Research Square

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Clinical and Subclinical Arteriosclerotic Disease in Octagenarians With Hip Fracture. A Case – Control Study.

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Abstract

Background: Osteoporosis and cardiovascular diseases share risk factors and pathophysiological mechanisms. Hip fracture and cardiovascular diseases are very common in older people.

Objectives: Evaluate clinical and subclinical arteriosclerotic disease in older patients with hip fracture compared with patients without fracture in order to increase knowledge about the relation between both diseases in old patients.

Method: Age- and sex matched case-control study of octogenarians with and without recent hip fracture. Vascular risk factors, subclinical vascular diseases (assessed by carotid plaques, carotid intima media thickness and arterial stiffness) as well as cardiovascular diseases were analyzed. Univariate and multivariate logistic models were used to estimate Odds Ratios (OR) with their 95% confidence intervals (CI) to assess the association arteriosclerosis and hip fracture.

Results: We analyzed 95 patients per group with a median age of 82 [79-87] years of whom 77.9% were female. Patients in both groups have elevated rates of vascular disease (25%) without differences between them. Patients with hip fracture had higher subclinical arteriosclerotic alterations with higher percentage of carotid plaques (OR 3.25 [1.06 - 9.97]) compared with the control group.

Conclusions: Old patients with hip fracture had significantly higher presence of subclinical alterations but not increase on rate of cardiovascular arteriosclerotic disease compared with those without hip fracture. Is mandatory to increase our knowledge in shared risk factors for both diseases to enhance fracture prevention or vice versa.

Background

Hip fracture is the most prevalent fracture associated with osteoporosis in older people and its incidence increases progressively in tandem with increased life expectancy [1]. In our clinic area (Catalonia northeastern area of Spain), the incidence of osteoporotic hip fracture is 2.23 per 1000 persons/year aged ≥ 50 years and is higher in females [2] in concordance with data of other European regions [3].

Cardiovascular diseases are the leading cause of death in both sexes from the age of 80 onwards, and the main cause of death is ischemic heart disease [4]. The prevalence of hip fracture and cardiovascular diseases are rising due to the increase of life expectation.

It is considered that vascular damage begins to appear from the third decade of life and its progression is modulated by risk factors shared with osteoporosis, as well as common pathophysiological mechanisms related to the process of calcification [5, 6]. The initial lesion is calcium deposit in endothelium with an increase of arterial stiffness and intimae media thickness as well as the genesis of plaques in the different vessels [5]. The mechanism of osteogenesis is similar to arterial calcification and involves

various cells, proteins, cytokines and metabolic pathways leading to tissues mineralization and inflammation [7–9].

Patients with worse bone mineral density have greater vessel calcification in both large and small vessels, as well as an increase in cardiovascular events [6, 10–14].

Most studies have focused on the relationship between osteoporosis and vascular arteriosclerotic diseases, however, only few studies have analyzed the relationship between subclinical vascular damage and hip fracture in old ages with controversial results and non including all subclinical vascular parameters in the evaluation [15–21].

The aim of this study is to analyze the cardiovascular arteriosclerotic disease (clinical and subclinical) in old patients with hip fractures and determine whether it is more prevalent than in patients without fractures. The objective is to improve knowledge for a better prevention of hip fractures and cardiovascular arteriosclerotic diseases in the future.

Methodology

Study population

Case-control study of patients aged ≥ 79 years admitted to the Orthogeriatric Unit (2017–2019) with the diagnosis of hip fracture.

For each case, an exact age and sex matched control patient without previous hip fracture was selected (± 2 years). These individuals were followed up for other medical reasons in internal medicine department and were selected by in-time sequence.

We excluded patients with advanced cognitive impairment (Pfeiffer questionnaire ≥ 8 points) [22] in whom the questionnaires could not be completed and who could not collaborate with the complementary tests. Patients with worsening during admission associated with a poor short-term clinical prognosis or with advanced oncological disease with a life expectancy of < 6 months were also excluded.

The project was approved by the Clinical Research Ethics Committee of the Hospital Clinic of Barcelona. All patients gave signed informed consent for the collection of hospital medical history data and the carrying out of complementary tests. Data were collected during hospital admission (clinical parameters) and 3 months after discharge (vascular ultrasound and measurement of arterial stiffness). In the control group, a single outpatient visit was used to collect data and carry out complementary tests.

Parameters analyzed

The questionnaires included epidemiological parameters (age, sex), functional assessment (Barthel Index [23] and Lawton Index [24] before admission or during the outpatient visit in controls), anthropometric analysis (body mass index [BMI], waist circumference, bicipital diameter), diseases and vascular risk

factors (substance abuse, hypertension, coronary heart disease [history of myocardial infarction or unstable angina], history of ischemic brain disease, diabetes mellitus, vascular dementia [with a previous brain CT scan] and peripheral vascular disease assessed previously by Doppler.

In the blood samples, the lipid profile was determined: total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides.

The subclinical vascular alterations were assessed using the following parameters:

- Carotid Intima media thickness (cIMT): This was measured by automated ultrasound analysis with a high frequency linear probe, using a specific program (QIMT®) that carried out multiple serial measurements of the selected segment in the posterior wall of the right common carotid artery and obtains the mean and maximum value for each image obtained. Normal values were obtained from studies in the Spanish population (75th percentile of carotid IMT was 0,88 mm in men and 0,81 mm in women) [25–27].
- Plaque in the common carotid artery, carotid bulb and internal carotid were measured using an ESAOTE MyLab 50® ultrasound scanner with a linear high frequency probe (≥ 7 MHz) administered by a trained operator. Plaque was defined as focal thickenings of the wall that were at least 50% greater than the thickness of the surrounding wall or that penetrated 0.5mm into the arterial lumen.
- Central blood pressure, augmentation index (AIx) and arterial stiffness were determined using the Sphygmocor® blood pressure analysis system. This non-invasive applanation tonometry system permits calculation of central blood pressure, pulse wave analysis, the increased in the peripheral and central index and the pressure of the peripheral and central pulse, and the calculation of the degree of arterial stiffness by calculating the pulse wave velocity (PWV) [28–31]. The AIx is based on blood pulse-wave reflection, and is an accepted measure of arterial stiffness [32, 33].

Statistical analyses

The qualitative parameters are expressed as absolute frequency and percentage (%). Quantitative parameters are expressed as medians and interquartile range (IQR: percentile 25th – 75th). Standardized differences (STD) were also reported to assess balance between groups. STD > 10% indicates unbalance [34]. In continuous parameters, STD was calculated based on medians.

Univariate and multivariate logistic models were used to estimate Odds Ratios (OR) with their 95% confidence intervals (CI) to assess the association of the risk factors and hip fracture. The parameters included in the multivariate logistic model were included by clinical criteria.

Statistical significance was established as $p < 0.05$. All the analyses were performed using the SAS v9.4 statistical package (SAS Institute, Cary, North Carolina, USA).

Results

We included 95 age- and sex-matched patients per group. The median age in both groups was 82 [79–87] years, with a predominance of females (77.9%). The characteristics of the two groups are shown in Table 1.

Table 1
Base-line characteristics of the two groups.

	CASE GROUP (n = 95)	CONTROL GROUP (n = 95)	STD (%)
Age (years); median [IQR]	82 [79–87]	82 [79–87]	0.8
Sex; n (%)	Male: 21 (22.1)	Male: 21 (22.1)	0
	Female: 74 (77.9)	Female: 74 (77.9)	
Functional assessment (points); median [IQR]	Barthel: 95 [85–100]	Barthel: 100 [95–100]	53.5
	Lawton: 8 [3–8]	Lawton: 8 [6–8]	42.1
Anthropometric variables; median [IQR]	BMI (kg/m2): 24.89 [21.6–27.5]	BMI (kg/m2): 25.97 [23.68–28.4]	31.9
	Waist circumference (cm): 91 [85–100]	Waist circumference (cm): 95 [90–103]	32.6
	Bicep circumference (cm): 25 [23–27]	Bicep circumference (cm): 26 [24–28]	37.2
Cardiovascular Risk factors; **n (%)**	Smoking: 24 (25.3)	Smoking: 11 (11.6)	35.9
	Hypertension: 69 (72.6)	Hypertension: 63 (66.3)	13.8
	Diabetes mellitus	Diabetes mellitus	31.7
	Type 1: 2 (2.1)	Type 1: 0 (0)	
	Type 2: 14 (14.7)	Type 2: 24 (25.3)	
	Dyslipidemia	Dyslipidemia	100
	TC: 138 [120–160]	TC: 193.5 [171–222]	100
	HDL: 37 [31–44]	HDL: 54 [45–66]	100
	LDL: 76 [60.5–91]	LDL:114.5 [91.5–134]	0.3
	TGC: 119 [90–150]	TGC: 112 [85–163]	
Cardiovascular disease; **n (%)**	Coronary heart disease: 5 (5.3)	Coronary heart disease: 9 (9.5)	16.2
	Stroke: 7 (7.4)	Stroke: 7 (7.4)	13.6
	Vascular Dementia: 10 (10.5)	Vascular Dementia: 7 (7.4)	11.1

n: number of cases; STD: Standardized difference; IQR: Interquartile range, expressed with percentiles 25th and 75th ; BMI: Body mass index; IMT: Intima media thickness; PWV: Pulse wave velocity; AIx: Augmentation Index; TC: Total cholesterol; TGC: Triglycerides; HDL: High-density lipoproteins; LDL: Low-density lipoproteins.

	CASE GROUP (n = 95)	CONTROL GROUP (n = 95)	STD (%)
	Peripheral vascular disease: 5 (5.3)	Peripheral vascular disease: 2 (2.1)	16.8
	Any CV disease: 24 (25.26)	Any CV disease: 24 (25.26)	0
Subclinical vascular assessment; **n (%) or** **median [IQR]**	Carotid plaque: 15 (22.7)	Carotid plaque: 8 (8.9)	38.6
	cIMT (mm): 830 [697–976]	cIMT (mm): 830 [650–980]	0.7
	PWV (m/s): 12.45 [11.1–14.4]	PWV (m/s): 12.4 [10.8–14.4]	4
	AIx (mmHg): 30.5 [20–44]	AIx (mmHg): 32 [26–39]	4
	Mean central arterial pressure (mmHg): 105 [94–116]	Mean central arterial pressure (mmHg): 105 [93–114.5]	5.2

n: number of cases; STD: Standardized difference; IQR: Interquartile range, expressed with percentiles 25th and 75th ; BMI: Body mass index; IMT: Intima media thickness; PWV: Pulse wave velocity; AIx: Augmentation Index; TC: Total cholesterol; TGC: Triglycerides; HDL: High-density lipoproteins; LDL: Low-density lipoproteins.

The most prevalent cardiovascular risk factor in both groups was blood hypertension (> 65% of patients).

No differences were found concerning on prevalence known cardiovascular disease in both groups, which was about 25%.

Hip fracture was unbalanced on carotid plaques compared to controls (15 vs. 8, STD = 38.6%). PWV was balanced between groups (STD = 4%), despite the prevalence of PWV > 10m/s [33] was higher than 85% in both groups.

In the multivariate analysis of risk factors and cardiovascular disease, significant differences were observed in smoking habit and levels of cholesterol and triglyceride compared with the control group. There is no difference in the other cardiovascular risk factors and no increase in cardiovascular disease in patients with femur fracture. As well as, the analysis showed that the presence of carotid plaques was associated with hip fracture [OR: 3.25 (95% CI: 1.06–9.97); P = 0.039] (Table 2).

Table 2
Multivariate analysis of the assessment of cardiovascular risk factors and cardiovascular disease between groups.

Parameters	Odds Ratio (95% CI)	p-value
Smoking	3.17 (1.26–7.93)	0.013
Hypertension	1.38 (0.72–2.62)	0.332
Diabetes Mellitus 2	0.55 (0.26–1.15)	0.281
Dyslipemia	TC: 0.67 (0.57–0.78)	< 0.001
	HDL: 0.91 (0.88–0.94)	< 0.001
	LDL: 0.58 (0.46–0.72)	< 0.001
	TGC: 0.97 (0.92–1.03)	0.3587
Coronary Heart disease	0.56 (0.19–1.66)	0.292
Stroke	1.75 (0.51–5.98)	0.572
Dementia	1.43 (0.54–3.75)	0.469
Carotid plaques	3.25 (1.06–9.97)	0.039
cIMT (mm)	1.01 (0.86–1.2)	0.867
PWV (m/s)	1.02 (0.86–1.21)	0.819
AIx (mmHg)	1.01 (0.98–1.03)	0.737
Mean central arterial pressure (mmHg)	0.97 (0.74–1.27)	0.822

TC: Total cholesterol; TGC: Triglycerides; HDL: High-density lipoproteins; LDL: Low-density lipoproteins, IMT: Carotid Intima media thickness; PWV: Pulse wave velocity; AIx: Augmentation Index; FDR: False discovery rate adjusted p-values.

Discussion

In the present study old patients with hip fracture had significantly more carotid plaques than individuals without hip fracture. In the multivariate analysis, the existence of carotid plaques remained significant related to the presence of hip fracture. Conversely, neither other subclinical arteriosclerotic parameters, nor the presence of established cardiovascular disease, were related with the existence of hip fracture.

We highlighted the main studies in concordance with our results: The study of Hamada et al [16] demonstrated, in a sample of Japanese middle-age (mean age 56,1 years) women, an increase of echogenic carotid plaques in patients who developed osteoporotic fracture or had lower bone mineral density (BMD) during a 10-years follow-up period. In the study of Naves et al [17] done in Spanish middle-age population, the severity of aortic calcification, assessed by X-Ray, was associated with osteoporotic

fractures, specially vertebral fractures. Other interesting prospective studies showed that severe aortic calcifications were associated with prevalent osteoporotic fractures in both sexes [18, 19, 35]. On the contrary, Samelson et al [20] did not found relationship between the severity of aortic calcification and risk of hip fracture. It is important to notice that last study was retrospective and the interpretation of calcifications were using old radiographies, which can lead to interpretation bias [20]. As mentioned before, all previous studies included middle-aged patients, and most of them used aortic calcification, assessed by X-Ray, in order to evaluate arteriosclerosis. Our study is focused on elderly population, and they were evaluated with ultrasound technique, and arterial tonometry.

The relation of arterial stiffness with risk of osteoporosis and bone fracture is not well established. Most studies have been performed in Asian and women populations, and especially related to osteoporosis or fracture risk [36, 37]. Arterial stiffness measured by means of PWV is considered the gold standard procedure [29, 30]. We found that the prevalence of a PWV > 10 m/s (as standard cut-off value for carotid-femoral PWV in the prediction of cardiovascular events) [31, 33] was higher than 85% in both groups, without showing differences between them. That maybe due to old age and high prevalence of hypertension in all patients studied, as the most important factors for arterial stiffness [29, 30], despite having or not hip fracture.

Analyzing the other subclinical arteriosclerotic parameters, no differences were found related to cIMT between groups in present study. Previous studies that have evaluated possible associations between low BMD or hip fracture with different measurements of subclinical arteriosclerosis have controversial results. That could be due to different characteristics of the samples (ages, sizes), retrospective/prospective/population-based/cross-sectional designs, etc. Our results are similar to a substudy of the Rancho Bernardo Study [21]. This population-based study was done in a huge age range of individuals (30–97 years; mean age 74 years) and assessed ankle brachial blood pressure Index (ABI). They concluded that an ABI lower or equal to 0.9 was not related to osteoporotic fractures. Instead, the results of a subanalysis from the Cardiovascular Health Study [15] (mean age 75,7 years) showed that the increase of the cIMT was related to the risk of hip fracture in old patients with and without previous cardiovascular disease, and independent of its association with higher BMD. Differences could be due to the large size sample (5193 individuals), and its longitudinal design.

We found a high prevalence of cardiovascular disease (25% of patients in each group) in line with other studies [38, 39]. No differences were found between patients with hip fracture and controls. The relationship between having a fracture and developing cardiovascular disease is well studied [40] but opposite is not frequently analyzed. Results from the review of Laroche et al. [6] suggest causality between having previous peripheral arterial disease or ischemic heart disease and developing a hip fracture. Our different results are maybe interfered by other risk factors in both groups (genetic, epidemiologic, psychosocial stress, other inflammatory disorders etc…) that may will confound [41–43].

In the present study, we made a comprehensive assessment of vascular risk in hip fracture patients and controls, addressing vascular risk factors, subclinical vascular lesions, and established cardiovascular

disease. The strenght of our cross-sectional prospective study is that we have consecutively included a representative sample of elderly people (mean age 82 years; >70% women; >60% hypertensives). Often, these are the patients admitted for a hip fracture in a hospital in most industrialized countries [44]. In addition, compared to previous studies, our patients have been thoroughly examined for subclinical vascular lesion (IMT, carotid plaques, arterial stiffness parameters) being at this moment the most completed study of subclinical vascular alterations and risk of hip fracture performed.

Limitations

This cross-sectional study excluded patients with severe dementia who probably had a high vascular disease: however, by excluding them as well in the control group, we consider there was no selection bias. Our results are exclusively for hip fracture risk, none evaluating other osteoporotic fractures, like vertebral fractures, that maybe are associated with severe cardiovascular alterations.

Conclusions

Old patients with hip fracture had higher arteriosclerotic alterations, especially an increase in atherosclerotic plaques. No increase in cardiovascular diseases had been found in patients with hip fracture compared to controls. Both groups had high prevalence of cardiovascular disease that could be due to other factors.

More studies are needed in this age-group of patients with hip fracture to enhance the results of our study and to optimize primary prevention of hip fractures, especially in those patients with high cardiovascular risk and vice versa.

Abbreviations

n: number of cases;

IQR: Interquartile range, expressed with percentiles 25^{th} and 75^{th};

CI: Confidence interval;

BMI: Body mass index;

IMT: Intima media thickness;

PWV: Pulse wave velocity;

AIx: Augmentation Index;

TC: Total cholesterol;

TGC: Triglycerides;

HDL: High-density lipoproteins;

LDL: Low-density lipoproteins;

BMD: Bone mineral density.

Declarations

Statements of Ethics: The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Subjects have given their written informed consent and that the study protocol was reviewed and approved by Comité de Ética de la investigación from Hospital Clinic de Barcelona (HCB/2017/0416).

Conflict of interest: VS: Travel grants from Bayer. Consultancy fees from LEO Pharma.

Rest of authors no conflict of interest.

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Authors contributions:

- ACR: conception of the study, acquisition of data, interpretation of data, drafting the initial manuscript.
- MNL: acquisition of data, interpretation of data, reviewed the manuscript for intellectual content.
- CSB: reviewed the manuscript for intellectual content
- VS: statistical analysis, interpretation of data, reviewed the manuscript
- ASL: acquisition of data, reviewed the manuscript
- BS: acquisition of data, reviewed the manuscript
- MA: acquisition of data, reviewed the manuscript
- MCB: reviewed the manuscript for intellectual content
- ALS: conception of the study, study supervision, reviewed the manuscript for intellectual content.

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