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Original Article

Association between frailty and peripheral arterial disease

Associação entre fragilidade e doença arterial periférica

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ABSTRACT

Background: Frailty has been associated with lifestyle, chronic diseases, and genetic alterations and with high levels of proinflammatory proteins, justifying the relationship proposed by the emerging literature that seeks associations between frailty and cardiovascular diseases. **Objective:** To investigate clinical and sociodemographic factors associated with frailty, emphasizing the relationship with peripheral arterial disease. **Methods:** Medical records of 76 patients were analyzed, considering the results of the ankle-brachial index test, fragility, sociodemographic and clinical variables. After the descriptive analysis, differences between groups were tested by chi-square test, student's t-test and Tukey's post hoc test, when they were appropriated. The value of $p < 0.05$ for statistically significant differences was considered. **Results:** The prevalence of frailty in the study sample was 22.3%, and 47.3% for pre-frail. Frailty was associated with female gender, hypertension, dyslipidemia and level of education. Changes in ankle-brachial index test were statistically associated with frailty. **Conclusion:** The results of this research show the necessary targeted efforts to prevent and treat frailty.

Key-words: Peripheral arterial disease, Cardiovascular disease, Chronic disease, Fragility.

RESUMO

Introdução: Fragilidade tem sido associada com hábitos de vida, doenças crônicas, alterações genéticas e níveis elevados de proteínas pró-inflamatórias, justificando a emergente relação proposta entre Fragilidade e doenças cardiovasculares. **Objetivo:** Investigar fatores clínicos e sociodemográficos associados à Fragilidade, enfatizando-se a relação com a doença arterial periférica. **Métodos:** Foram analisados prontuários de 76 pacientes, considerando-se valores do Índice Tornozelo-Braquial (ITB), Fragilidade, variáveis sociodemográficas e clínicas. Após análise descritiva, testou-se as diferenças pelo teste Qui-quadrado, t de Student e Post Hoc de Tukey, quando apropriado. Considerou-se $p < 0,05$ para diferenças significativas. **Resultados:** A prevalência de frágeis foi de 22,3% e de pré-frágeis 47,3%. Fragilidade associou-se ao sexo feminino, hipertensão arterial, dislipidemia e ao analfabetismo funcional. Alterações no ITB foram estatisticamente relacionadas à Fragilidade. **Conclusão:** Os resultados dessa pesquisa alertam para necessidade de esforços direcionados a intervenções para prevenção e tratamento adequado da Fragilidade.

Palavras-chave: Doença arterial periférica, Doenças cardiovasculares, Doenças crônicas, Fragilidade.

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Introduction

The peripheral arterial disease (PAD) comprises a distinct group of diseases and syndromes, which affect the arterial, venous and lymphatic systems. It is featured by stenosis, aortic occlusion or limb arterial occlusion that affects the regular flow of blood or lymph [1]. Prognosis is related to the mortality increase, ulcers, amputation risk, deterioration of function capacity and life quality. It is also an independent strong predictor for arterial coronary and cardiovascular disease.

PAD or other comorbidities presence may enhance the appearance of geriatric complications, such as Fragility, which currently is an important challenge for public health [3]. Fragility, based on sarcopenia, neuroendocrine deregulation and immune dysfunction, presents the functional reservation loss and the capacity diminish to respond to stressful stimuli, which is considered the state between the health ideal and the decline for dependence and death [4]. However, besides the problems related to senescence, researches point the relation between fragility with lifestyle, chronic diseases, genetic alterations and with high levels of proinflammatory proteins[5], justifying the proposed relation by the emerging literature that searches association between fragility and cardiovascular diseases [6].

The high prevalence of cardiovascular disease and the adverse outcome of fragility confirm the necessity to improve the associative knowledge among the factors, contributing to elaborate strategies in order to prevent negative outcomes, such as falls, hospitalizations and deaths [4].

By the afore mentioned, the objective of the present study was to investigate clinic and sociodemographic factors associated to fragility, emphasizing the relation with PAD.

Methods

The current study was performed at Nephrology Treatment, Research, Study Interdisciplinary Center of Federal University of Juiz de Fora, state of Minas Gerais, Brazil (NIEPEN).

It is a descriptive survey of cross-sectional cohort, sample composed by 76 individuals from both genders with average age 64.17 + 11.2 years.

Inclusive criteria

For the research, patients from Hiperdia Minas Center of secondary health attention were considered, which according to the analysis of medical record, have been assessed for fragility and ankle-brachial index (ABI), with a maximum interval of six months for more or less between performing both.

Criteria for conducting the ABI were those adopted by the unit where the patients are cared. These patients aged over 65 years old and/or diabetic, hypertensive, smokers, with family history of PAD, complaints of intermittent claudication, diminish of peripheral arterial pulse, skin thophic alterations, dyslipidemia, hyper-homocysteinemia or presence of inflammatory markers [7]. The fragility evaluation is part of physical education care protocol, in which patients are selected according to the daily demand.

Patients who did not perform the fragility evaluation and the ankle--brachial index were not included in the research. If the patient performed only one test or did not complete it, their participation was excluded from the study sample.

If the patient did not conclude the fragility evaluation or did it partially, it happened due to medical contraindications, which are: amputations, extreme physical sequelae of stroke, Parkinson disease, pregnancy, advanced stage of neoplasias and infection by Human Immunodeciency Virus (HIV)

Clinical and sociodemographic data

Clinical and sociodemographic data were collected through the patient medical record analysis, and the following parameters were selected: gender, race (self reporting), level of education, smoking and alcoholism, systemic arterial hypertension, diabetes, chronic kidney disease, dyslipidemia, obesity (Body Mass Index), left ventricular hypertrophy, angina/acute myocardial attack, myocardial revascularization/angioplasty, transient ischemic attack, coronary disease, retinopathy and heart insufficiency.

Fragility

To determine fragility, Fried et al. [4] proposal was adopted. This is a construct based on the evaluation of hand grip strength, weight loss > 5kg, no-nintentional, in the previous year; fatigue; walking speed and physical activity level. Frail individuals are considered when they score 3 or more evaluated criteria, pre-frail individuals when they score 1 ou 2 points and non-frail the ones who did not score.

Peripheral arterial disease

To check the PAD presence, the Ankle-Brachial Index (ABI) was applied. For that, the systolic blood pressure measured was divided at the tibial region by the systolic blood pressure measured at the humeral region [8].

To interpret data, the most affected limb was considered. Values lower than 0,90 refer to peripheral flow obstruction and higher than 1,30 indicate arterial stiffness. Results between 0,90 and 1,30 are considered as PAD absence perceived by the test and are pondered as regular ones.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) 20.0 program was used to interpret data. To data extrapolatory analysis of the sample in general and of the Frailty categories, descriptive statistics was used such as frequency, mean and standard deviation, when they are appropriate. Differences between groups were tested in proportion cases by chi-square test, and in case of continuos variables, by the student's t-test, followed by Tukey's Post Hoc test. The value of $p<0.05$ was considered for the significance test among the variables and groups.

Ethical aspects

All the ethical principles were respected, according to 196/96 Resolution of National Health Council. The present study was previously approved by Humam Being Reasearch Ethics Committee of Santa Casa de Misericórdia in Juiz de Fora, MG under the technical opinion 566.668 (CAAE 25682813.4.0000.5139).

Results

Table I presents clinical and sociodemographic descriptive results typical of the studied total sample and its division among the Frailty groups

Table I - Clinical, laboratory and sociodemographic data divided in frail, pre-frail and non-frail groups.

Variables	Total n= 76	Non Frail n = 23	Pre-Frail n = 36	Frail n = 17	P
Age (years old), average ± SD	64.17 ± 11.2	63.09 ± 9.8	62.39 ± 11.0	69.41 ± 12.4	0.362
Female gender, n (%)	45 (59.2)	8 (34.8)	26 (72.2)	11 (64.7)	0.035*
Body Mass Index (kg/cm²) average ± SD	31.04 ± 7.4	28.7 ± 6.8	32.9 ± 7.6	30.1 ± 7.1	0.522
Diabetes, n (%)	50 (65.8)	14 (60.9)	28 (77.8)	8 (47.1)	0.494
Systemic Arterial Hypertension, n (%)	70 (92.1)	23 (100)	33 (91.7)	14 (82.4)	0.042*
Chonic Kidney Disease, n (%)	33 (43.4)	11 (47.8)	12 (33.3)	10 (58.8)	0.982
Dyslipidemia, n (%)	10 (13.2)	5 (21.7)	5 (13.9)	0 (0.0)	0.049*
Left ventricular Hypertrophy, n (%)	13 (17.1)	4 (17.4)	9 (25.0)	0 (0.0)	0.212
Angina/Accute myocardial Attack, n (%)	8 (10.5)	2 (8.7)	4 (11.1)	2 (11.8)	0.075
Heart Insufficiency, n (%)	11 (14.5)	3 (13.0)	4 (11.1)	4 (23.5)	0.401
Transient Ischemic Attack, n (%)	3 (3.9)	0 (0.0)	1 (2.8)	2 (11.8)	0.070
Hypothyroidism, n (%)	9 (11.8)	2 (8.7)	5 (13.9)	2 (11.8)	0.728
Coronarian Disease, n (%)	5 (6.6)	0 (0.0)	3 (8.3)	2 (11.8)	0.127
Myocardium revascularization/ Angioplasty, n (%)	4 (5.3)	1 (4.3)	2 (5.6)	1 (5.9)	0.823
Retinopaty, n (%)	9 (11.8)	3 (13.0)	3 (8.3)	3 (17.6)	0.728
Smoking, n (%)	25 (32.9)	7 (30.4)	13 (36.1)	5 (29.4)	0.895
Alcoholism, n (%)	14 (18.4)	6 (26.1)	7 (19.4)	1 (5.9)	0.944
Functional Illiteracy, n (%)º	30 (39.5)	2 (8.7)	17 (47.2)	11 (64.7)	0.001*

*Significative difference p<0.05. º education level lower to 4 years

Frailty high prevalence found (22.3%) is statistically significative and connected to female gender, systemic arterial hypertension, dyslipidemia and to education level.

Results of frailty analysis are shown at table II by the ABI test results.

Data present statistical signifivative difference among the groups. From the individuals with ABI alteration, 32.3% were frail and 51.6% were pre-frail.

Table II - Relation between fragility and ABI test results.

Variable	Total	Non Frail	Pre-Frail	Frail	P
	n = 76	n = 23	n = 36	n = 17	
Regular ITB, n (%)	45 (59.2)	18 (40)	20 (44.4)	7 (15.6)	0.017*
Altered ITB, n (%)	31 (40.7)	5 (16.1)	16 (51.6)	10 (32.3)	

*Significative difference p<0.05.

The relation among fragility criteria and ABI are found at Table III. Three out of five criteria evaluated for fragility are checked - physical education level, hand grip strenght and walking speed - individuals with ABI altered scored more than patients without alteration. For the exhaustion report and non-intentional weight loss variables, no significative difference was found, however, the high prevalence is remarkable in both groups.

Table III - Relation among the fragility criteria and ABI test results.

Fragility Criteria	Regular ITB	Altered ITB	P
	n = 45	n = 31	
Exhaustion report, n (%)	24 (53.3)	17 (54.8)	0.898
Physical activity level, n (%)	11 (2.4)	19 (61.3)	0.001*
Hand grip strenght, n (%)	7 (15.6)	12 (38.7)	0.023*
Walking speed, n (%)	3 (6.7)	7 (22.6)	0.045*
Weight loss, n (%)	9 (20.0)	6 (19.35)	0.945

*Significative difference p<0.05.

Discussion

The objective of the present study was to investigate clinical and sociodemographic factors associated to frailty, emphasizing the relation with peripheral arterial disease.

From the 76 individuals assessed, 22.3% were considered frail. Such values are expressively higher than the national average, which has been pointed in studies that follow the same fragility evaluation protocol, as demonstrated by Duarte et al. [9] who evaluated 1399 elderly of SABE study in São Paulo city and found a prevalence of frail elderly of 8.5%. When compared to international studies, the results are still relevant because they are superior than the average found by Manfredi et al. [10], which was 7.7% when 60816 elderly who live in European countries were assessed. And when it comes to North American studies, whose percentage was 6.9%, the average is also superior, verified by Fried et al. [4].

We also found 47.3% of the evaluated as pre-frail. Our results are superior than what was found by a Brazilian multicenter study [9], whose average was 41.5% and by an European multicenter study, which found a prevalence of 42.9% of pre-frail [10]. However, these data become more pertinent due to the

dynamic features of Fragility. A pre-frail individual presents enough physiological reservations to properly respond to some stressing events, but the fragility presents silent features and may rapidly get worse to a frail framework and its associated complications [11], and in contrast, it may positively respond to the treatment and evolve to a non-frail classification. Trevisan et al. [12] showed the syndrome negative evolution in a study evaluating 2,925 Italian elderly. The transition from the robust to pre-frail and from the pre-frail to frail happened with 954 individuals and 745 died. The individuals were revaluated after 4.4 years and the mortality rate was 2.4 times higher in frail individuals [12]. Duarte et al. [9] found a syndrome negative evolution, being 11.8% coming to death, 0.3% being institutionalised and 39.8% higher in frail individuals.

Responding to the initial objective of our study, it was verified that from the frail total sample, the individuals with altered ABI, 32.3% were classified as frail and 51.6% as pre-frail. These values are substantial even when compared to studies which analyzed Fragility associated with other clinical conditions. For example, Xue et al. [13] found a prevalence of 21% of Fragility in 171 patients hospitalized and reported that atherosclerosis was a risk factor for fragility. At the same study [9], ABI presented lower indexes in frail patients than in pre-frail and non-frail, suggesting a correlation between Fragility and cardiovascular disease.

Although physiopathology of cardiovascular disease and Fragility are complicated, both present common biological paths, which might explain the association, found among the variables.

Inflammatory state, reflected by rolling inflammatory markers, such as interleukin-6 and C-reactive protein, as well as thrombotic markers (VIII e D-dimers) bring strong correlation between the disease and frailty. Systemic inflammation induces to the activation of atherosclerotic plaques in the cardiovascular disease through oxidation of lipoproteins, being associated with arterial rigidity and promoting a muscle catabolic neuro-hormone state [14], essential component at the frailty circle. Besides, it permeates a boosting imbalance of osteopenia, anorexia, immune and cognitive decline, hematological and metabolic problems [6], which are also associated to Fragility. Reinforcing such relation, it was already proved that frail inflammatory individuals present up to 16% more chances to develop early frailty when compared to non-inflammatory individuals.

Another feasible association between Fragility and PAD is by oxidative stress. It is defined as an imbalance between formation and removal of oxidative agents in the organism, and has been related to vascular pathogenesis, linked to arterial stiffness and to arterial lumen reduction [16]. In a cellular level, the oxidative stress has also been postulated as a feasible mechanism that leads to Fragility. Due to cellular division alterations and to protein production associated to pathological processes and/or aging, there is a telomere loss. Such loss, brokered by oxidative imbalance, is strongly linked to a physiological decline in elder adults and to mortality increase. Nevertheless, these results have not been extrapolated to a relation with Fragility so far, what indicates further studies should be done [17].

According to Longo et al. [1], less than 50% of patients with PAD are symptomatic. However, symptomathology must be considered in the relation found. The intermittent claudication associated with cramps, tiredness, pain in rest or during effort are linked to diminish in walking speed and time, deterio-

ration in the musculoskeltal function, low quality of life and intolerance to the exercise [18]. Thus, they may explain the association between Fragility and PAD.

The other clinical and sociodemographic variables assessed and the associations with Fragility found also regard special attention.

It is verified that 64.7% of frail and 72.2% of pre-frail are women, expressing a significative difference when compared to men in similar clinical framework. According to Fried et al. [4], such difference is due to the lower thin mass percentage and to muscle strenght in female gender, besides the higher tendency to sarcopenia, anorexia and food inadequacies among women.

In our sample, 39.5% of the individuals were functional illiterate, which are superior than the national average of 27% [18]. According to Ribeiro et al. [20], low level of education is prevalent among users of Unique Health System (UHS in English and SUS in Portuguese), which may explain the difference from the national average, which considers individuals cared by public and private service. Similarly, the author observes that UHS low income users present a worse self health report. It is also verified that a low level of education might be a difficult factor to know diseases and to join to suitable treatments, which makes health worse [21]. Besides, the association between frailty and low level of education was also found by Duarte et al. [9] who found a 15.4% higher proportion of frailty among illiterate elderly, and by Wanaratna et al. [22] who checked Fragility was 4.04% more frequent in elderly, low level of education women.

Besides the smaller opportunities to health care access, this higher prevalence might be explained by low nutritional intake [22]. Arterial hypertension, diabetes and chronic kidney disease also expressed high prevalences. However, the predominance was already expected because it is a reference center, which cares the population with these pathologies. Despite of this fact, only the systemic arterial hypertension was considered significative in frailty incidence. The arterial hypertension was identified by Beneto et al. [27], in literature review, as presenting high rates of morbidity and mortality among frail individuals.

Frailty is related to diminish of physiological reservations, causing difficulties to maintain homeostasis [4]; this way, Buto et al. [23] analyzed baroreflex, one of the cardiovascular homeostasis mechanisms in frail people. The baroreflex presented decoupling between the cardiac period and systolic arterial pressure in frail and pre-frail people compared to non-frail ones [23]. There are few studies that verified the relation between arterial hypertension and frailty. Among them, Newman et al. [25] checked there is a 15% increase of fragility risk for each 10mmHG increase of systolic arterial pressure. For Fattori [26], the arterial hypertension potentially explains alteration of blood flow to the tissues, accelarating the sarcopenia proccess, which is a decisive variable of frailty framework. Benetos et al. [27] reported in a longitudinal study that the use of anti-hypertension therapy may bring risks to frail elderly, increasing the mortality rate.

Dyslipidemias are considered any alteration of lipoprotein reference values, considering total cholesterol, triglycerides, low and high density lipoprotein (LDL-c and HDL-c) and non-HDL cholesterol [28]. The association found in our study does not point relation between frailty and dyslipidemia. According to Bastos-Barbosa et al. [24], there are few studies which verified the relations between these variables, and these ones have not presented positive

associations so far. The exception seems to be with HDL-c. For example, the study named "iLSIRENTE study" evaluated 359 individuals and showed worse functional performance and mortality by all causes associated to lower HDL levels in frail elderly [29].

This information was confirmed by Chanti-Ketterl et al. [30] who reported lower functional capacity in elderly women with lower HDL levels. Although the important association among PAD, clinical and sociodemographic variables with Fragility, our work is limited. The insufficient sample of altered ABI patients made the group division impossible with values inferior than 0.9 and superior than 1.3. However, the same share strong association with inflammation, oxidative stress, endotelial function deterioration, besides the heart, cerebrovascular disease prognosis and high level of mortality. Another limiting factor is related to the cross-sectional character of the study, which prevents us from determining casual relation among the study variables. The data collection through medical report make a better explanation of the studied associations impossible.

Conclusion

We checked that, among the individuals with ABI alterations, there is a high prevalence of frailty. The inflammatory state, the oxidative stress and deterioration of endothelial function are found as main factors that resulted the association between the two syndromes. Efforts headed to an early detection of fragility are needed as well as interventions, aiming an improvement of both framework. The clinical and sociodemographic factors which have association were hypertension and dyslipidemias, gender and level of education, respectively, and they may indicate the necessity of primary intervention.

Thus, the association between frailty and autonomy significative negative outcomes, life quality and mortality reinforces the necessity of a continuous search for comprehension of their physiopathological basis.

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