Relationship between Coronary Risk Factors, Insulin Growth Factor-1, C-Reactive Protein, and Protein Mass in Frail Elderly

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Abstract: Objectives: To study the assess the relationship between coronary risk factors, insulin growth factor, C-reactive protein, and protein mass in frail elderly. **Method:** A case-control study conducted among three groups each one comprised 30 elderly participants (60years or older) recruited from the inpatients wards and the outpatient clinic of Ain Shams University Hospitals. Participants were categorized to frail and non-frail using Fried's criteria into 3 groups; Group A: 30 frail elderly females, group B: 30 frail elderly males and group C: 30 controls. All participants were subjected to comprehensive geriatric assessment, measuring of protein mass using dual-energy x-ray absorptiometry by GE Lunar DPX-MD Plus. Measurement of Insulin growth factor-1 (IGF-1), C-reactive protein (CRP), glycated haemoglobin, total cholesterol, triglycerides (TG) and lipoproteins (HDL and LDL) in serum was done. **Results:** The mean lean body mass was significantly lower among the frail group than controls ($P<$ 0.01). Mean IGF-1 level was significantly higher in the control group (68.02+ 3 vs. 57.21 ± 17, $P = 0.05$). The frail group had a highly statistical significant lower levels of TG and higher levels of CRP than the control groups (P <0.001) also the case group had a statistically significant lower levels of LDL ($P < 0.05$) and higher significant statistical levels of glycated haemoglobin (P <0.01). **Conclusion:** Frailty is associated with higher coronary risk including high levels of CRP, glycated haemoglobin and lower levels of TG and LDL. There was borderline significance between frailty and IGF-1.

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1.Introduction:

The concept of frailty has attracted a steeply increasing interest among researchers and clinicians [1].Chronic inflammation and an over-production of pro-inflammatory cytokines, e.g. C-reactive protein (CRP) have been proposed as the biological basis of frailty [2]**.** Inflammatory marker levels can predict cardiovascular events. Many studies suggest that among the inflammatory markers, CRP has been shown to be most consistently associated with coronary risk [3]. There is a complex physiological interaction between Insulin growth factot-1 (IGF-1), inflammatory cytokines, biochemical and molecular pathways mediating catabolism of muscle protein, contributing to age-related muscle loss and reduced physical performance, and consequently to physical frailty [4].

Frail diabetic patients are a specific group that is in need of addressing diverse clinical features beyond mere diabetes control [5].

Von Känel and colleagues stated that the pro-inflammatory cytokines (IL-6, CRP and D-dimer) all increase with age; and elevated plasma levels of these three have also been identified as biological accompaniments of frailty [6]. One such study by Blaum and colleagues showed that increased level of glycated haemoglobin was associated with greater prevalence of pre-frail and frail status independent of other confounding factors such as body mass index (BMI), inflammation, and presence of comorbidities [7].

This study aimed to assess the relation between several coronary risk factors, and protein mass in frail elderly.

2.Methodology:

This is a case-control study on 90 participants aged 60 years or above recruited from the inpatient wards and outpatient clinics of Ain Shams University hospitals from June 2009 to November 2010.

The study was approved by ethical committee of the faculty of medicine – Ain Shams University. Informed consent was taken from all participants prior to inclusion in the study.

The sample was divided into three subgroups; ***Group A:*** 30 frail elderly females, ***Group B:*** 30 frail elderly males. Both groups diagnosed by Fried's criteria [8] as applied by Avila-Funes and colleagues

[9], ***Group C (controls):*** 30 age- and sex-matched healthy elderly subjects (15 males and 15 females) who are not frail and have no organ dysfunction.

Patients who refused to participate, those who were pre-frail at evaluation, those with an acute infection and those on medications with anti-inflammatory effects were all excluded from the study.

After assessment of frailty, each participant was subjected to comprehensive geriatric assessment in the form of detailed history, complete physical examination, cognitive function assessment using the validated Arabic version of the Mini Mental Status Examination (MMSE) [10-11] mood assessment using the validated Arabic version of the Geriatric Depression scale 15-items [12-13] and functional assessment by; Activities of daily living (ADL) [14], Instrumental activities of daily living (IADL) [15].

Lab investigations:

Then a venous blood sample was withdrawn from each participant for measurement of the following: Glycated Haemoglobin (HBA1c) by ion-exchange chromatographic separation and colorimetric detection kit (Biosystems, SA, Barcelona, Spain). Quantitation of CRP was performed by immunoturbidimetric assay using Biosystems CRP kit. Additionally IGF-1 was measured by ELISA using kits supplied by DRG (DRG international, New Jersey, USA). Finally assessment of lipid profile was measured; Total cholesterol (TCHOL): Richmond in 1973 determined after enzymatic hydrolysis and oxidation, using Stanbio cholesterol colorimetric detection kit (USA) [16]. LDL cholesterol and VLDL cholesterol were precipitated from serum or plasma by means of magnesium chloride/dextran sulfate reagent during a 10 minutes incubation (at room temperature) followed by 10 minutes centrifugation at 4000 rpm. HDL cholesterol was then determined in the supernatant fluid, using Stanbio HDL cholesterol kit (described above). LDL cholesterol was determined as the difference between total cholesterol and the cholesterol content of the supernatant (HDL and VLDL) after precipitation of the LDL fraction by polyvinyl sulfate in the presence of polyethylene-glycol monomethyl ether. Triglycerides were assessed by means of stanbio liquicolor kit (USA) for the quantitative enzymatic-colorimetric determination of triglycerides in serum or plasma.

Lean body mass measurement (LBM):

Lean body mass was measured in grams by dual-energy x-ray absorptiometry using GE Lunar DPX-MD Plus, pencil beam, bed scanner by measuring the total body mass in grams and calculating the total sum of lean mass of the legs, arms and trunk .

Statistical analysis:

Finally, analysis of data was performed by using the 16th 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 and frequency and percentage for all qualitative variables were presented. Comparison between quantitative variables was done using t-test to compare two groups and ANOVA to compare four groups. Comparison of qualitative variables was done using Chi square test. Spearsman's correlation co-efficient was used .Significant level measured according to *P* value (Probability), $P > 0.05$ insignificant, $P < 0.05$ significant and $P < 0.01$ highly significant.

3.Results:

The study sample consisted of 60 frail elderly (30 males and 30 females) and a control group of 30 non-frail elderly.

Comparison between mean age among cases versus controls was not significant ($P = 0.41$).

The mean lean body mass was significantly lower among the frail group 35.4 ± 4 (g) than controls 40.4 ± 4 (g) ($P \leq 0.01$).

As for IGF-1; the mean level was significantly higher in the control group than the frail group (68.02 ± 3 vs. 57.21 ± 17 ng/ml) ($P = 0.05$).

The frail group had a highly statistical significant lower levels of TG and higher levels of CRP than the control group with ($P < 0.001$), also the case group had a statistically significant lower levels of LDL ($P < 0.05$) and higher significant statistical levels of glycated haemoglobin ($P < 0.01$) than the control group while there was no significant statistical difference between case and control groups as regards HDL and total cholesterol (Table 1).

Comparing between frail males and females regarding cardiovascular risk factors, the frail females had a statistically significant higher levels of TG ($P < 0.01$) and statistically significant lower levels of CRP ($P < 0.05$). There was no significant statistical difference between frail females and frail males as regard HDL, LDL, total cholesterol and glycated haemoglobin (Table 2).

In the control group, LBM correlated positively with both BMI ($P < 0.01$), and negatively with CRP ($P < 0.01$) while LBM didn't show a statistically significant linear correlation with either serum TG, LDL, HDL, IGF or HbA1c. On the other hand, in the frail group, there was a significant statistical positive correlation between LBM and both BMI and IGF-1 with ($P < 0.05$ for both) while there was no significant statistical correlation between lean body mass and TGD, HDL, LDL, TCHOL, CRP and glycated haemoglobin (Table 3)

Studying Correlation between CRP and IGF-1 & HBA1C in the frail group revealed no significant correlation (r= -0.14, *P* = 0.28, r= -0.016, *P* =0.9 respectively).

Table (1): Comparison between frail and control groups as regards cardiovascular risk factors: lipids profile, C-reactive protein and glycated haemoglobin.

	Case	Control	T-test	
	Mean ± SD	**Mean ± SD**	**T**	***P*-value**
Triglycerides (mg/dl)	112.22 ± 48.06	141.27 ± 42.49	2.81	**0.006****
HDL(mg/dl)	31.85 ± 13.45	35.3 ± 6.5	1.33	0.188
LDL(mg/dl)	103.12 ± 42.29	121.7± 28.64	2.17	**0.03***
Total cholesterol (mg/dl)	159.4 ± 49.33	176.93 ± 37.3	1.72	0.09
CRP (mg/dl)	15.07 ± 7.46	5.17 ± 1.69	-9.68	**0.00****
HBA1C (%)	7.03 ± 1.63	5.52 ± 0.56	-6.23	0.00*

*(significant) **(highly significant) HDL(high density lipoproteins) LDL(low density lipoproteins) CRP(C-reactive protein).

Table (2): Comparison between frail males and females as regards cardiovascular risk factors: lipids profile, C-reactive protein and glycated haemoglobin.

	Frail males	Frail females	T-test	
	Mean ± SD	**Mean ± SD**	**T**	***P*-value**
Triglycerides (mg/dl)	94.7±45.25	129.7±44.94	-3.0	**0.004***
HDL(mg/dl)	31.73±15.13	31.7±11.91	0.009	0.99
LDL(mg/dl)	97.17±41.60	109.07±42.84	-1.09	0.28
Total cholesterol (mg/dl)	148.37±52.73	170.43±43.78	-1.76	0.083
CRP(mg/dl)	17.43±9.1	12.7±4.33	2.57	**0.014***
Glycated haemoglobin (%)	7.13±1.79	6.93±1.48	0.479	0.634

*(significant) HDL (high density lipoproteins) LDL (low density lipoproteins) CRP(C-reactive protein.

Table (3): Correlation between lean body mass and different risk factors in case and control groups.

	Lean body mass			
	Control		Case	
	R	***P*-value**	**R**	***P*-value**
BMI (kg/m^2)	0.717	**<0.001****	0.294	**0.023***
TGD (mg/dl)	0.167	0.378	0.199	0.127
HDL (mg/dl)	0.132	0.488	0.161	0.219
LDL (mg/dl)	-0.048	0.800	0.252	0.052
TCHOL (mg/dl)	-0.087	0.648	0.223	0.087
IGF (ng/ml)	0.269	0.158	0.269	**0.038***
CRP (mg/dl)	-0.480	**0.007****	0.032	0.809
HBA1C (%)	-0.159	0.400	0.180	0.170

*(significant) **(highly significant) BMI(body mass index) TGD(triglycerides) HDL(high density lipoproteins) LDL(low density lipoproteins) TCHOL(total cholesterol) IGF(insulin growth factor) CRP(C-reactive protein) HBA1C(glycated haemoglobin)

4.Discussion:

In the current study a highly significant relationship was found between frailty – diagnosed using Fried's criteria- and lean body mass measured by DEXA ($P \leq 0.01$) indicating that Fried criteria [8] as applied by Avila-Funes and colleagues [9] are indeed an accurate easy to apply clinical method for the diagnosis of frailty.

In this study, the control group had significantly higher mean levels of IGF-1 than the frail group (68.02± 3 vs. 57.21 ± 17 ng/ml) ($P = 0.05$) and lean body mass of frail group – measured by DEXA – had a significant statistical positive correlation with insulin growth factor-1. A similar conclusion was reached in several other studies where decreased IGF-1 level was associated with frailty and lower lean body mass [17-19]. Even clinical trials using IGF-1 to treat low lean body mass are starting to show similar conclusions [20]**.**

Cappolla and colleagues in 2003 also suggested that increased levels of inflammatory markers may be the drive to lower IGF-1 and lower muscle mass in elderly [19].

In fact, this study showed an interesting finding that among controls, a highly significant negative correlation between lean body mass and CRP was present; a finding that was also concluded in the study of Cesari and colleagues which showed that CRP is negatively correlated with lean body mass among elderly [21]. Walston and colleagues in a large population study found that frail elderly had higher levels of CRP and other inflammatory markers even after adjustment for age, sex and race; concluding that frail elderly are at higher cardiovascular disease risk. They also found that LDL levels were lower in frail elderly and yet; the relationships of mean total cholesterol, HDL, and triglyceride levels with frailty level were weak [22].

No linear correlation between inflammatory markers and frailty was found in this study. The results of the study of Waltson, et al 2003 showed that frail elderly have higher glycated haemoglobin levels when compared to the controls even after excluding diabetic patients from the study [22]. HbA1c level of 6.5% or greater in older women was significantly associated with higher likelihood of pre-frail and frail status in the cohort study of Blaum and colleagues [23].

Because frailty is multifactorial and frail elderly display heterogeneous characteristics it is difficult to establish a correlation between various markers of inflammation and frail status, especially in the presence of underlying chronic inflammation. This was observed in a case-control study of Pai and colleagues in which a non-linear but still strong association between CRP and the presence of increased risk of coronary heart disease in both sexes [24]. We can say that whether to include CRP, lipid profile, IGF and HbA1c levels in the work-up of frailty, and whether controlling the levels of the former factors will help to improve frailty status depends on more future research in this area.

This study showed highly significant statistical positive correlation between lean body mass and BMI among non-frail elderly. Another study also concluded that BMI is a strong predictor of lean body mass in non-frail women and men [25].

High body mass index is the most predictive factor for sarcopenia [26]. This study showed that lean body mass had a significant positive correlation with body mass index among frail elderly.

Conclusion:

Frailty is associated with high levels of CRP, glycated haemoglobin and lower levels of TGS and LDL. There was borderline significance between frailty and IGF-1.

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