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Muscle wasting in young patients with dilated cardiomyopathy

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Abstract

Background Muscle wasting can be accelerated by chronic diseases such as heart failure and is one of the major causes of disability, morbidity, and mortality in this population. We aimed to investigate the incidence of muscle wasting and its associated factors in dilated cardiomyopathy patients younger than 55 years of age.

Methods Between April 2014 and December 2015, all symptomatic patients with a diagnosis of non-ischaemic dilated cardiomyopathy who were referred to heart failure clinic were included in our study.

Dual energy X-ray absorptiometry was used to evaluate body composition and identify muscle wasting. Muscle mass was calculated as the ratio of an individual's total lean mass of legs and arms (also called appendicular skeletal muscle) to their squared height (kg/m^2). The muscle mass values of less than 5.45 kg/m^2 for women and 7.26 kg/m^2 for men were considered low.

Results A total of 55 patients (32 male) were included. The mean (standard deviation) of age was 37.3 (10.1) years, and the mean of left ventricular ejection fraction was 21.4%. Most of the patients were in the New York Heart Association classes of II and II–III. Twenty-six patients (47.3%) met criteria for muscle wasting. Patients with muscle wasting had lower left ventricular ejection fraction, lower 6-min walk distance, and higher New York Heart Association function class and hospitalization rate.

Conclusions We concluded that muscle wasting might be present in younger patients with heart failure, particularly in those who are in worse clinical condition.

Keywords Muscle wasting; Chronic heart failure; Dilated cardiomyopathy; Wasting

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Introduction

Muscle wasting and impaired skeletal muscle function in elderly should not be underestimated in heart failure.[1,2] The adaptive changes in musculoskeletal system following the occurrence of heart failure play key roles in the development of many symptoms related to heart failure syndrome including exercise intolerance and fatigue.[1–5] Although muscle wasting was first introduced as a phenomenon secondary to ageing, it is more prevalent in patients with a chronic illness such as heart failure, chronic renal failure, and chronic lung disease.[1,6–8] In most studies regarding muscle wasting in heart failure, elderly patients have been selected.[2–5,9] The results of these studies indicate a higher prevalence of muscle wasting in older patients with heart failure compared with healthy subjects who are at the same age.[2–5,9] There are only scant data regarding the presence of muscle wasting in younger patients with heart failure,[3] and it is not known whether heart failure could possibly be a risk factor for muscle wasting regardless of ageing process or not.

In the current study, we sought to investigate the incidence of muscle wasting and its associated factors in younger patients with idiopathic dilated cardiomyopathy (DCM) who were referred to our centre.

Methods

Patient selection

Between April 2014 and December 2015, among patients referred to the outpatient heart failure clinic of Rajaie Cardiovascular, Medical and Research Center, a tertiary centre for cardiovascular diseases in Iran, 55 patients were consecutively enrolled according to the following inclusion/exclusion criteria.

The inclusion criteria comprised idiopathic, non-ischaemic DCM with a left ventricular ejection fraction (LVEF) ≤40%, age under 55 years, a New York Heart Association (NYHA) class of I to III, and participant willingness to be enrolled into the study. All study participants had to be on guideline-directed medical therapy for at least 3 months.

The patients with NYHA class IV and those with severe oedema and ascites, history of any other chronic diseases including any degrees of renal dysfunction (with or without history of haemodialysis), connective tissue diseases, chronic obstructive pulmonary disease, skeletal myopathies, endocrine disorders (diabetes mellitus and thyroid disorders), chronic gastrointestinal diseases, malignancies as well as patients with history of cachexia (more than 5% weight loss over the last 6 months) were excluded.

The study was approved by research and ethic committee of Rajaie Cardiovascular, Medical and Research Center, and written informed consent was obtained from all patients.

A thorough clinical history was obtained and a detailed physical examination was performed for all patients. The presence of fatigue, dizziness, and loss of appetite were asked and recorded. The NYHA function class was assessed considering the severity of the limitations in ordinary physical activities, where class I indicates no symptom, class II indicates presence of symptoms in ordinary activities, class III indicates symptoms at less than ordinary activities, and finally, class IV indicates symptoms of dyspnoea at rest.[10] The body mass index (BMI) was calculated by dividing the weight to square of height.

The patients were also asked for their hospitalization history during the last 6 months, and any history of hospitalization due to any cardiovascular causes including decompensated heart failure was recorded.

The functional capacity and exercise tolerance of patients were assessed by a 6-min walk test (6MWT) according to the standard protocol.[11]

Laboratory tests

All blood was collected from all patients after 12–14 h overnight fasting. The laboratory tests including complete blood count, haemoglobin level, lipid profile (triglyceride, total cholesterol, low density lipoprotein, and high density lipoprotein), blood urea nitrogen, creatinine, serum albumin, serum total protein, N-terminal brain natriuretic peptide (pro BNP), and 25 hydroxy vitamin D3 were performed at our laboratory on the day of blood collection.

Evaluation of skeletal muscle mass

Dual energy X-ray absorptiometry (DXA) was used to evaluate body composition and muscle mass as well.

Dual energy X-ray absorptiometry scanning

The DXA scans were performed by a Hologic Discovery Wi DXA system (Hologic Inc. Bedford, MA, USA, 2011), using the fan beam with perpendicular orientation to the longitudinal axis of the body. Participants received one whole-body scan using the manufacturer's standard scan and positioning protocols. Spine phantom quality control scans were acquired in advance for all studies.

Scan analysis

Using the region of interest placement recommended by the manufacturer, all of the images were analysed using the Hologic Apex 3.3 and Auto Whole Body 13.3 software. The analysis resulted in total, subtotal (headless), and standard sub-regional (right and left arms, right and left legs, and trunk) measures of the following parameters: bone mineral content in grammes (g), projected bone area (Area) in cm^2, bone mineral density (bone mineral density = bone mineral content/Area) in g/cm^2, fat mass in grammes and lean mass in grammes as well as per cent fat. Total body %Fat, fat mass/height ratio (kg/m^2), Android/Gynoid ratio, %Fat trunk/%Fat legs, and trunk/limb fat mass ratio were also derived from these standard regions.

Identifying the muscle wasting

According to previous studies,[12,13] relative skeletal muscle mass was considered to define muscle wasting. The relative skeletal muscle mass was calculated by dividing the appendicular skeletal muscle mass to the square of height. The values less than 7.26 kg/m^2 in men and 5.45 kg/m^2 in women were considered as muscle wasting.[12,13]

Statistical analysis

IBM SPSS statistics 19 for Windows (IBM Corp, Armonk, NY, USA) was used for all statistical analyses. One sample Kolmogorov Smirnov test was used to assess the normal

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distribution of variables. Categorical variables were expressed as number (percentage), and quantitative variables were expressed as mean (standard deviation) or median (interquartile range) as appropriate. Student's *t*-test, chi-squared, and Mann–Whitney tests were used for comparisons and associations, as appropriate. Multivariate analysis was performed using binary logistic regression to assess the independent predictor for muscle wasting. *P* values <0.05 were considered significant.

Results

A total of 55 patients (32 males) with DCM were included in this study. The mean (standard deviation) of age was 37.3 (10.1) years. The mean LVEF was 21.4% and most of the patients (50.9%) were in NYHA class II or II–III. Table 1 depicts demographic and clinical characteristics of study population. Table 2 shows patients' medications.

Assessment of skeletal muscle mass by DXA scanning showed that 26 patients (47.3%) met criteria for muscle wasting. The comparison of baseline, clinical, and laboratory characteristics of patients with and without muscle wasting is summarized in Tables 3 and 4.

There was no difference between two groups in terms of age. Muscle wasting was more prevalent in men (56% in men vs. 34% in women), but this difference was not statistically significant ($P = 0.1$).

In this study, patients with muscle wasting had significantly lower BMI (22.4 vs. 26.1 kg/m^2, $P < 0.001$), lower LVEF ($P = 0.01$), and higher NYHA class ($P = 0.01$).

The study participants were asked whether they have history of fatigue, dizziness, and loss of appetite, and there was no significant difference between the two groups with and without muscle wasting. There was also no statistically significant difference between the two groups regarding their disease duration. However, the patients with muscle wasting had a lower 6-min walk distance (338 vs. 440 m, $P = 0.003$) and had been hospitalized more frequently over the last 3 months ($P = 0.008$).

Regarding patients' medications (Table 2), all patients were treated with angiotensin converting enzyme inhibitors/angiotensin receptor blockers, beta blockers, Spironolactone, and diuretics according to the guidelines. However, only 11% were taking the maximum tolerated or recommended optimum dose of the regimen. There was no statistically meaningful difference between the two groups regarding heart failure medical therapy ($P = 0.8$).

Laboratory findings

As shown in Table 4, although the serum level of N-terminal pro BNP was higher in patients with muscle wasting, it was not statistically significant. There were also no statistically significant differences between the two groups regarding the measures of lipid profile, serum albumin, and protein level or vitamin D3 level.

The bone density was also evaluated in this study. None of our study participants had osteoporosis in DXA examination, and as it was expected, the presence of osteopenia was accompanied with salient lower Vitamin D3 level (12.4 ± 4.4 to 23.9 ± 18.9, *P* value 0.002).

Table 1 Demographic and clinical characteristic of study population ($n = 55$)

Characteristics	Value
Gender (*n*, %)	
Female	23 (42)
Male	32 (58)
Age, year, mean (SD)	37.3 (10.1)
BMI, kg/m^2, mean (SD)	24.3 (3.7)
NYHA class (*n*, %)	
I, I–II	20 (36.4)
II, II–III	28 (50.9)
III	7 (12.7)
GDMT, number (%)	55 (100)
GDMT at maximum recommended dose, number (%)	10 (18.2)
LVEF, %, mean (SD)	21.4 (9.4)
Creatinine (mg/dL), mean (SD)	0.8 (0.2)
6MWT (metre), mean (SD)	395.9 (139.8)
Pro BNP (ng/dL), median (IQR)	835 (132–1700)
Haemoglobin (g/L), mean (SD)	13.9 (2)
Serum albumin (g/L)	42.9 (5)
Serum total protein (g/L)	69.8 (6.4)
Sodium (mmol/L)	137.3 (4.2)
Potassium (mmol/L)	4.2 (0.4)
Triglyceride (mg/dL)	156.6 (86)
Cholesterol (mg/dL)	177.9(54.7)
HDL (mg/dL)	40.6 (11.2)
LDL (mg/dL)	102.5 (35.4)

6MWT, 6-min walk test; BMI, body mass index; BNP, brain natriuretic peptide; GDMT, guideline-directed medical therapy; HDL, high density lipoprotein; IQR, interquartile range; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SD, standard deviation.

Table 2 Medications and devices of study population ($n = 55$)

Medication	Number(%)
ACEI/ARB	55(100)
Beta blocker	55(100)
MRA	55(100)
Diuretics	55(100)
Hydralazine +Isosorbide dinitrate	11(20)
Digoxin	18(32.7)
Warfarin	12(21.8)
Amiodarone	7(12.7)
ICD/CRT	22

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; ICD, implantable cardiac defibrillator; CRT, cardiac resynchronization therapy; MRA, Mineralocorticoid Receptor Antagonists.

Multivariate analysis

A logistic regression model with backward elimination method was applied to assess the adjusted associations

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Table 3 Comparison of baseline and clinical findings between patients with and without muscle wasting, *n* = 55

Characteristics	Muscle wasting		*P* value
	Yes *n* = 26	No *n* = 29	
Gender, number (%)			
Female	8 (30.8)	15 (51.7)	0.1
Male	18 (69.2)	14 (48.3)	
Age (year), mean (SD)	36 (11.4)	38.5 (8.8)	0.3
BMI (kg/m^2), mean (SD)	22.4 (2.6)	26.1 (3.8)	<0.001
LVEF (%), mean (SD)	18.1 (8.2)	24.3 (9.5)	0.01
NYHA class, number (%)			
I	6 (23.1)	14 (48.3)	0.01
II	14 (53.8)	14 (48.3)	
III	6 (23.1)	1 (3.4)	
Fatigue	15 (57.7)	11 (38)	0.1
Dizziness	4 (15.4)	1 (3.4)	0.1
Loss of appetite	13 (50)	11 (38)	0.4
Duration of illness (year), median (IQR)	2 (1–2)	2 (2–2.5)	0.1
Admission within the past 3 months	12 (46.2)	4 (13.8)	0.008

BMI, body mass index; IQR, interquartile range; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SD, standard deviation.

Table 4 Comparison of laboratory findings between patients with and without muscle wasting, *n* = 55

Characteristics	Muscle wasting		*P* value
	Yes *n* = 26	No *n* = 29	
NT-pro BNP (ng/dL), median (IQR)	836 (139–2400)	833 (100–1462)	0.5
6-MWT distance (metre)	338 (140)	440 (124.5)	0.01
Haemoglobin (g/L)	13.8 (2)	13.8 (1.9)	0.8
Serum total protein (g/L)	71 (7.1)	69 (5.1)	0.3
Serum albumin (g/L)	43.1 (5.1)	43.2 (4.9)	0.9
BUN (mg/dL)	20.2 (6.7)	17.7 (5.8)	0.1
Creatinine (mg/dL)	0.8 (0.2)	0.9 (0.17)	0.5
Sodium (mmol/L)	136 (4.6)	138 (3.9)	0.1
Potassium (mmol/L)	4.2 (0.4)	4.2 (0.4)	0.6
Triglyceride (mg/dL)	140.5 (91.3)	167.6 (83.2)	0.4
Cholesterol (mg/dL)	156.8 (66)	191.6 (42.6)	0.1
LDL (mg/dL)	95.5 (44.7)	107.3 (28)	0.4
HDL (mg/dL)	38.1 (5.4)	42.5 (14)	0.3
Vitamin D3 level (ng/mL)	16.1(11.7)	22.4 (18.5)	0.1
Osteopenia in BMD, number (%)	10 (38.5)	11 (37.9)	0.9
ASM/height ratio (kg/m^2)	5993.2 (976.3)	7089 (819.7)	0.0001

6MWT, 6-min walk test; ASM, appendicular muscle mass; BMD, bone mass densitometry; BUN, blood urea nitrogen; HDL, high density lipoprotein; LDL, low density lipoprotein; NT-pro BNP, N-terminal pro brain natriuretic peptide.

between muscle wasting and other predictors which had been detected in bi-variate analysis. It was found that among the several variables including gender, NYHA class, BMI, pro BNP, 6MWT, and LVEF only BMI had independent associations with the presence of muscle wasting. [Beta: −1.104, *P*-value: 0.01, odds ratio (95% confidence interval): 0.331 (0.134–0.82)].

The multivariate analysis for the investigation of association between muscle wasting and recent hospitalization after adjustment of other predictors revealed muscle wasting could not be an independent predictor for recent hospitalization. The strongest predictor for recent hospitalization was NYHA function class in this study. [Beta: 1.64, *P*-value: 0.01, odds ratio (95% confidence interval): 5.1(1.4–18.3)].

Discussion

In this study, we found considerable numbers of DCM patients aged less than 55 years who showed evidence of muscle wasting. The muscle wasting or sarcopenia, defined as ageing-related muscle mass loss, is generally considered a problem in people aged 60 years and above.[6,12–15] The prevalence of muscle wasting and sarcopenia in healthy people between 60 and 70 years has been reported between 5% and 30% in different studies. This prevalence is increased in elderly with a chronic disease such as heart failure. However, there is no consensus with regard to the precise age range for this syndrome.[1–3,6,9,12–16]

After the first definition of sarcopenia by Irwin Rosenberg, many investigators have studied different aspects of this phenomenon in different subgroups of population including healthy persons and patients suffering from chronic illnesses like chronic heart failure or renal failure.[4,6,7,12–14,17]

Akiyama *et al.* presented a prevalence of 20% for muscle wasting in patients over 70 years who were admitted with acute heart failure.[18] In another study in Japan, 57% of heart failure patients between 43 and 90 years showed evidence of sarcopenia.[3] In a cohort of 200 patients with heart failure and a mean age of 70 years, the prevalence of sarcopenia was about 19.5%.[4]

In this study, we aimed to evaluate the presence of muscle wasting in younger patients with heart failure. The result of our study indicates that muscle wasting is relatively prevalent in this group of patients particularly in those with lower LVEF, higher NYHA function class, lower 6MWT distance, and higher hospitalization rate. These findings are similar to the results of SICA-HF study[4] which shows muscle wasting is more prevalent in heart failure patients with more critical condition. These patients have lower LVEF and worse exercise capacity in treadmill performance or 6MWT. However, our study population were younger (<55 years old with a mean of 37 years), and it means that as Anker *et al.*[19] mentioned, the skeletal muscle is lost earlier in chronic diseases such as heart failure, and this muscle mass loss can be accelerated in heart failure independent of ageing process.

In the present study, BMI was lower in patients with muscle wasting compared with those without. This finding is similar to other studies.[4] It has been shown that heart failure patients with higher BMI have better outcome in terms of

mortality and hospitalization (obesity paradox),[20] and the strong association between BMI and muscle wasting in the present study may be an explanation for this finding. A heart failure patient with higher BMI may have a better skeletal muscle composition as a result of less metabolic and neurohormonal derangements and therefore better clinical outcome.

For as far as we have studied and researched, only a few studies have investigated younger heart failure patients regarding muscle wasting. Obata *et al.* reported a prevalence of 45.5% for muscle wasting in heart failure patients aged under 65 years.[3] Although the prevalence of muscle wasting in the Obata *et al.* study is similar to our study, considering the lower mean of age in our study (37.3 ± 10.1), it seems that muscle wasting would be more prevalent in Iranian population.

Although muscle wasting is more expected with ageing, we observed a high prevalence in our quite young population of heart failure patients. This can be attributed to the following factors.

The muscle wasting in the setting of heart failure is multi-factorial. Impaired cardiac performance results neurohormonal and metabolic abnormalities. The inflammatory process secondary to heart failure leads to an imbalance between anabolism and catabolism. The catabolic signals directly affect skeletal muscle and lead to protein break down and muscle mass loss. It has been shown that inflammatory cytokines such as interleukin-6 and tumour necrotizing factor-α intensify the catabolic pathways and result in structural and functional impairment of skeletal muscles which play an important role in pathogenesis of heart failure and its progression.[1,2,4,9,16] This imbalance between catabolism and anabolism seems to be independent of the LVEF because a recent study by Bekfani *et al.* has shown similar prevalence of muscle wasting in patients with heart failure-preserved ejection fraction.[21] The current study was run at a tertiary cardiovascular referral centre specialized in care of advanced heart failure and cardiac transplantation. Most of the young heart failure patients were those referred from other cities to be listed for cardiac transplantation, and a large number had to be hospitalized at the very first visit, apparently sick debilitated end-stage heart failure patients in whom muscle wasting is expected. A more severe neurohormonal and metabolic abnormality may be the reason for development of muscle wasting in a much earlier state.

Being physically active and exercise training can significantly improve the skeletal muscle dysfunction in patients with heart failure.[1,15,16,22] Geilen *et al.* showed that exercise training results in reduction of proteasome systems involved in muscle proteolysis in skeletal muscle of younger and older patients with heart failure.[22] Unfortunately, regular exercise and physical activity is not common among Iranian population even in healthy persons, and many people in Iran are physically deconditioned.[23–25] This may be another explanation for high prevalence of muscle wasting in our study population. The assessment of muscle mass in normal young Iranian population would be useful for a better explanation of this issue.

Another issue in evaluation of patients with muscle wasting is nutritional problems. It has been shown that malnutrition and low protein intake can be responsible for muscle wasting in heart failure patients, particularly in those with sedentary life style and physical inactivity.[26–29] Although the albumin and protein level were within the normal limits in our study population, it cannot be easily concluded that the protein turnover is not disturbed in our study population.

Heart failure has been revisited and known as an important entity requiring medications and devices to help and specialized physicians and nurses to take care of heart failure patients to live better and longer. Yet there are many old fashioned (and sometimes incorrect) recommendations to heart failure patients like prohibiting exercise activity, insisting on the low-fat low-calorie diet famous for primary prevention of coronary artery disease, insisting continuation of medications that have been found futile in the presence of advanced heart failure (like Statins), and not addressing the common mood-anxiety disorders. On the other hand, it is worthy to note that heart failure patients cannot benefit from 'ventricular assist device' treatment in our country because of cost issues, and many go into severe right ventricular failure and multi-organ involvement.

Study limitations

The careful selection of patients to reduce confounders is the strength of the present study; however, some limitations are present in this study:

1) Although the evaluation of muscle mass by DXA is an approved method, there are some limitations in the assessment of fat free mass by this method, and other methods such as computed tomography scanning and magnetic resonance imaging are more precise modalities for assessment of skeletal muscle mass.
2 We could find a good relationship between the 6-min walk distance, as a surrogate for skeletal muscle function, and muscle wasting, but it would be better if we could measure muscle power and function by more specific tests.
3 It would be better if we could assess exercise capacity by ergospirometry.
4 Small sample size and lack of follow-up data are other limitations of this study.
5 Our study is by far the first report of muscle wasting in Iranian heart failure patients, and we believe further

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studies are needed to investigate whether factors related to race and ethnicity play any role in higher prevalence of muscle wasting in heart failure patients.

Conclusions

We concluded that muscle wasting might be present in younger patients with heart failure particularly in those who are in worse clinical condition. This is the first study of muscle wasting in heart failure patients in Iran and could be the basis of further evaluations and basic and clinical trials in this issue.

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Conflict of interest

None declared.

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