The Intersection of Frailty and Subclinical Atherosclerosis: Implications for Cardiovascular Risk

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Abstract

Background: Frailty as well as atherosclerotic diseases are commonly prevalent among elderly subjects and usually share both complex pathway and risk factors. Hence it was important to study if there is an association between frailty and risk factors of atherosclerosisat its early stages (subclinical atherosclerosis) using the Ankle Brachial Index (ABI), carotid intima media thickness (CIMT) and Abdominal Aortic Diameter (AAD) as markers of subclinical atherosclerosis.

Material and Methods: A cross-sectional study conducted on 90 elderly participants (60-year-old and above), free of cardiovascular symptoms. They were dividedaccording to modified Fried criteria into: non-frail, pre-frail and frail groupsand they were subjected to comprehensive geriatric assessment, calculation of ABI, and radiological investigations including: carotid duplex to measure CIMT and abdominal ultrasound to measure AAD.

Results: The study showed that frail participants had lower mean ABI value than non-frail group. Frail and pre-frail participants had higher maximum CIMT values than non-frail group. The mean AAD increased from 19.88 mm in the non-frail to 20.40 mm in the pre-frail group and 21.17 mm in the frail group, but this difference still not reaching a statistical significance.

Conclusion: The study concluded that frailty is associated with subclinical atherosclerosis.

Introduction

Frailty remains an evolving concept lacking both a unique definition and diagnostic criteria to be used in clinical practice and epidemiological researches[(1)].But the most acceptable definition is postulated by Fried et al. defined frailty as: "A physiologic syndrome characterized by decreased reserve and resistance to stressors, resulting from cumulative decline acrossmultiple physiologic systems, and causing vulnerability to adverse outcomes"[(2)].The criteria established for frailtyinclude: reduced muscle strength, unintentional weight loss, fatigue, low physical activity, and slow walking[(3)].Fried's concept of frailty postulates that frailty is initiated by the accumulation of factors such as lack of physical exercise, inadequate nutrition, injuries, disease, and drugs[(3)].

From a clinical perspective, frailty is crucial because it constitutes a condition of greater risk of adverse health outcomes, such as falls, hospitalization, disability and death[(3,4)]. Frailty is important from a societal perspective because it identifies groups of people in need of extra medical attention and at risk of high dependency. Frailty is also on concern when considering financial healthcare planning to better select management and prevention programs[(5)].

The existence of a relationship between the vascular system and frailty has been claimed since more than a decade. However, the precise stage of the vascular disease from which this association is present remains unclear although it may be of great clinical relevance as to target populations suitable for intervention and prevention[(6)].Atherosclerosis develops subclinically over many years,hence needs to be identified by screening for modified cardiovascularrisk factors.

Peripheral arterial disease (PAD) is a major under-diagnosed vascular pathology[(7)]. PAD and coronary artery disease (CAD) share similar risk factors profile and were believed to also share a common pathogenesis[(7)].Detection of atherosclerosis affecting peripheral arteries at an early stage can help to reduce the effects of cardiovascular

diseases.In this context, measuring the ankle brachial index(ABI) may be regarded as a simple, reliable and inexpensive but effective method of detecting subclinical atherosclerosis in peripheral artery disease[8,9].

Decreased arterial flow indicates systemic atherosclerosis, and is regarded as an independent cardiovascular risk factor, together with an increase in carotid intima media thickness (CIMT)[8,9].CIMT measurement is an approved test that is simple, reliable and non-invasive in terms of determining subclinical atherosclerosis at the level of the carotid arteries. CIMT has also been recommended by the American Heart Association, American Society of Echocardiography and Society for Vascular Medicine as a screening test for heart disease in healthy individuals[10,11]. Newman et al. 2001 have demonstrated in their Cardiovascular Health Study that subclinical CVD (measured using CIMT and ABI) is associated with frailty in the elderly[12].

Abdominal Aortic Diameter (AAD), as a marker of subclinical aortic atherosclerosis, depends on many physiologic factors including age, sex and body surface area and is affected by a number of cardiovascular risk factors, that previously well studied[13,14].But the relation between AAD and frailty have not been demonstrated previously. So we tried to spot light on that issue.

Materials and methods

Study Design and setting

A cross-sectional study included 90 elderly subjects 60 years old or more recruited from the inpatient wards and the outpatient clinics in Ain Shams University hospitals.The study sample was divided into 3 groups according to Fried'scriteria[15] as applied by Avila-Funes et al.[16] of frailty;

Inclusion Criteria: Elderly both males and females who are 60 years or more, free of cardiovascular symptoms, who approved to participate in the study.

Methods

1. **Ethical considerations:** Informed consent was taken from every participant in the study, the study purpose & methods were explained to all of them. The study methodology was reviewed and approved by the Research Review Board of the Geriatrics and Gerontology Department Faculty of Medicine Ain Shams University, and the Ethical Committee Unit of the Faculty of Medicine Ain Shams University.

2. **Comprehensive geriatric assessment:** detailed history and physicalexamination, cognitive function assessment using Arabic version of Minimental status examination (MMSE)[17, 18], functional assessment byArabic version of Activities of daily living (ADL)[19,20], and Arabic version of Instrumental activities of daily living (IADL)[21,22]. Arabic version of Geriatric depression scale 15 items (GDS-15) was used to screen for depression [23,24] (Those items are done as a routine assessment ofelder patients).

3. **Frailty assessment:** Frailty was defined according to the construct previously validated by Fried *et al*. in the CardiovascularHealth Study[15]. All five components from the original phenotype were retained; however, the metrics used tocharacterize the frailty criteria were slightly different and defined as follows[16]:

- ***Shrinking***: Recent and unintentional weight loss of ≥3 kg in the prior year was identified and body mass indexcalculated. Participants who answered "yes" for weight loss or had a body mass index < 21 kg/m2 wereconsidered to be frail for this component.
- ***Poor endurance and energy***As indicated by self report of exhaustion, identified by two questions from theCenter for Epidemiological Studies-Depression scale (CES-D)[25]: "I felt that everything I did was an effort"and "I could not get going." Participants were asked: "How often, in the last week, did you feel this way?" 0= rarely or none of the time; 1 = some or a little of the time; 2 = a moderate amount of the time; or 3 = mostof the time. Participants answering "2" or "3" to either of these questions were considered as frail by exhaustion.
- ***Slowness:*** Meets criteria for frailty if time to walk 6 m was ≥8 seconds for height ≤173 cm or >7 secondsfor height >173 cm in males, and ≥8 seconds for height ≤159 cm or >7 seconds for height >159 cm in females.

- ***Weakness:*** Participants answering "yes" to the following question were categorized as frail for this component:"Do you have difficulty rising from a chair?"
- ***Low physical activity*** A single response was used to estimate physical activity. Individuals who denied doingdaily leisure activities such as walking or gardening and/or denied doing some sport activity per weekwere categorized as physically inactive. Those who reported doing them were considered to be active.

Participants were considered to be ''frail'' if they had three or more frailty components among the five criteria; they were considered ''pre-frail'' if they fulfilled one or two frailty criteria, and ''non-frail'' if none.

4. **Abdominal Ultrasound:**All participants were examined in the supine position and/or in the left decubitus position when necessary. Fasting instructions were given to the participants prior to the examination. The examination was carried out with the aid of an Alpinion-Korae- E-CUBE-9 ultrasound unit equipped with a 3.5-MHz transducer. The abdominal aorta was examined in the axial plane with scans perpendicular to the longitudinal plane. Aortic diameters were measured at the renal level. The maximum diameter of the aorta was measured from leading edge to leading edge. A maximum antero-posterior or transverse diameter ≥ 3 cm was considered a diagnostic criterion for Abdominal Aortic Aneurysm (AAA).

5. **Carotid duplex:**For measurement of CIMT,all subjects were examined in the supine position with the neck extended and the head tilted slightly towards the opposite of the examined side. Both left and right common carotid arteries were depicted.Examinations were performed with the aid of an Alpinion-Korae- E-CUBE-9 ultrasound unit equipped with a 7.5-MHz transducer**.** The CIMT was measured which is the blood–intima to media–adventitia interfaces width, normal intima media thickness is usually less than 0.8mm[(26)].

6. **Ankle-brachial index:**The ABI is the ratio of systolic blood pressure measured at the ankle to systolic blood pressure at the brachial artery. A pneumatic cuff placed around the ankle is inflated to 20 to 30 mmHg above systolic pressure and subsequently deflated at 2 mmHg interval while the onset of flow is detected with a Doppler probe placed over the dorsalispedis and/or posterior tibial arteries. Thus denoting ankle systolic blood pressure. Brachial artery systolic pressure can be assessed in routine manner by using a stethoscope to listen for the first korotkoffsound[(27)].

Statistical analysis

Analysis of data was performed by using the 22th version of Statistical Package of Social Science (SPSS). Description of all data in the form of mean (M) and standard deviation (SD) for all quantitative variables.Frequency and percentage for all qualitative variables. Correlation coefficient was also used to find linear relation between different variables using Pearson correlation co-efficient. Comparison between quantitative variables was done using t-test to compare two groups and ANOVA (analysis of variance) to compare more than two groups; Tukey's HSD (Honest Significant Difference) test is used in ANOVA to create confidence intervals for all pairwise differences.Comparison of qualitative variables was done using the Chi-square test.Significant level measured according to P value (Probability), P> 0.05 insignificant, P < 0.05 significant and P<0.01 highly significant.

Results

Thestudy included90 elderly subjects 60 years old or more, both males and females. Who were categorized into 3 groups according to Fried criteria of frailty; non-frail group contributed 24 (26.67%) subjects, pre-frail group comprised 20 (22.22%) subjects and frail group included 46 (51.11%) patients**(Fig. 1)**. Of which, 65 subjects were recruited from inpatient wards and 25 subjects were recruited from outpatient clinics atAin Shams University hospital. The mean age of the studied population was 67.3±7.4 years, 66.67% were males, 33.33% were females, and 72.22% of our participants were married. The majority of our participants were living with their families (88.89%), and were illiterate (61.11%). As regards special habits, 36.67% were smokers and 20 % were ex-smokers**(Table 1)**.

Regarding clinical characteristics;frail and pre-frail participants had higher percentage of ADL & IADL affection than non-frail group (p value <0.001) andhad lower MMSE scores compared to non-frail group (p value <0.001). Frail participants were also more depressed (p value= 0.001) and more commonly malnourished or at risk of

malnutrition (p value <0.001) compared to pre-frail and non-frail groups. Frail participants had lower BMI values compared to non-frail group (p value= 0.040).

The mean age of the frail group was 69.9±8.8 years; which was higher than that of pre-frail and non-frail groups (64.5±4.2 and 64.5±4.1 years respectively) and this difference was statistically significant (p value = 0.002).There was highly significant difference between the study groups as regards education as illiteracy was higher among frail group compared to pre-frail and non-frail groups (p value < 0.001).There was no significant difference between study groups regarding gender, marital status, living arrangement or smoking habit**(Table 1)**.

Our study showed that frail participants had lower mean ankle-brachial index value than non-frail group(p value= 0.002). Frail and pre-frail participants had higher maximum carotid intima media thickness (CIMT) values than non-frail group (p value <0.001). While there is no significant difference between the study groups as regards mean abdominal aortic diameter**(Table 2)**.

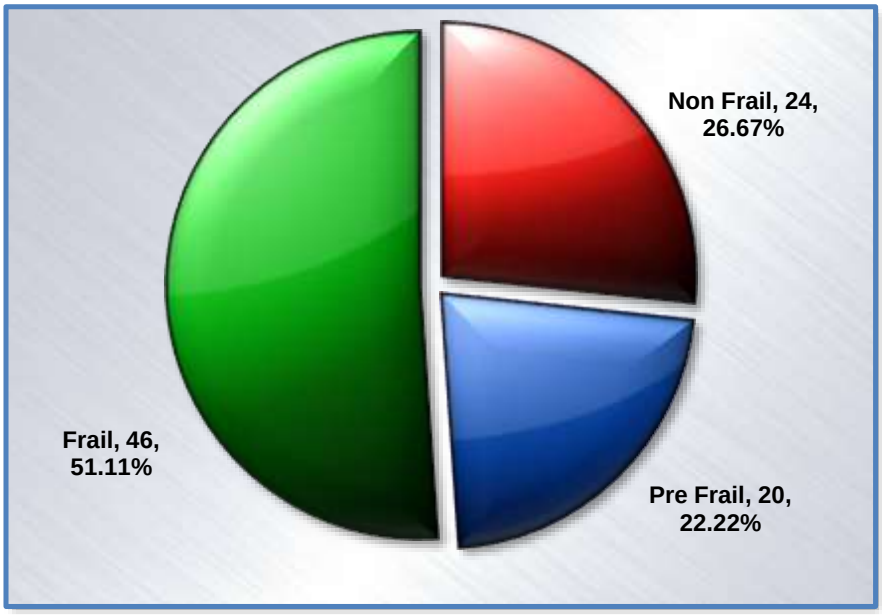

Figure (1): Prevalence of frailty and pre-frailty among study group

Table (1):Comparison between study groups regarding socio-demographic characteristics:

		Non-frail		Pre-frail		Frail		Total				N & PF	N & F	PF & F
										ANOVA		TUKEY'S Test		
										F	P			
Age	Range	60-73		60-71		60-89		60-89		6.652	**0.002**	1.000	**0.009**	**0.014**
	Mean ±SD	64.583±4.272		64.550±4.123		69.935±8.810		67.311±7.407						
		N	%	N	%	N	%	N	%	Chi-Square		Chi-Square		
										X^2	P			
Gender	Male	19	79.17	14	70.00	27	58.70	60	66.67	3.103	0.212	-	-	-
	Female	5	20.83	6	30.00	19	41.30	30	33.33					
Marital Status	Married	19	79.17	15	75.00	31	67.39	65	72.22	8.022	0.236	-	-	-
	Single	1	4.17	1	5.00	0	0.00	2	2.22					
	Widow	3	12.50	4	20.00	15	32.61	22	24.44					
	Divorced	1	4.17	0	0.00	0	0.00	1	1.11					
Living	Alone	4	16.67	3	15.00	3	6.52	10	11.11	2.037	0.361	-	-	-

Arrangement	With family	20	83.33	17	85.00	43	93.48	80	88.89					
Education	Literate	17	70.83	9	45.00	9	19.57	35	38.89	17.847	**<0.001**	0.083	**<0.001**	**0.033**
	Illiterate	7	29.17	11	55.00	37	80.43	55	61.11					
Smoking	Yes	9	37.50	11	55.00	13	28.26	33	36.67					
	No	11	45.83	6	30.00	22	47.83	39	43.33	4.529	0.339	-	-	-
	Ex-smoker	4	16.67	3	15.00	11	23.91	18	20.00					

N; non-frail, PF; pre-frail, F; frail

Table (2): Comparison between study groups regarding studied markers of subclinical atherosclerosis:

		Non-frail	Pre-frail	Frail	ANOVA		N&PF	N&F	PF&F
					F	P	TOUKEY'S Test		
ABI	Range	0.96-1.3	0.78-1.42	0.53-1.66	6.030	**0.004**	0.255	**0.002**	0.321
	Mean ±SD	1.145±0.102	1.052±0.180	0.977±0.232					
Max. CIMT	Range	0.5-1	0.7-1.8	0.7-2.2	19.209	**<0.001**	**<0.001**	**<0.001**	0.659
	Mean ±SD	0.733±0.146	1.140±0.352	1.213±0.355					
AAD	Range	13-24	14-25	15-26	1.868	0.161	-	-	-
	Mean ±SD	19.880±2.252	20.400±2.583	21.178±3.056					

N; non-frail, PF; pre-frail, F; frail,ABI; Ankle Brachial Index, Max.CIMT; Maximum Carotid Intima Media Thickness, AAD; Abdominal Aortic Diameter.

Discussion

Frail subjects are more likely to have subclinical CVD [(12)], and subjects with subclinical CVD are more likely to have impaired physical or mental function during the follow-up[(28)] raising the possibility of an association between frailty and CVD risk.

Varying degrees of frailty are common in elderly patients, but because different definitions, criteria and instruments are used, it is difficult to make simple comparisons of prevalence between studies and populations[(29,30)], and according to previous studies, the prevalence of frailty in community-dwelling elderly adults varies from 4.0% to 59.1%[(30-32)]. In the current study,frailty was found in 46 (51.11%) subjects, while pre-frailty was found in 20 (22.22%) subjects. The remaining 24 (26.67%) subjects were non-frail. The prevalence of frailty in our study population was higher than most of reported prevalence in previous epidemiological studies. This could be related to the fact that this study is hospital-based.

Concerning the socio-demographic characteristics of study groups, the mean age was 69.9±8.8, 64.5±4.1 and 64.5 ± 4.2 years in frail, pre-frail and non-frail groups consequently. Our study revealed a significant increase in mean age of frail participants compared to pre-frail and non-frail participants with no significant difference between pre-frails and non-frails. This supports the results obtained by many other studies that reported a significant association between age and frailty [(33-36)]; this association mostly due to age-related loss of muscle and bone mass, reduced nutritional intake, low physical activity and associated comorbidities. Bergman et al. 2007 found that aging had no effect on frailty and this may be due to the heterogeneity of functional decline observed with chronological aging, and the fact that chronological age alone is only a rough proxy of a person's vulnerability to adverse outcomes[(37)]. Some people appear to be frail at the age of 70 years, whereas others only reach this state in their 90s[(37)].

Regarding educational level, we found that illiteracy was significantly higher among frail participants compared to pre-frail and non-frail groups. A similar conclusion was reached in a cohort study of Espinoza et al. 2012 who observed an association between low schooling levels and the onset of new cases of frailty[(38)]. Hoogendijk et al. 2014 also reached the same conclusion; that those older adults with a low educational level had higher odds of being frail compared with those with a high educational level[(39)]. Explanatory factors of this result may be related to lower income, self-efficacy, cognitive impairment, obesity, and other social factors.

Many studies found controversy regarding the effect of smoking on frailty, the prospective study of Chamberlain et al. 2016 found that, behavioral factors including smoking were significantly associated with frailty in those aged 60-69 and 70-79 years[40]. On the other hand, Gobbens and vanAssen 2016 in their retrospective studyreported that the lifestyle factors including less smoking did not improve the prediction of total frailty[41]. Also Chang et al. 2012 in their analytical study using data from the Women's Health and Aging Studies (WHAS) I and II found that smoking status did not differ significantly among the participants classified according to frailty status[42]. Our study found no significant difference between study groups as regards smoking habit.

Regarding peripheral arterial disease and its association with frailty status, our study revealed that the ABI was inversely related to frailty status as frail participants had lower mean ABI than pre-frail and non-frail groups. This finding was also seen in a cross-sectional community-based study consisted of 1036 individuals carried out by Lin et al. 2015 revealed that frailty syndrome in the elderly is associated with subclinical peripheral arterial disease indicated using the ABI. As walking performance is one of the indicators of frailty and can be associated with peripheral vascular disease[43].

Singh et al. 2012in their study using data from the National Health and Nutritional Examination Survey observed that prevalence of frailty in participants with low ABI was higher than in participants with normal ABI[44].

The current study showed that frail and pre-frail participants had higher CIMT than non-frail group. That means these patients are at a higher risk for peripheral arterial diseases, cerebrovascular events and vascular complications compared with the non-frail group. This was also observed by Elbaz et al. 2005,in their sub-analysis from the three-City Study in the Dijon center, which showed that those who had slow gait speed were more likely to have carotid intimal media thickening and silent carotid plaques[45]. A similar conclusion was reached in a cohort study of Newman et al. 2001 who reported that mean internal carotid IMT increased from 1.31 mm in the non-frail to 1.42 mm in the intermediate group and 1.51 mm in the frail group[12].Avila-Funes et al. 2014also concluded in their cross-sectional study that there is an independent association between carotid IMT and frailty[46]. This association between carotid structure changes and frailty suggests that frail elderly adults have early atherosclerosis and vascular damage, which may explain, at least partly, why several adverse health-related outcomes are frequently observed in frail elderly adults.

Regarding the relation between abdominal aortic diameter and frailty, Laughlinet al. 2011 in their cross-sectional study suggest a link between subclinical atherosclerotic disease and enlargement of the abdominal aortic diameter[47].To our knowledge, no previous studies exist on the association between abdominal aortic diameter and frailty. The current study showed that mean AAD increased from 19.88 mm in the non-frail to 20.40 mm in the pre-frail group and 21.17 mm in the frail group. But this difference still not reaching a statistical significance (p value=0.161), this may be related to the selection criteria of our participants as we investigated those who are asymptomatic for cardiovascular diseases.

Conclusion

Prevalence of frailty in our study group was 51.11%, while pre-frailty was 22.22%.

Frailty is associated with advanced age and lower educational level. Frailty is associated with lower means of ABI, higher CIMT values and higher mean of AAD despite not reaching a significant level; which means that there is an association between frailty and subclinical atherosclerosis..

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