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Original article

Loop diuretic use is associated with skeletal muscle wasting in patients with heart failure

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ABSTRACT

Background: Loop diuretics are widely used for the management of fluid retention in patients with heart failure (HF). Sarcopenia, defined as decreased skeletal muscle mass, is frequently present in patients with HF and is associated with poor prognosis. The effects of loop diuretics on skeletal muscle in HF patients have not been fully elucidated. Here, we investigated the impact of loop diuretics on the skeletal muscle mass in patients with HF.

Methods: We conducted a subanalysis of a cross-sectional study from 10 hospitals evaluating 155 patients with HF (age 67 ± 13 yrs, 69% men).

Results: We compared the HF patients who were treated with loop diuretics (n = 120) with the patients who were not (n = 35). The thigh and arm circumferences were significantly small in the group treated with loop diuretics compared to those not so treated (39.9 ± 4.8 vs. 43.5 ± 6.9 cm, $p < 0.001$ and 26.7 ± 3.5 vs. 28.9 ± 6.2 cm, $p < 0.001$, respectively). In a univariate analysis, higher age, lower body mass index, lower hemoglobin, and loop diuretic use were significantly associated with smaller thigh circumference. In a multivariable analysis, the use of loop diuretics was independently associated with smaller thigh circumference (β = −0.51, 95% confidence interval −0.98 to −0.046, $p = 0.032$).

Conclusion: Loop diuretics are associated with decreased thigh and arm circumferences in patients with HF, independent of the severity of HF. Our findings revealed for the first time the adverse effects of loop diuretics on skeletal muscle wasting. These findings will have a significant impact in clinical practice regarding the frequent use of loop diuretics in HF patients.

Introduction

Loop diuretics are widely used for the management of fluid retention in patients with heart failure (HF). Current guidelines recommend loop diuretics as a first-line treatment for relieving symptoms of fluid overload and congestion in HF patients [1–3], and the effectiveness of loop diuretics is a mainstay in clinical practice. However, several studies revealed that the use of diuretics is associated with adverse clinical outcomes in HF [4–7]. We also observed that loop diuretic use was associated with significantly increased risks of cardiac death and rehospitalization in a long-term follow-up of HF patients in a multi-hospital registry [8].

Skeletal muscle wasting is frequently present in patients with HF in a phenomenon known as 'secondary sarcopenia' [9]. Sarcopenia occurs in HF patients not only as a result of inactivity; HF can also promote the development of sarcopenia through multiple pathophysiological mechanisms [10]. We have described aberrant muscle alterations that are involved in HF including muscle atrophy, a reduction in muscular strength, a switch in myofibers from slow type I to fast type II, and impaired energy metabolism due to the reduction in mitochondrial density and oxidative function [9,11,12]. These changes are important factors that limit exercise capacity, and they are related not only to worse symptoms but also to the severity and prognosis of patients with HF [13–16].

The effects of loop diuretics on skeletal muscle have been largely unknown. In 2017, Mandai et al. reported that loop diuretics impair muscle myogenesis [17]. Loop diuretics inhibit the function of Na^+-K^+-$2Cl^-$ cotransporter (NKCC) 1, which is highly expressed

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in the skeletal muscle and plays an essential role in the differentiation of myoblasts, which leads to muscle generation and regeneration. Mandai et al. showed that the inhibition of NKCC1 by loop diuretics impaired both the differentiation of C2C12 myoblasts in vitro and exercise-induced muscle hypertrophy in vivo, suggesting that loop diuretic treatment may be involved in the pathogenesis of sarcopenia [17].

A clinical study by Hanai et al. revealed that the use of higher doses of loop diuretics in patients with liver cirrhosis was associated with a more rapid loss of muscle mass, independent of the severity of liver disease, and that the higher doses also worsened the patients' prognoses [18]. Similarly, Ishikawa et al. reported that loop diuretic use by renal failure patients was associated with an increased risk of sarcopenia [19].

Loop diuretics have thus been implicated as a risk factor for skeletal muscle depletion, and we speculated that loop diuretics may also adversely affect muscle wasting in HF patients — and that their use may be one of the causes of worsening prognoses among HF patients. It has not been known whether loop diuretics exert effects on skeletal muscle wasting in patients with HF. We conducted the present study to clarify the effects of loop diuretics on skeletal muscle wasting in HF patients by using the data of a multicenter cohort study of patients with HF. We used the patients' thigh and arm circumferences as an estimation of skeletal muscle wasting [20,21].

Patients and methods

Study design

This study was a subanalysis of a cross-sectional study conducted using a database of a multicenter prospective cohort study of patients with chronic HF. All of the enrolled patients treated at the participating 10 institutes provided their written informed consent to join in this cohort. The study was approved by the institutional ethics committee at each participating site and was conducted in accordance with the ethical principles described in the Declaration of Helsinki (2013 revised version).

The patient eligibility criteria were as follows: age ≥20 years; one or more hospitalizations due to worsening HF before enrollment; outpatients considered to be in stable New York Heart Association (NYHA) functional class I–III for >1 month since the prior hospitalization and with no signs of congestion or edema; and available written informed consent from the patient. Patients were excluded if they had nephrotic syndrome, liver cirrhosis, cancer, a history of gastrointestinal surgery within the prior 3 months, or poorly controlled diabetes (HbA1c >7.0%). We also excluded patients who were taking a steroid, anticancer agent, or antidepressant since these drugs are known to affect appetite, dietary content, and body composition.

Clinical variables

We reviewed all of the patients' medical records for the evaluation of demographic characteristics: age, gender, body mass index (BMI), causes of HF, NYHA functional class, medication(s), echocardiography measurements, blood test results, and the thigh and arm circumferences. Information was also collected about the patients' medical histories (e.g. hypertension, diabetes, and chronic kidney disease) and the patients' nutrition or activity status including the controlling nutrition status (CONUT) score [22], geriatric nutritional risk index (GNRI) [23], Lawton index [24], and whether they were participating in exercise training.

Statistical analyses

Continuous variables are expressed as the mean ± SD or the median and interquartile range (IQR) as appropriate. Categorical variables are presented as numbers and percentages. Comparisons between two groups were made using Welch's t-test for continuous variables and the chi-square test for categorical variables. Normality was tested using the Shapiro-*Wilk* normality *test*. We conducted a univariate linear regression analysis to evaluate the association between thigh circumference and other clinical variables including loop diuretic use. We then conducted a multivariable linear regression model including age, male gender, BMI, NYHA class III, hemoglobin, and the use of loop diuretics to identify the independent variables associated with thigh circumference. Values of $p < 0.05$ were considered significant. All analyses were performed using JMP Pro 14.0.0 software (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics in patients with HF

A total of 155 patients were included in this study (Fig. 1). The baseline characteristics are summarized in Table 1. The mean age of the patients [107 men (69%) and 48 (31%) women] was 67 ± 13 years. The cause of HF was ischemic heart disease in 32% of the patients, and 90% of the patients were NYHA functional class I–II. The patients' echocardiographic data showed that the left ventricular end-diastolic diameter (LV EDD) was 57 ± 11 mm and the left ventricular ejection fraction (LVEF) was 45 ± 14%.

Among the 155 patients, 120 patients (77%) were treated with loop diuretics, and 35 patients (23%) were not. The BMI was significantly lower in the patients who were treated with loop diuretics compared to those who were not (22.9 ± 3.9 vs. 25.6 ± 7.2, $p = 0.038$). The echocardiography findings did not differ between the two patient groups. The uric acid and plasma brain natriuretic peptide (BNP) levels were higher in the loop diuretic use group. The use of angiotensin-converting enzyme inhibitors (ACE-Is) and those of angiotensin II receptor blockers (ARBs) and β-blockers did not differ between the two patient groups. The proportion of patients treated with spironolactone was significantly higher in the loop diuretic use group (68% vs. 26%, $p < 0.001$). The patients' nutritional status based on the CONUT score and GNRI did not differ between the two patient groups; nor did the patients' activity status based on the Lawton index or the proportion of patients undergoing exercise training.

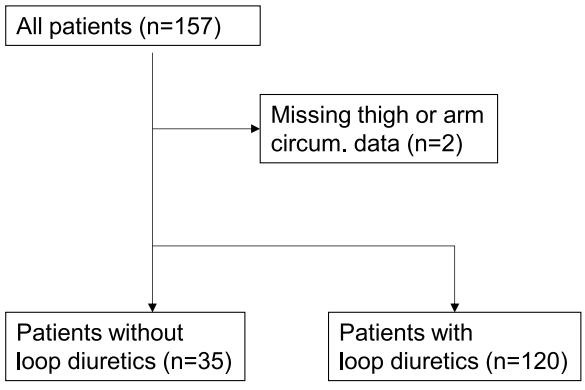

Fig. 1. Flowchart of the study.
Circum., circumference.

Table 1
Characteristics of the heart failure patients.

	All patients (n = 155)	Patients without loop diuretics (n = 35)	Patients with loop diuretics (n = 120)	*p*-Value
Male, n (%)	107 (69%)	23 (66%)	84 (70%)	0.629
Age, years	67 ± 13	67 ± 12	67 ± 13	0.900
Weight, kg	62 ± 14	67 ± 17	60 ± 13	0.032
BMI, kg/m^2	23.5 ± 5.0	25.6 ± 7.2	22.9 ± 3.9	0.038
Causes of heart failure:				
ICM, n (%)	49 (32%)	12 (34%)	37 (31%)	0.699
HHD, n (%)	24 (16%)	9 (26%)	15 (13%)	0.057
DCM, n (%)	48 (31%)	11 (31%)	37 (31%)	0.947
VHD, n (%)	34 (22%)	3 (9%)	31 (26%)	0.030
NYHA classification:				0.121
I–II, n (%)	140 (90%)	34 (97%)	106 (88%)	
III, n (%)	15 (10%)	1 (3%)	14 (12%)	
Medical history:				
Hypertension, n (%)	84 (54%)	23 (66%)	61 (51%)	0.120
Diabetes mellitus, n (%)	39 (25%)	12 (34 %)	27 (23%)	0.157
CKD, n (%)	6 (4%)	1 (3%)	5 (4%)	0.724
Laboratory test results:				
Albumin, mg/dL	4.2 ± 0.4	4.1 ± 0.3	4.2 ± 0.4	0.568
Creatinine, mg/dL	1.2 ± 0.8	1.1 ± 1.0	1.2 ± 0.8	0.601
Uric acid, mg/dL	6.9 ± 2.0	6.2 ± 1.7	7.1 ± 2.0	0.013
Sodium, mEq/L	140.3 ± 2.7	141.1 ± 3.3	140.0 ± 2.4	0.069
Potassium, mEq/L	4.3 ± 0.4	4.3 ± 0.4	4.3 ± 0.4	0.953
Hemoglobin, g/dL	13.1 ± 1.9	13.2 ± 1.5	13.0 ± 1.9	0.588
BNP, pg/mL	152 (66, 372.15)	126.3 (74.4, 267.8)	156 (56.9, 395)	0.016
Echocardiographic parameters:				
LV EDD, mm	57 ± 11	55 ± 8	57 ± 12	0.282
LV ESD, mm	45 ± 14	45 ± 15	42 ± 10	0.145
LVEF, %	45 14	48 ± 14	43 ± 16	0.113
Medication:				
ACE-Is, n (%)	79 (51%)	17 (49%)	62 (52%)	0.747
ARBs, n (%)	40 (26%)	6 (17%)	34 (28%)	0.183
β-blockers, n (%)	134 (87%)	30 (86%)	104 (87%)	0.885
Aldosterone antagonists, n (%)	91 (59%)	9 (26%)	82 (68%)	<0.001
Other diuretics, n (%)	10 (7%)	0 (0%)	10 (8%)	0.077
Nutrition and activity status				
Exercise training, n (%)	39 (25%)	10 (29%)	29 (24%)	0.540
Lawton index	5.1 ± 1.6	5.5 ± 1.8	5.0 ± 1.8	0.090
CONUT score	1.8 ± 1.6	1.5 ± 1.7	1.9 ± 1.5	0.259
GNRI score	105.8 ± 10.7	108.1 ± 10.5	105.1 ± 10.7	0.150

Data are mean ± SD or median (first quartile, third quartile) for continuous variables.
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; CKD, chronic kidney disease; DCM, dilated cardiomyopathy; HF, heart failure; HHD, hypertensive heart disease; ICM, ischemic cardiomyopathy; LV EDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LV ESD, left ventricular end-systolic diameter; NYHA, New York Heart Association; VHD, valvular heart disease.

Muscle wasting in the HF patients with loop diuretics use

The thigh and arm circumferences were both significantly smaller in the HF patients treated with loop diuretics compared to those not so treated (39.9 ± 4.8 vs. 43.5 ± 6.9 cm, $p < 0.001$ and 26.7 ± 3.5 vs. 28.9 ± 6.2 cm, $p < 0.001$, respectively) (Table 1, Fig. 2).

Independent factors associated with muscle wasting

Table 2 shows the correlation coefficients between muscle wasting and other clinical parameters. In the univariate analysis, the following were significantly associated with a decrease in thigh circumference: higher age (β = −0.11, 95%CI: −0.18 to −0.044, $p = 0.001$), lower BMI (β = 0.99, 95%CI: 0.91–1.08, $p < 0.001$), lower hemoglobin (β = 0.97, 95%CI: 0.52–1.42, $p < 0.001$), and the use of loop diuretics (β = −1.77, 95%CI: −2.79 to −0.76, $p = 0.001$). The multivariable linear regression analysis revealed that loop diuretics use was independently associated with smaller thigh circumference (β = −0.51, 95%CI: −0.98 to −0.046, $p = 0.032$), conditional upon the other predictors (Table 2).

Discussion

Our analyses of 155 patients with HF revealed that loop diuretic use was associated with smaller thigh and arm circumferences in the patients. In the multivariable analysis, smaller thigh circumference was independently associated with loop diuretic use, suggesting that the use of loop diuretics may be one of the critical risk factors of muscle wasting in HF patients, independent of the severity of the disease. These results have clinical significance because loop diuretics — which are one of the most commonly used drugs for fluid retention in patients with HF — can thus decrease the body's skeletal muscle mass, which worsens the prognosis of these patients.

Muscle wasting (i.e. sarcopenia), which is characterized by a progressive decline in skeletal muscle mass, is a highly prevalent complication in HF [9], and it is not only related to worse symptoms; muscle wasting also directly contributes to adverse outcomes in HF patients [13–16,25]. Fulster et al. reported that 19.5% of their study's HF patients had muscle wasting [9], which was 2–4 times the prevalence of muscle wasting in a general

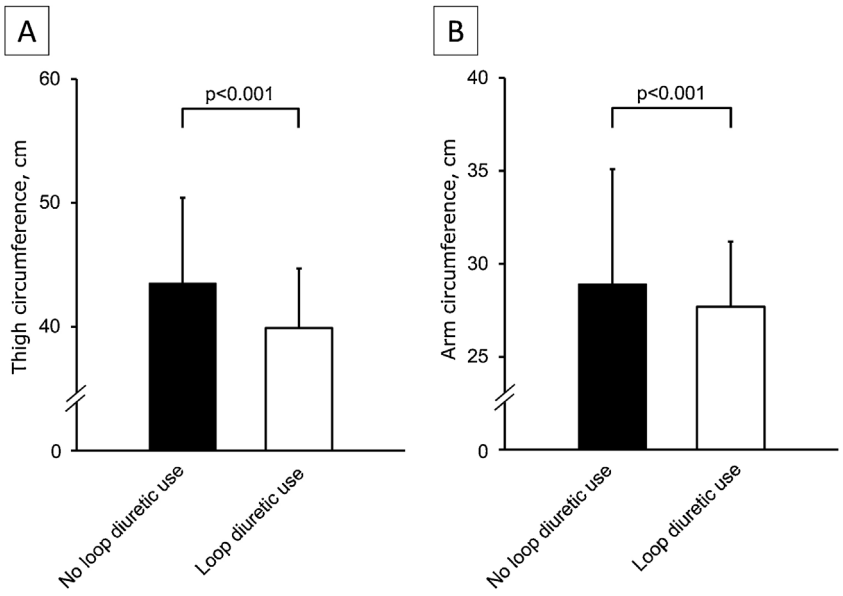

Fig. 2. The thigh (A) and arm (B) circumferences of heart failure patients treated with loop diuretics and not treated with loop diuretics.

Table 2
Univariate and multivariable linear regression model of thigh circumference and other clinical variables.

	Univariate analysis		Multivariable analysis	
	Beta (95%CI)	*p*-Value	Beta (95%CI)	*p*-Value
Age, years	−0.11 (−0.18 to −0.044)	0.001	−0.04 (−0.076 to −0.013)	0.007
BMI, kg/m^2	0.99 (0.91–1.08)	<0.001	0.94 (0.86–1.00)	<0.001
Use of loop diuretics	−1.77 (−2.79 to −0.76)	0.001	−0.51 (−0.98 to −0.046)	0.032
NYHA class III	−0.78 (−2.27 to 0.71)	0.426	0.12 (−0.55 to 0.79)	0.717
Hemoglobin, g/dL	0.97 (0.52–1.42)	<0.001	0.21 (−0.04 to 0.45)	0.096
Male	0.15 (−0.38 to 3.41)	0.117	0.76 (−0.17 to 1.70)	0.109

Male and female were assigned values of 1 and 0, respectively.
BMI, body mass index; NYHA, New York Heart Association.

population of the same age [26]. HF itself can promote the development of sarcopenia through multiple pathophysiological mechanisms [10], causing lowered muscle strength, lowered exercise capacity and endurance, lower cardiac function, and adverse events including HF-related hospitalization and death due to HF [9,25,27]. It is therefore essential to determine any factors that cause such muscle wasting in patients with HF.

There is a growing body of evidence that the use of loop diuretics is associated with worse outcomes in HF. Loop diuretics are reported to worsen neurohormonal activation [28,29], including activation of the renin-angiotensin-aldosterone system (RAAS) [30] and the sympathetic nervous system [31,32], which is reported to induce myocardial fibrosis, oxidative stress, and the stimulation of proinflammatory cytokines, which are known to play a detrimental role in HF progression [33–36]. In addition, in HF patients the use of loop diuretics can reduce the glomerular filtration rate (GFR) and cause electrolyte disturbances, which are common and independent risks for cardiovascular adverse outcomes [37–40]. As such, these factors may be possible explanations of the phenomenon of loop diuretics causing poor prognoses in HF. In terms of skeletal muscle, the RAAS [41,42], sympathetic nervous system activity [43], and renal function [44,45] are all reported to affect muscle wasting. It can thus be presumed that loop diuretics have a negative impact on skeletal muscle.

As more direct evidence, Mandai et al. recently reported that loop diuretics impair myogenic differentiation and exercise-induced muscle hypertrophy in their in vivo and in vitro investigations [17]. Loop diuretics are an inhibitor of the NKCC, and Mandai et al. suggested that the inhibition of NKCC1 (which is strongly expressed in skeletal muscle [46]) downregulates depolarization-induced Ca^{2+} signaling, which is one of the essential regulators of skeletal myogenesis [46,47]. This can be considered one of the possible direct mechanisms underlying skeletal muscle wasting attributable to loop diuretics.

Indeed, similarly to our results, clinical studies observing liver cirrhosis patients [18] and renal failure patients [19] showed an independent association between loop diuretic use and a reduction in skeletal muscle mass. In HF patients, the pathophysiology of the disease and the mechanism of volume overload or the frequency loop diuretics used are different from those of liver cirrhosis or renal failure patients, and the effect of loop diuretics on skeletal muscle impairments also differ. The similar results of these studies, taken together with our present findings, support the hypothesis that loop diuretics may be involved in the loss of skeletal muscle mass and the development of sarcopenia.

In addition, in the present study, the thigh circumference of the patients treated with loop diuretics did not differ between those undergoing exercise training or not, whereas among the patients

not being treated with loop diuretics, those undergoing exercise training showed a larger thigh circumference than those without training (39.7 ± 4.5 vs. 39.9 ± 5.0 cm, $p = 0.764$ and 47.5 ± 9.4 vs. 41.9 ± 5.0 cm, $p = 0.030$, respectively). Regarding the report that exercise-induced muscle hypertrophy was impaired by loop diuretics [17], it is possible that this present finding is a result of loop diuretics adversely affecting exercise training, which is a great disadvantage since exercise training is the only intervention for skeletal muscle impairments in HF patients to date. However, this cross-sectional study cannot evaluate any causal relationship between loop diuretics and skeletal muscle, and further evaluations of this possibility are necessary.

We used the thigh and arm circumferences as an estimation of skeletal muscle wasting; we did not measure the patients' actual muscle mass, e.g. by computed tomography (CT), dual-energy X-ray absorptiometry (DEXA), or a bioelectrical impedance analysis (BIA). The thigh and arm circumferences are reported to well reflect the body's muscle mass [20,48], but their accuracy may be low compared to validated equipment. However, the measurement of the thigh or arm circumference is an easy and noninvasive method which needs no specialized equipment or cost and can be measured repeatedly. This may be beneficial in clinical practice considering the fact that CT, DEXA, and BIA are not always available in healthcare facilities, and there are issues regarding radiation exposure and the interference with implanted metal devices that is commonly observed in HF patients.

In addition, the thigh or arm circumference has been used as an estimation of muscle mass in other studies of HF patients, and its decrease has been shown to be associated with lowered exercise capacity and adverse clinical outcomes [21,49,50]. One concern about this measurement, especially in HF patients, is the effect of edema. The patients in this study were treated with an optimal diuretic dose by cardiology specialists and showed no signs of congestion or edema, as cited in the inclusion criteria. Moreover, it is important that the use of diuretics remained as an independent determinant of thigh circumference even after the adjustment of NYHA or BMI. Nevertheless, the influence of fluid retention must be considered carefully when applying this method to general practice.

There are several limitations of this study to address. First, we did not evaluate any association based on the dose or type of loop diuretics, or the period of loop diuretic use; this was due to a lack of data. Hanai et al. showed that a higher dose of loop diuretics was associated with a more rapid decline in muscle mass in liver cirrhosis patients [18], but a more detailed and large-scale study is needed to examine the dose-, type-, and duration-dependent effects on the skeletal muscle of HF patients.

Second, there is a lack of data about the use of diuretics other than loop diuretics, such as tolvaptan. As a selective V2 receptor antagonist, tolvaptan is effective for the treatment of volume overload in HF patients, and it was reported to have no effect on renal function or hemodynamics [51] or the RAAS [52]. In addition, since tolvaptan has no effect on the NKCC, it is possible that tolvaptan does not affect skeletal myogenesis. The use of tolvaptan combined with loop diuretics rather than using high doses of loop diuretics may help prevent skeletal muscle loss and therefore reduce adverse events, but further research is needed to clarify this possibility.

Finally, the use of diuretics is strongly confounded by the severity of HF, and consequently the patients treated with diuretics will be at increased risk of muscle wasting. Our analyses demonstrated that the use of loop diuretics was independently associated with reduced muscle mass even after the adjustment for the patients' NYHA class, a parameter of HF severity. However, we cannot completely exclude the possibility that the cardiac function before diuretic introduction or as-yet unknown factors affect the associations among these variables.

Conclusion

Our study revealed for the first time that loop diuretic use is associated with muscle wasting in patients with HF, independent of the severity of HF. Our results will have a significant impact in clinical practice, since loop diuretics are widely used to treat HF patients. Careful consideration is necessary when administering loop diuretics, especially for HF patients at risk of sarcopenia or undergoing exercise therapy. Considering the skeletal muscle, it may be beneficial for HF patients to use a combination of a loop diuretic and other non-loop diuretics rather than a high dose of loop diuretics.

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Disclosures

The authors declare that they have no conflicts of interest related to this study.

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