, smoking, dyslipidemia and limitation for exercises), only limitation to perform exercises as recommended was statistically significant in terms of mortality rate (p < 0.001). Analysis of association of factors, such as DM + smoking, hypertension + DM, etc., was not significant. Therefore, according to this analysis, mortality was probably more related to non-performance of exercises than to presence of other risk factors.

Discussion

Prevalence of PAD increases with age, and is more prevalent in the age group between 50-70 years.[1-4] It reaches frequencies of 16% in men and 13% in women aged 60 years or older.[4] The main risk factors include hypertension, smoking, DM and dyslipidemia, which may cause, alone or in association, progressive and sometimes generalized development of atherosclerotic plaques in the arteries.[1-4,7,14] DM and smoking are considered the most important risk factors, each implying three to four times increased relative risk for the development of PAD.[7,14-16] In a previous study, conducted in our institution, the risk profile of patients with PAD was similar to that found in this study regarding hypertension (58.7%), DM (37.3%), and dyslipidemia (33.3%).[17] DM control, maintaining glycosylated hemoglobin below 7%, reduces MI incidence[4,7] and risk of microvascular complications, but does not

prevent macrovascular complications.[18-20] Smoking is perhaps the main independent risk factor for the development and progression of PAD;[20] this habit increases risk for PAD, reduces success rate of vascular surgeries, and increases incidence of amputation in patients with IC. Smoking cessation should be strongly encouraged, since it reduces PAD progression and reduces MI incidence and death due to vascular causes.[4,7,8,21-25] Control of dyslipidemia using statins and maintaining low-density lipoprotein under 100 mg/dL,[14] implies lower risk for MI.[4] There are studies showing that use of statins also improves time of walking programs 1 year after the therapy.[4] There is no study showing that hypertension treatment favorably implies PAD progression, but its control should be properly performed, since it reduces cardiovascular morbidity and mortality in patients with PAD.[4,7] In this study, these were also the main factors and characteristics found in our patients.

Coexistence of risk factors, especially hypertension, DM and smoking, are common in these patients and increase prevalence of PAD and other atherosclerotic manifestations, such as CAD and CVD, implying higher overall (relative risk = 3.1), cardiovascular (relative risk = 5.9) and CAD (relative risk = 6.6) mortality.[4,26] According to the Transatlantic Inter-Society Consensus (TASC),[7] there is an increased relative risk for the development of PAD from 2.3 to 3.3 and 6.3 in patients with one, two or three associated risk factors, respectively. Particularly the association of smoking and other risk factors dramatically increases risk of PAD progression.[6,7,27,28] In the present study, the coexistence of factors and deaths due to CAD and CVD were present and similar between themselves.

Exercise programs, preferentially supervised,[3,25] have shown improvement in claudication distance, peripheral circulation and cardiopulmonary function[2-4,9,10,20,25,29-36] and generate better quality of life for the patients when associated with control of risk factors. A meta-analysis of 10 controlled trials showed significant increase in initial and final claudication distance, with improvement of up to 150% [12,25] in patients who performed the exercise program correctly. The mechanism responsible for improvement in the patient's walking is still not clear.[25] Some authors suggest that it is due to reduction in collateral circulation resistance, determined by periodic increase in blood flow when walking.[20,25,37-41] Others believe that improvement is due to an adaptation mechanism of the muscle cell, with improvement in oxidative or anaerobic metabolism and subsequent improvement in oxygen intake by the muscles.[25,42] Most patients are able to perform a walking program of 1 hour a day, following the orientation to walk until the pain is so intense that it prevents continuation; the patient should then stop, wait for the pain to disappear and resume walking.[20,25,30] It seems that 1 hour, three times a week, is enough,[25,31] but there is no consensus as to whether intense exercises could bring better benefits compared with the usual walking program.[32,43] A recent study published by Gardner et al.[30] showed that the results of performing intense exercises are similar to those of conventional walking exercises in relation to gains in walking distance. For other authors, intense exercises are even less effective.[4,12,43] In order to have a significant improvement in claudication distance, it is necessary to perform the exercise program for, at least, 6 months.[4,34,43] Wolosker et al.[34] observed that such improvement was also more expressive in patients who correctly followed the guidance of performing the exercise program and smoking cessation; it was significant over the first 6 months and maintained a small gain throughout the subsequent months. In that study,[34] for the patients who performed the exercise program, but did not stop smoking, there was significant improvement over the first 6 months; however, gains were inexpressive after that period. Curiously, smokers obtained a larger gain than non-smokers over the first 6 months. For those who did not perform the exercise program, either smokers or not, gains were also inexpressive. In the present study, mean reported claudication distance was lower for smokers when compared with non-smokers. Such distance was shorter for diabetics, probably because they are more susceptible to trauma, ulcers and Charcot-Marie-Tooth disease affecting feet, which are factors that may make walking difficult.[44] The distance was shorter for those in the limiting group, probably because they did not perform the walking program as recommended as a result of the clinical limitations listed above.

When the walking program is performed correctly, in addition to improvement in quality of life by increasing walking distance, there is also improvement in lipid profile, blood pressure levels and glucose,[31,38,39,45] especially when associated with other measures, such as smoking cessation and a balanced diet. There are also positive effects on the muscle, cardiovascular and neurohumoral system,

optimizing the patient's functional skills.[20,31,45] Improvement in ventricular performance[31,46] and in myocardial contractility[31,47] were observed, as well as reduction in ischemic response in patients with angina.[31,48] All our patients were properly advised to follow the recommendations described above, and it is likely that those who adhered to them were benefited from these advantages.

On the other hand, the patients with limitations to perform the walking program as recommended did not have the previously mentioned advantages, which might eventually contribute to lower survival rates. This study showed higher mortality rate for the patients who did not perform the exercises correctly.

When angina, arthropathy and COPD caused enough discomfort to prevent performing the exercises, they were considered as limitations. When partial stroke sequelae and minor amputations impaired patients' walking, they were also considered as limitations. Patients with major amputations and prosthesis who had not been totally rehabilitated or had rehabilitation difficulties were also part of this group. The cause of a lower survival rate in this group of patients could be associated with the limitation for performing the exercise, without having the benefits and advantages related to it, or especially with associated diseases or risk factors, which independently or in association contributed to exercise limitation. In this study, we observed that for patients with limitation, DM, hypertension and dyslipidemia were more frequent, which may favor a higher mortality rate. However, there was no statistical difference when these risk factors were analyzed in general or in each particular group (limiting and non-limiting). Although these factors were not associated with higher mortality rates in our sample of patients, it is possible that results might have been different for a larger sample. Similarly, associated diseases, such as angina, stroke sequelae, COPD and amputations did not contribute to a higher general mortality rate or for a particular group (limiting or non-limiting) of this sample. Therefore, it is possible that, in this sample of patients, limitation to exercises, without a clear and significant influence of associated diseases or risk factors, may have contributed to lower survival rates in these cases, because the patients did not have the benefits and advantages provided by regular exercises.

In conclusion, proper and regular exercises and smoking cessation improve claudication distance, in addition to reducing mortality in these cases, whether through positive effects from the exercise, or by controlling risk factors and their adverse effects.

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