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FIELD OF GENERAL MEDICINE

Correlation of arterial changes in the elderly frailty syndrome

DOCTORAL THESIS SUMMARY

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INTRODUCTION

Atherosclerotic disease affects the arterial vascular wall through the alteration of endothelial functions and the development of lipid deposits and/or fibrous lesions at the level of the tunica media, with effects on the diameter of the lumen and blood flow, being responsible for a series of debilitating peripheral arterial pathologies or cardio-embolic events, thus contributing to an increased rate of morbidity and mortality worldwide.

The frailty syndrome represents an accumulation of age-related deficits in normal functions, which also associates with cumulative functional decline, resulting in the depletion of biological reserves, progression of disability incidence rate, prolonged and repeated hospitalizations, or high mortality. Within the elderly population, physical frailty represents one of the major public health issues due to the impact it can have in triggering or aggravating cardiovascular diseases.

As I believe that the mechanisms linking the frailty syndrome and undesirable cardiovascular events have not been well defined so far, I considered it appropriate and necessary to conduct a research that could correlate the clinical aspects identified among elderly patients with the existing histopathological substrate.

GENERAL PART

1. MORPHOLOGICAL ALTERATIONS OF THE ARTERIAL WALL IN ATHEROSCLEROSIS

Alteration of endothelial actions with reduced vasodilation and aberrant endothelial activation due to anomalies in the leukocyte-platelet-endothelium relationship represents the initial stage of the atherosclerotic process and is mainly caused by the loss of the endothelium's ability to produce vasodilatory and antiatherogenic nitric oxide (Kitta et al., 2009). Adaptive intimal xanthoma and intimal thickening are considered the earliest manifestations of atherosclerotic disease (Yahagi et al., 2016). Oxidized low-density lipoprotein (oxLDL) represents an immunologic antigen with a key role in the immune response in atherosclerosis

(Hermansson et al., 2010) that promotes the binding of monocytes to endothelial cells through an intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) independent mechanism.

Arterial calcification of the tunica media represents a chronic systemic vascular condition, distinct from atherosclerosis, resulting from disseminated and progressive precipitation of calcium phosphate at this level, with effects on vascular hemodynamics alteration, ultimately associated with chronic ischemia (Lanzer et al., 2021).

The morphology of arterial walls and atherosclerotic plaques can be described using modern imaging methods such as coherent anti-Stokes Raman scattering (CARS) microscopy, multiphoton microscopy, electron-optic microscopy, confocal microscopy or polarized light microscopy; all of which can establish an early diagnosis.

2. ATHEROSCLEROSIS

Age-mediated increases in interleukin 6 levels in the aorta occur in a positive feedback loop with mitochondrial vascular dysfunction; both playing a role in the development of atherosclerosis (Tyrrell et al., 2020). Defining the individual hemodynamic profile helps to identify the causes of lack of therapeutic control arterial hypertension and draws attention to a cautious approach in attempting to lower systolic blood pressure to <140 mmHg in elderly patients (Aurelian et al., 2018).

A glomerular filtration rate with values between 45 and 60 ml/min/1.73m^2 increases the risk of vascular-related death by 40%, while a clearance <30 ml/min/1.73m^2 triples this risk (Matsushita et al., 2010). Hyperhomocysteinemia is an independent risk factor for atherosclerosis, while hyperuricemia causes endothelial dysfunction and increased oxidative stress, consequently accelerated atherosclerosis could be a consequence of the combined effect of hyperhomocysteinemia and hyperuricemia (Zhao et al., 2017).

Studies using non-invasive imaging for assessing vascular changes in children and adolescents provide indirect evidence for the early development of atherosclerosis, which is associated with cardiovascular disease in adulthood (Groner et al., 2006).

Intima-media thickness increases with age and varies by sex, with a value greater than 0.9 mm indicating an increased cardiovascular risk (Di Tullio et al., 2008). Arterial stiffness involves a decrease in compliance with which the arterial system transmits cardiac contraction during diastole and is measured by pulse wave velocity; a value >10 m/s being pathognomonic for the presence of structural lesions in the aortic wall (Van Bortel et al., 2012).

The ankle-brachial index shows increased specificity and sensitivity for the diagnosis of peripheral atherosclerosis in the lower limbs, and values <0.9 or >1.4 are associated on average with a 2-3 times increase in cardiovascular risk or mortality (Aboyans et al., 2018).

3. FRAILTY AND CARDIOVASCULAR RISK IN THE ELDERLY PATIENT

Research conducted in the United States of America has identified a prevalence of frailty ranging from 4% to 16% for individuals aged ≥65 years (Fried et al., 2001), reaching a value of 39.5% for those ≥95 years (Lee et al., 2016). The prevalence in Europe has varied from 6% to 44%, depending on the instrument used (Theou et al., 2013).

Frailty represents a precursor condition to disability and, in its early stages, might even be reversible (Gill et al., 2006). The prevalence of cardiovascular diseases increases with age, similar to frailty, so the question arises as to whether one causes the other, mutually exacerbating each other, or whether they are two pathologies with individual evolution but common risk factors.

Various assessment tools have been proposed in order to identify frailty, such as the Fried physical frailty phenotype (Fried et al., 2001), the Groningen frailty index (Peters et al., 2012), the frailty index (Kojima et al., 2018) or the clinical frailty scale (Church et al., 2020).

For the assessment of cardiovascular risk, the Framingham study was created, followed by the SCORE risk, later adapted for the elderly population as SCORE2-OP or the SMART risk scale (Dorresteijn et al., 2013).

The existence of the frailty syndrome imposes an additional risk on the elderly, assessment and screening tools for abuse being particularly necessary in order to improve the quality of life of these individuals and maintaining human dignity, while their systematic use is useful even in the Romanian context, where, despite the fact that the suspicions are numerous, their number still remains uncertain (Capisizu et al., 2017).

PERSONAL CONTRIBUTION

4. WORKING HYPOTHESIS AND GENERAL OBJECTIVES OF THE RESEARCH

Physical frailty and sarcopenia are major public health issues in the elderly population, the latter having a higher likelihood of developing cardiovascular diseases and an increased predictability for major events (Mihalache et al., 2022).

The research aims to analyze subclinical atherosclerosis in the elderly population by examining morphological changes in the arterial wall and its correlation with the frailty syndrome.

The proposed research objectives included: assesing the prevalence of subclinical atherosclerosis and the impact of associated risk factors on the elderly population admitted to a chronic disease hospital; identifying histopathological changes in the vascular wall associated with atherosclerosis; quantifying the relationship between the frailty syndrome and atherosclerosis; creating a free and original online screening tool for the detection of the frailty syndrome and, last but not least, conducting a comparative analysis of the prevalence of the frailty syndrome within the general population in relation to the hospitalized patients.

5. GENERAL RESEARCH METHODOLOGY

The doctoral research was conducted as a descriptive cross-sectional study on an initial group of 248 subjects aged ≥65 years admitted to the Geriatrics and Gerontology Clinic of the "Sf. Luca" Hospital for Chronic Disease, over a period of 12 months (01.01.2019 – 31.12.2019).

Exclusion criteria were: age under 65, failure to provide consent, presence of bedridden syndrome, severe neurodegenerative disease diagnosis and acute infectious disease diagnosis (Mihalache et al., 2022).

Data collection sources consisted of observation sheets, specific questionnaires, and functional and histopathological paraclinical investigations carried out in order to identify atherosclerotic changes.

Descriptive assessment methods included clinical and biological evaluation, analysis of existing risk factors, histopathological study of atherosclerotic lesions, as well as vascular evaluation of the subjects by means of carotid ultrasonography, ankle-brachial index and arterial stiffness.

Geriatric assessment methods involved the evaluation of functional status through the Activities of Daily Living (ADL) scale, Instrumental Activities of Daily Living (IADL) scale and Global Assessment of Functioning Scale (GAFS), the evaluation of neuro-cognitive status through the Mini-Mental State Examination (MMSE), Clock Drawing Test (TDC), Geriatric Depression Scale (GDS) and Reisberg's Global Deterioration Scale and, last but not least, the assessment of frailty status through the Fried's phenotype (FF), Groningen Frailty Index (GFI), Clinical Frailty Scale and the Short Physical Performance Battery (SPPB).

The collected data were entered into a database designed and created using Microsoft Excel 2016 from the Microsoft Office software suite and the data processing was performed using IBM SPSS Statistics 17 software.

6. STUDY: PREVALENCE OF SUBCLINICAL ATHEROSCLEROSIS AND IMPACT OF RISK FACTORS IN THE ELDERLY

6.1 Introduction

The study aims to describe the profile of the elderly patients admitted to the Geriatrics and Gerontology Clinic, highlighting general characteristics and associated risk factors.

6.2 Materials and methods

The study group consists of 139 subjects, selected based on the criteria previously outlined, from among the patients admitted to the Geriatrics and Gerontologu in 2019. The same protocol was applied to all subjects, regardless of when they were enrolled in the study.

Categorical variables (gender, background, etc.) were divided into categories, and for numerical variables (age, number of dependents, educational level), intervals were determined, and means, medians, standard deviations, etc., were calculated.

6.3 Results

The studied group had an average age of 73.92 ± 6.79 years, with subjects being divided into three subgroups according to the geriatric-specific age categories: 61% young seniors, 29% older seniors, and 10% oldest seniors, with a predominantly female structure (75.54%) and with no statistical differences ($p > 0.05$) across age groups, the values being similar for both genders.

The participants of the study had predominantly middle-level education (49.7%), 61.9% of the subjects live toghether with their families, while 38.1% lead an independent solitary life.

The Body Mass Index (BMI) varied between 17.5 and 48 kg/m2, with an average BMI of 27.34 ± 6.62 kg/m^2, the study group being classified overall as overweight, with the highest prevalence in the young seniors subgroup. The average abdominal circumference was 106.6 ± 13.2 cm. Both BMI and abdominal circumference showed a regression trend with increasing age, with abdominal circumference showing a significant correlation ($p = 0.043$) with the subject's gender.

The nutritional assessment (MNA) identified an overall good nutritional status (71%), noting that the subgroup aged ≥85 years is at risk of malnutrition.

Analysis of the risk factors associated with atherosclerotic disease revealed that the age of smokers is statistically significantly lower ($p=0.028$), the average blood glucose level of the group is high (127 ± 44.8 mg/dl) and the presence of hyperlipidemia is evident (Mihalache et al., 2022). The assessment of cardiovascular risk in relation to abdominal circumference and plasma indices showed a good correlation ($p=0.025$) and the average values of hematite sedimentation rate showed a significant increase ($p=0.011$) with advancing age.

56.1% of the study group showed a degree of functional dependence according to ADL, with 80.6% of the subjects needing assistance to perform instrumental activities of daily living (p>0.05) and 48.2% of the participants showing altered GAFS scores, revealing significant differences (p=0.000) in relation to age.

Cognitive assessment through MMSE and TDC classified the group in the mild cognitive impairment stage (p=0.01) in relation to age. 13% of the sujects exhibit a global functional impairment, the results showing a positive correlation (p=0.000) in relation to age groups.

Carotid ultrasonography identified intima-media thickness changes >0.9 mm in 52.5% of the subjects (p=0.027) in relation to age groups (40% for young seniors, 57% for older seniors, and 57.1% for oldest seniors).

Subclinical atherosclerosis specific alterations include changes in the ankle-brachial index in a proportion of 50.4% (p=0.01), a high average aortic pulse wave propagation velocity (10.69 ± 2.2 m/s) and a progressively increasing aortic augmentation index from 27.37 ± 17.96% among young seniors to 42.79 ± 13% for those aged ≥85 years, equivalent to attributing arterial stiffness characteristics to the entire group and indicating an increased cardiovascular risk.

6.4 Discussions

The group was predominantly female (75.54%), with an average age of 74.14 years, a high prevalence also confirmed by other studies on atherosclerosis (Spannella et al., 2020). Predominantly urbam composition (77.7%), with medium educational level (49.6%), in which subjects live together with their spouse and/or children in a proportion of 61.9%, without significant differences (p>0.05) in relation to age groups. 40% of the subjects ≤85 years live independently, however this percentage decreases to 21% for the subgroup aged ≥85 years, a difference that can be attributed to degenerative psychosomatic or pathological deficiencies that occur with advancing age.

Interestingly, both extremes of the Body Mass Index (BMI) were found within the female subgroup, drawing attention to phenotypic diversity, with the distribution of overweight values similar to those reported in the literature (Bhatt et al., 2006). The fact that both

anthropometric indices (BMI and WC) showed a regression trend with aging could be associated with the reduction in daily physical activities and the inevitable loss of skeletal muscle mass that comes with age (McCarthy & Berg, 2021).

In subjects not diagnosed with diabetes, fasting blood glucose levels >126 mg/dl were present in 2.1% of subjects, and borderline elevated values (115-126 mg/dl) were identified in 3.6% of the study group, values lower than those reported by the REACH study (4.9% and 36.5%, respectively) (Bhatt et al., 2006). My study confirms the existing correlation between the plasma atherogenic index and cardiovascular risk (He et al., 2018). The prevalence of proinflammatory status identified within the group showed statistically significant correlation (p=0.011) with advancing age.

The prevalence of atherosclerosis identified ultrasonographically by intima-media thickness was 52.5% (p=0.027), and that identified by the existance of atheroma plaques was 46% (p=0.31) in relation to age, with a notably higher proportion among the female population.

Schreuder et al. concluded that blood flow velocity has an inverse proportional relationship with age, leading to decreasing blood velocities in the carotid arterial axis (Schreuder et al., 2009), a hypothesis confirmed by the results of the current study, as adjusted average values of peak systolic velocity (PSV) decreased from 60.1 ± 20.6 cm/sec (for young seniors) to 53.3 ± 18.5 cm/sec (for oldest seniors).

The ankle-brachial index (ABI) is a good predictor of subclinical atherosclerotic disease, with changes showing a statistically significant correlation (p=0.01) with age.

7. STUDY: HISTOPATHOLOGICAL CHANGES OF THE ARTERIAL WALL IN THE ELDERLY

7.1 Introduction

The development of atherosclerotic lesions involves the extravasation of potentially atherogenic lipoproteins into the subendothelial space, where they undergo changes, acquiring proinflammatory, chemotactic and cytotoxic characteristics (Glass & Witztum, 2001), in addition to a transendothelial migration process of blood cells.

7.2 Materials and methods

The histopathological study of atherosclerotic lesions aimed both at the positive diagnosis of atherosclerosis, as well as at the analyzsis and recording of the particularities found in a sample group of 10 patients. In order to perform the histopathological study, fragments of aortic, carotid and muscular arteries, as well as cardiac tissue, were collected during autopsy, processed and stained according to the method presented in Chapter 5.

7.3 Results

The study group consisted of 10 subjects with an average age of 84.4 ± 5 years, and the gender ratio female:male being 6:4, with the largest proportion of subjects (60%) belonging to the group of oldest seniors ($\geq$85 years), where we observed a dominance of the female sex.

In terms of traditional risk factors for atherosclerosis, the average body mass index was 20.6 ± 1.5 kg/m^2, 4 subjects were active smokers, with a present hyperlipidemic status (average total cholesterol = 232.2 ± 58.7 mg/dl, average LDL-cholesterol = 151.8 ± 36.8 mg/dl, average triglycerides = 147.1 ± 50.5 mg/dl), hyperglycemic status present (average blood glucose = 122.5 ± 26.2 mg/dl), presenting inflammatory syndrome (average ESR = 50.6 ± 13.1 mm/h), impaired renal function (average eGFR = 33.8 ± 14.8 ml/min/1.73m^2) and hyperuricemia was identified in 5 subjects.

In terms of ultrasonographic assessment, average intima-media thickness (IMT) = 1.3 ± 0.1 mm, atheroma plaques were identified in 6 subjects, and the average peak systolic velocity (PSV) showed high values (145.5 ± 38.8 cm/sec). All subjects showed typical changes for subclinical atherosclerosis revealed through modifications of the ankle-brachial index and arterial stiffness phenomena.

Measurements were performed on the harvested fragments of the ascending aorta (AAo) as well as the right common carotid artery (RCCA) and the left common carotid artery (LCCA): average AAo diameter = 38.1 ± 0.99 mm, average LCCA diameter = 6.81 ± 0.51 mm and average RCCA diameter = 6.86 ± 0.54 mm. The difference in carotid circumferences in relation to gender (average male RCCA = 7.37 mm vs. average female RCCA = 6.47 mm) showed statistical significance (p=0.001), however the average AAo diameter was higher in females (38.16 mm) (p=0.13).

Aortic diameter and age were in a directly proportional relationship, independent of gender (p=0.06). Analysis of the carotid vessels reveals a strong statistical association between LCCA diameter and age among females ($R2 = 0.858$), while for the RCCA there was a similar correlation strength ($R2$ for males = 0.542 vs. $R2$ for females = 0.608).

Endothelial morphological changes involved intimal thickening, lipid accumulation, and inflammation which were associated with prothrombotic dysfunctions, revealed by the presence of atheromatous plaques that globally influence the vascular lumen diameter (t-student test, $p<0.001$). Vessels of neoformation were identified at the intimal level, and macrophages, T cells, smooth muscle cells, extracellular matrix rich in elastic fibers and proteoglycans, as well as intracellular and extracellular lipids were identified in the atheroma plaques. Injury to the vascular endothelium and rupture of the atheroma plaque predisposes to intraluminal thrombus formation.

Evaluation from the geriatric perspective reveals a low-functioning group, with a high degree of dependence of the subjects, moderate cognitive impairment (MMSE $= 17.9 \pm 5$ points, TDC $= 6.6 \pm 2.8$ points), significant level of depression (GDS $= 10.4 \pm 2.7$ points), high global deterioration (average Reisberg score $= 6.3 \pm 0.7$ points) and at risk of malnutrition (MNA $= 22.4 \pm 2.1$ points); the group fitting entirely within the frailty class regardless of the used instrument.

7.4 Discussions

I observed that the most common change in the intima is represented by fibrous thickening, identifying the tendency of the internal elastic lamina to regress with advancing age. Ultrasonographic evaluation of the carotid artery revealed specific atherosclerotic changes: increased IMT, elevated PSV and the presence of atheromatous plaques. Both the dimensional variations of the media and intima and the histopathological changes occuring in the arterial walls with advancing age support the assertion that disruptions in homeostasis have a significant impact on the progression of age-related atherosclerotic manifestations.

The main implications of the aortic changes encountered with advancing age relate to their magnitude, the average aortic diameter being 38.1 ± 0.99 mm, with autopsy studies indicating a positive correlation between aortic surface area and age. With age, the greatest

difference in diameter occurs in the ascending aorta and the greatest difference in aortic stiffness occurs in the abdominal region (Hickson et al., 2010). Analysis of carotid diameters reveals a strong statistical association between the diameter of the left common carotid artery and age among women (R2 = 0.858), while for the right carotid artery there is a similar strength of correlation (R2 for males = 0.542 vs. R2 for females = 0.608).

In the study group, the average diameter of the ascending aorta was 38.1 mm, the average diameter of the left common carotid artery was 6.81 mm, the average diameter of the right common carotid artery was 6.86 mm, and the average intima-media thickness was 1.3 ± 0.1 mm, indicating that atherosclerotic manifestations globally influence the diameter of the vascular lumen (Student's t-test, $p < 0.001$).

The aging process is accompanied by complex structural and functional changes within the arterial system, consisting of autophagy, migration and proliferation of smooth muscle cells, as well as in arterial calcification leading to a progressive increase in mechanical stiffness of the vessles, oxidative stress and inflammation being the most important pathological processes underlying endothelial dysfunction in the elderly (Jeon et al., 2018). Proportional to age, vascular smooth muscle cells undergo functional changes that alter the normal structure of the vascular wall, increasing its susceptibility to the atherosclerotic process.

8. STUDY: RELATIONSHIP BETWEEN FRAILTY AND SUBCLINICAL ATHEROSCLEROSIS IN THE ELDERLY

8.1 Introduction

This study aims to investigate both the relationship between frailty and subclinical atherosclerosis in the elderly by identifying risk factors that may influence frailty among the elderly, correlating the screening tools used to diagnose the frailty syndrome, as well as the role that atherosclerosis plays within this geriatric syndrome.

8.2 Materials and methods

Frailty was assessed using three distinct instruments: the Fried phenotype (FF), the Groningen Frailty Index (GFI) and the Clinical Frailty Scale (CFS). The predictive power of

these three methods was tested in order to optimally characterize the study group. The same 139 subjects previously mentioned in section 6.2 were chosen as the study group, and the same inclusion and exclusion criteria and the same protocol were used in the assessment carried out according to the methodology presented in Chapter 5.

8.3 Results

The studied group had an average age of 73.92 ± 6.79 years and, based on the three screening instruments used, could be defined as frail (average GFI = 4.15 ± 2.48 points), prefrail (average FF = 2.5 ± 1.56 points) and non-frail/prefrail (average CFS = 4.47 ± 2.11 points).

According to the Fried analysis, the average frailty score increases proportionally across age groups (p=0.010), a situation also validated by the application of the Clinical Frailty Scale (p=0.014). In the case of qualitative assessment, the distribution of frailty in relation to subject's age group shows a correlation (p=0.004) for GFI and CFS (p=0.004), while FF is at the borderline of statistical significance (p=0.053).

The presence of the frailty syndrome according to GFI: 52.4% in females vs. 52.9% in males, CFS: 50.5% in females vs. 52.9% in males, while FF identified that 87.6% of females and 94.3% of males show a degree of frailty.

The average age varied in relation to the degree of frailty, increasing as frailty worsened (p=0.005), and the body mass index decreased as frailty progressed (p=0.000), similarly for abdominal circumference (p=0.021).

52.5% of frail subjects were at risk of malnutrition or even malnourished, and the nutritional status assessed using MNA correlated strongly with the frailty syndrome (p=0.000).

88.2% of subject who smoke, 85.7% of subjects diagnosed with diabetes and 84.9% of those diagnosed with cardiovascular disease show a change in robustness status, falling into the prefrailty and frailty classes.

Frail subjects exhibit varying degrees of autonomy depending on the assessment tool used: 42% of subjects based on ADL, 16.7% based on IADL and 20% based on GAFS.

Regardless of the scale used to assess functionality, a trend of decreasing functional capacity is observed as the frailty syndrome progresses.

The frail subgroup is characterized by mild cognitive impairment (average MMSE = 22.21 ±5.43 points, average TDC = 8.03 ±2.45 points) and depressive disorder (average GDS = 5.97 ±4.54 points), as such the assessment of cognitive impairment through MMSE correlates with frailty (p=0.024).

Regardless of the frailty screening tool used, plasma atherogenic index and ankle-brachial index did not show statistically significant correlations (p>0.05), while intima-media thickness and aortic pulse wave propagation velocity showed a strong association (p=0.001) (Mihalache et al., 2022). Based on this analysis, we can assert that intima-media thickness and arterial stiffness influence frailty (p<0.05 between frailty classes, statistically significant, positive, medium strength of association). Carotid atheroma plaques were identified in approximately 80% of frail subjects, demonstrating a strong correlation (p=0.000, Fischer's exact test).

8.4 Discussions

The present study identified an average prevalence of frailty of 51.6% within the group, prevalences obtained from the use of four distinct assessment tool; value which correlates with the existing literature, reported 55% in Switzerland (Tröster et al., 2020). The prevalence of frailty was higher among male subjects, regardless of the assessment tool used, which contradicts the literature data studied, though it can be justified by the numerical inequality between the two sexes present within the group.

Body mass index and abdominal circumference decrease with the progression of frailty (p=0.000 and p=0.021, respectively), a fact confirmed by the impact that low BMI has on institutionalization and mortality rates among the elderly (Tröster et al., 2020). There is a regressive trend in functional capacity as the frailty syndrome progresses.

Cognitive impairment correlates with frailty (p=0.024) and represents a risk factor for disability, dementia, decreased quality of life and, last but not least, mortality (Arai et al., 2018).

Plasma atherogenic index showed no significant correlations (p>0.05) with frailty, while intima-media thickness and aortic pulse wave propagation velocity showed a strong association (p=0.001) with it (Mihalache et al., 2022). An increase in IMT by one standard deviation is associated with an increased likelihood of the subject being frail (Avila-Funes et al., 2014). Analysis of the ankle-brachial index correlated (p=0.037) with frailty, as quantified through the clinical frailty scale. An improvement of one point in the SPPB score reduced the probability of institutionalization of frail subjects by 23% (Tröster et al., 2020).

9. STUDY: ANALYSIS OF GENERAL POPULATION FRAILTY USING THE ORIGINAL WEB APPLICATION „FRAILTY" AND COMPARISON WITH THE STUDY GROUP

9.1 Introduction

Frailty in the elderly is a multidimensional syndrome that involves the mutual influence of biological, psychological and social factors. In the light of the past three years, telemedicine has gained momentum, demonstrating its role and necessity in today's society.

The purpose of this study is to develop a web application called "Frailty" in order to inform and raise awareness among the general population about the existence of the frailty syndrome.

9.2 Materials and methods

Within the original web application https://fragilitate.webloft.ro/, we defined the frailty syndrome and its clinical implications, thus familiarizing the general population with its terminology and impact. We constructed a simple and relatively short self-assessment tool that provides respondents with the opportunity to reflect on their sensory capacities, nutritional, cognitive, and social status, evaluating existing comorbidities and their level of physical activity.

PHP version 8.1 with Laravel 9 framework was used in the development of the web application "Frailty". Storage of the information entered by the respondents was achieved

through a MySQL database, version 8. Bootstrap 5.1 CSS framework was employed as the frontend technology. All data was collected online, anonymously, without storing personal data that could lead to identification of the respondents.

9.3 Results

The study group consisted of 134 subjects aged between 55 and 83 years, with an average age of 67.6 ± 7.4 years, its structure consisting of 33.6% pre-geriatric adults, 51.5% young seniors, and 14.9% seniors, mostly from urban areas (98.5%), with a female predominance of 67.9%, showing a significant difference across age groups (p=0.02).

Educational level analysis by gender did not identify significant differences in relation to age (p>0.05). The majority of subjects living alone are young and belong to the high-income category, while middle-income respondents live predominantly in cohabitation. The prevalence of smoking decreases with advancing age (p<0.001).

Body Mass Index (BMI) varied between 18 and 43.4 kg/m^2 (both extremes found within the high-income female subgroup), with an average BMI of 28 ± 6.14 kg/m^2, placing the group in the overweight category, with a relatively even distribution of subjects between the normal weight (35.1%), overweight (27.6%) and obese (36.9%) categories (p=0.0001).

A high prevalence of comorbidities (80.6%) was identified in the general population, with the majority of the group having two prevalent chronic conditions (32.8%), the most common being cardiovascular and osteoarticular disorders (58.2% and 47.8%, respectively).

The prevalence of the frailty syndrome in the general population, obtained through the "Fragility" web application, was 40.3%. Frail subjects were predominantly female (70.4%) (p=0.055), who do not live alone (77.7%). All frail subjects were from urban environments. A lower monthly income is characteristic of the frailty syndrome (74.1%) (p=0.004) and the level of education does not impose an additional risk.

Frail subjects were predominantly of normal weight (46.3%), non-smokers (77.7%) and with prevalent pathologies (77.7%). The presence of at least 3 concomitent pathologies predisposes to frailty (p<0.001), and the type of condition that has been associated with frailty at a rate of 100% was the category of oncological diseases.

9.4 Comparative frailty analysis. Discussions

We conducted a comparative analysis between Group 1 (subjects included from inpatients at the Geriatrics and Gerontology Clinic) and Group 2 (obtained through the use of the "Fragility" web application), the two groups being of similar size and could be divided into 3 subgroups based on age criteria. Group 1 included young seniors (61%), older seniors (29%) and oldest seniors (10%), while Group 2 had the following structure: pre-geriatric adults (33.6%), young seniors (51.5%) and older seniors (14.9%). Both groups were predominantly female, with a higher proportion in Group 1 (75.5%). Group 2 was predominantly urban (98.5%) compared to Group 1, justified by the broader accessibility of online services and technology in this environment.

The proportion of subjects with higher education was higher in Group 2 (33.6% vs. 15.8% in Group 1), and they were predominantly male regardless of the group investigated. Moreover, economic power was greater within Group 2. In both groups, the number of individuals living alone decreases with advancing age (p<0.05).

The average BMI was higher in Group 2 (28 ±6.1 kg/m^2), but both groups are characterized by overweight, which draws attention to the general risk of obesity prevalent in our country, but also to the existing cardiovascular risk.

The prevalence of comorbidities in the two groups was different, being 96.4% in Group 1 and 80.6% in Group 2, which justified by the context and selection method of the two groups. The chronic disease category with the highest prevalence was cardiovascular, with a prevalence of >90% in Group 1 and 58.2% in Group 2. This was followed by diabetes (45.3%) in the first group, as opposed to osteoarticular pathology (47.8%) in the second.

Comparative analysis of the two groups through the Groningen Frailty Index identified a difference in the prevalence of this syndrome of 12.2% in favor of Group 1 (52.5%). Consequently, due to the statistically significant difference (p=0.02), we can say that frailty is a risk factor for hospitalization.

The prevalence of chronic diseases among hospitalized frail individuals (94.5%) is higher than that in the general population (77.7%); this difference is statistically significant (p=0.004), with frailty increasing the risk of hospitalization (Vermeiren et al., 2016).

10. CONCLUSIONS AND PERSONAL CONTRIBUTIONS

10.1 Conclusions

Through this doctoral research, I have accomplished the proposed aim and objectives, which aimed at: detecting atherosclerosis in the elderly population of our country by identifying the demographic and clinical characteristics of the subjects, performing a descriptive examination of endothelial structural changes, examining arterial vascular changes through the analysis of vascular stiffness, vascular intima-media thickness and ankle-brachial index, as well as analyzing the frailty status and, last but not least, developing a web application for identifying frailty in the general population.

The research comprised four studies conducted on different groups, including a first group of 139 subjects aged over 65, hospitalized in the Geriatrics and Gerontology Clinic of the „Sf. Luca" Hospital for Chronic Disease, who met the inclusion criteria for the study and consented to participate, a second group of 10 subjects on whom the histopathological study was performed, and a third group formed through the "Fragility" web application, consisting of 134 respondents.

In the first part of the research, we aimed to identify atherosclerotic risk factors and the prevalence of subclinical atherosclerosis among the elderly population. As a result, 55% of the studied group can be classified as overweight, and increased values of body mass index and abdominal circumference are associated with good nutritional status. Increased abdominal circumference is characteristic of the urban environment and correlates with the subject's gender (p=0.04).

The age of smokers participating in the study was statistically significantly lower (p=0.028), despite the fact that the reported smoking across defined age groups did not confirm the same trend (p>0.05) at the group level.

Hyperlipidemia characterized the research group, and the plasma atherogenic index correlates with cardiovascular risk (p<0.05). Existing inflammatory status is directly associated with aging (p=0.11).

Atherosclerotic phenomena were ultrasonographically identified in the carotid arteries in a proportion of 52.5%, with a notably higher prevalence among the female population and a significant correlation (p=0.027) among age groups. The prevalence of atherosclerotic plaques did not associate with advancing age (p=0.31).

The analysis of subclinical atherosclerosis manifestations in peripheral arteries identified changes in the ankle-brachial index in a proportion of 50.4%, showing statistically significant correlations (p=0.01) across age groups.

In terms of arterial stiffness, the aortic pulse wave propagation velocity had higher values within the subgroup of individuals aged ≥85 years. The average aortic augmentation index was 31.6 ±17.7% within the group, with varying values across subgroups, the highest being recorded in those aged ≥85 years (42.8 ±13%), suggesting increased peripheral vascular resistance.

The histopathological study of arterial walls in the elderly was conducted on a group of 10 subjects with an average age of 84.4 ±5 years, and the gender ratio of female:male was 6:4. Analyzing these numbers in relation to the overall study group revealed a mortality rate of 5.7% among females and 11.8% among males.

The main implications of the aortic changes observed with aging relate to their magnitude (average diameter of the ascending aorta = 38.1 ±0.99 mm). Analyzing this relationship revealed larger diameters in older ages, and there is a positive correlation between the two types of variables, although without statistical significance (p=0.06). However, age would still be an influencing factor for the progression of aortic diameter over time.

The average diameter of the common carotid arteries was higher than that reported in literature, and the caliber difference between genders (average common carotid diameter = 7.37 mm in males vs. 6.47 mm in females) is not accidental (p=0.001), being associated with the smaller body size of females.

Atherosclerotic manifestations significantly influence the overall diameter of the vascular lumen (t-student test, p<0.001). Macroscopically, irregularities in the vascular lumen were identified by the presence of atheroma plaques complicated with lipid streaks, granulation tissue and thrombi that can constitute factors for systemic embolization.

The fibrotic transformation of the muscular wall is caused by a chronic inflammatory process generated by diffusely distributed lymphomonocytes. Intimal neoformation vessels were identified, and the respective artery lumens showed varying degrees of stenosis, ranging up to complete obstruction. Macrophages, T cells, smooth muscle cells, extracellular matrix rich in elastic fibers and proteoglycans, as well as intra and extracellular lipids, were identified within the atheroma plaques.

The frailty syndrome evaluated through the Fried phenotype and the clinical frailty scale correlated with advancing age (p=0.010, respectively p=0.014).

85.7% of diabetic subjects, 84.9% of those diagnosed with cardiovascular disease and 88.2% of smokers exhibit a change in robustness status. Nutritional status is closely correlated with the frailty syndrome (p=0.000), and 52.5% of frail subjects were at risk of malnutrition or even malnutrition.

The background, the number of people in the residence and the educational level of the subjects cannot be considered risk factors for frailty syndrome (p>0.05), but cognitive impairment has shown a statistically significant correlation with frailty (p=0.024).

Intima-media thickness and arterial stiffness influence frailty (p<0.05 between frailty classes, statistically significant, positive, medium strength of association). Carotid atheroma plaques were identified in approximately 80% of frail subjects, demonstrating a strong correlation (p=0.000, Fischer's exact test). Frailty quantified through the clinical frailty scale is statistically associated with ankle-brachial index variation (p=0.037).

Physical frailty assessed through SPPB and subclinical atherosclerosis shows a statistically significant correlation (p=0.001) through the compared average values of IMT (0.89 ±0.14 mm for robust vs. 1.35 ±0.28 mm for frail) and PWV (9.2 ±1.1 m/s for robust vs. 12.39 ±1.89 m/s for frail). The subject's physical capacity was positively correlated with the presence of atherosclerotic plaques at the carotid level (p=0.000).

To continue the research endeavor, we developed a web application called "Frailty" which defined a group of 134 respondents (aged >55 years), predominantly female (67.9%), living with their life partner and exhibiting a higher prevalence of cardiovascular and osteoarticular conditions (58.2% and 47.8%, respectively).

The prevalence of frailty syndrome among the general population was 40.3%, with the most affected segment being the 65-74 age group (55.6%).

Frail subjects come from an urban environment, have a predominantly female distribution (70.4%) at the borderline of statistical significance (p=0.055), do not live alone (77.7%) and have a lower monthly income (74.1%) (p=0.004). Level of education is a neutral factor for frailty.

Comparative analysis between the study group within the Geriatrics and Gerontology Clinic (Group 1) and the general population obtained through the "Frailty" application (Group 2) revealed a higher body mass index in the general population (28 ± 6.1 kg/m^2), with the status of the smoking subjects being similar, identifying a regression trend associated with advancing age.

The prevalence of comorbidities was higher in the first group, which was justified by its composition (patients admitted to a hospital unit with beds), while the second group was obtained through the voluntary participation of the general population without a connection to an acute/post-acute medical moment at that time.

The category of chronic diseases with the highest prevalence was cardiovascular disease (prevalence >90% in Group 1, and 58.2% in Group 2), followed by diabetes (45.3%) in the first group, and osteoarticular pathology (47.8%) in the second group.

Comparative analysis of frailty in the two groups identified a statistically significant difference (p=0.02) in the prevalence of this syndrome by 12.2%, in favor of Group 1 (52.5%), supporting the hypothesis that frailty is a risk factor for hospitalization. The prevalence of chronic diseases among hospitalized frail subjects reaches a proportion of 94.5% compared to 77.7% in the general population (p=0.004).

10.2 Personal contributions

An novel element brought about by this study is illustrated by the analysis of correlations between the frailty syndrome and the atherosclerotic changes found in the arterial wall among the elderly population. I consider this research to be of multidisciplinary interest for the development of new approaches in current medical practice.

The main novelty element is represented by the originally developed web application (https://fragilitate.webloft.ro) through which I aimed to inform and raise awareness among the general population about the existence of this geriatric syndrome, which can be overlooked or mistakenly attributed to the physiological aging of the body, but which has significant repercussions on the quality of life, the individual's health status and ultimately, on mortality.

The importance of a free online health assessment application cannot be overestimated in today's digital era, as it serves as a valuable screening tool that allows anyone to conveniently assess and monitor their health status, at any time as long as they have an internet connection. By providing a comprehensive set of questions related to the frailty syndrome, the application enables users to identify warning signs or existing risk factors they might not have been aware of, thus encouraging them to take an active role in managing their own health.

The originality of this doctoral research lies in the web application "Frailty", the first of its kind in our country, accessible to the general population and which has the capacity to make individuals responsible for their own well-being, while saving time and economic resources for both the interested individuals and the healthcare system. Early detection can lead to timely interventions, reducing the incidence of frailty syndrome, tailoring healthcare services to the needs of frail individuals, achieving better health outcomes, and ultimately lowering costs in the healthcare sector.

The high prevalence of comorbidities among the elderly population identified in this doctoral research, along with the manifestations of atherosclerosis and the frailty syndrome, should serve as a trigger for both healthcare professionals to take active measures to identify risk factors specific to frailty and for decision-makers to efficiently calibrate the resources available in the healthcare system to cope with an increasingly aging population.

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