Renal Replacement Therapy

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Diaphragmatic dysfunction in hemodialysis patients: risk factors and effect of incentive spirometry training

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Abstract

Background Diaphragmatic dysfunction (DD) in hemodialysis patients is a scarcely studied issue. Incentive spirometry (IS) is a commonly prescribed maneuver used to prevent or manage pulmonary complications. The present study aimed to identify the prevalence and risk factors of DD in 100 HD patients. Moreover, we assessed the role of IS in management of DD in those patients.

Methods The present study followed a hybrid design with two phases. In the first cross-sectional phase, 100 consecutive maintenance HD patients for at least 3 years were evaluated for the presence of DD using ultrasound. In the second interventional phase, patients with DD (n = 43) were randomly assigned to receive IS (n = 22) or standard care (n = 21) for management of DD.

Results Comparison between patients with DD and patients without regarding clinical and laboratory data revealed that the former group had significantly higher frequency of males [29 (67.4%)/14 (32.6%) vs. 26 (45.6%)/31 (54.4%), $p = 0.03$] with lower BMI [23.8 ± 3.8 vs. 26.3 ± 3.5 kg/m^2, $p < 0.001$] and longer HD duration (82.2 ± 42.1 vs. 64.8 ± 36.9 months, $p = 0.031$). Moreover, it was noted that DD group had significantly higher frequency of patients with moderate/severe malnutrition (81.4% vs. 45.6%, $p = 0.005$), lower Hb levels (9.6 ± 1.5 vs. 10.3 ± 1.4 gm/dL, $p = 0.011$), lower albumin levels (3.4 ± 0.4 vs. 4.1 ± 0.5 gm/dL, $p < 0.001$) and higher hsCRP levels [median (IQR) 113.6 (90.9–130.4) vs. 91.1 (50.9–105.6) mg/dL, $p < 0.001$] as compared to patients without DD. While no significant differences were found between patients receiving study interventions at baseline, patients submitted to IS training showed significant improvement of diaphragmatic excursion measurements as compared to the standard care group.

Conclusions In conclusion, DD is commonly encountered in HD patients. Probable risk factors include longer HD duration and low albumin levels. Use of IS can improve diaphragmatic excursion in affected patients.

Keywords Hemodialysis, Diaphragmatic dysfunction, Incentive spirometry

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Background

Through decades, hemodialysis (HD) had steadied its role as the primary treatment option for end stage renal disease (ESRD). Since invention eight decades ago, the procedure had witnessed massive developments in terms of technological innovations and clinical protocols. Unfortunately, use of HD is not without significant drawbacks and one of these is the associated malnutrition-inflammation complex [1]. The consequences of malnutrition in HD patients encompass, among others, muscle wasting, weakness and sarcopenia which are linked to poor clinical outcomes [2].

The diaphragm is the principal breathing muscle and any local or systemic condition that interferes with its appropriate contractility can lead to diaphragmatic dysfunction (DD) and related clinical consequences including dyspnea, easy fatiguability and sleep disturbances [3]. Notably, HD patients were reported to have poor respiratory muscle strength parameters and pulmonary function tests in comparison to healthy counterparts [4]. In spite of the fact that DD in HD patients is a scarcely investigated issue. It was found to be related to troublesome symptoms including dyspnea, fatigue, and hiccup [5] and serious clinical outcomes including non-fatal cardiovascular events and all-cause mortality [6].

Diagnosis of DD is challenging. While application of volitional tests is restricted by the patient effort, other non-volitional tests e.g. neuromuscular stimulation are technically sophisticated [7]. Recently, ultrasound is increasingly used for assessment of diaphragmatic integrity, excursion and thickness [8]. Management options of DD entails training of respiratory muscles, noninvasive ventilation and surgical intervention in advanced cases [9].

Incentive spirometry (IS) is a commonly prescribed maneuver used to prevent or manage pulmonary complications postoperatively [10–13], after stroke [14]. The present study aimed to identify the prevalence and risk factors of DD in HD patients. Moreover, we assessed the role of IS in management of DD in those patients.

Methods

The present study was conducted et al.-Azhar University Hospitals, Cairo, Egypt. The study protocol was approved by the ethical committee of Al-Azhar University Faculty of Medicine and all patients provided informed written consent before enrollment.

Study design and selection criteria

The present study followed a hybrid design with two phases. In the first cross-sectional phase, 100 consecutive maintenance HD patients for at least 3 years were evaluated for the presence of DD using ultrasound. In the second interventional phase, patients with DD (n = 43) were randomly assigned to receive IS (n = 22) or standard care (n = 21) for management of DD. Patients were excluded if they had history of cardiovascular or cerebrovascular events, cognitive impairment, associated lung disease, malignant conditions or advanced liver disease.

Baseline assessment

Upon recruitment, all patients were submitted to careful history taking, thorough clinical examination and standard laboratory work up. Nutritional status was assessed using the malnutrition inflammation score (MIS) [15]. Patients with MIS < 6 were identified to have mild malnutrition while those with MIS ≥ 6 were identified to have moderate/severe malnutrition.

Ultrasound diagnosis of DD

The diaphragm was assessed during tidal, deep and sniff breathing using ultrasound scanner equipped with 3.5 MHz curvilinear and 8 MHz linear probes (SSI6000, Sonoscape, Nanshan, China) for diaphragmatic excursion (M-mode) and thickness (B-mode). Only the right diaphragm was assessed. It was found to sufficient and more precise for diagnosis of DD in comparison to the left side for technical considerations [16]. All sonographic measurements were made at baseline and after the IS protocol by the same sonographer. Patients were diagnosed with DD if they had diaphragmatic excursion of < 10 mm or the presence of paradoxical movement [17, 18] and/or if they had diaphragm thickening fractions < 20% [8].

Randomization and blinding

Patients were randomized to receive IS or standard care using computer-generated random tables and sealed envelope technique. Sonographers weren't aware of the type of intervention received by the patients.

Incentive spirometry protocol

IS training was achieved using UNA01 flow-oriented incentive spirometer (UniCare, China). Patients were adequately trained to use the device. The respiratory training protocol consisted of hourly 5–10 episodes during wake time for 8 weeks.

Statistical analysis

Data obtained from the present study were presented as number and percent, mean and standard deviation (SD) or median and interquartile range (IQR) and compared using chi-square test, t test or Mann–Whitney U test. Binary logistic regression analysis was used to identify predictors of DD in the studied patients. All statistical computations were processed using SPSS, 27 (IBM, IL, USA) with p value < 0.05 was considered statistically significant.

Results

The present study included 100 HD patients comprising 55 men and 45 women with an age of 60.7 ± 8.7 year. DD was diagnosed in 43 patients. Comparison between patients with DD and patients without regarding clinical and laboratory data revealed that the former group had significantly higher frequency of males [29 (67.4%)/14 (32.6%) vs. 26 (45.6%)/31 (54.4%), $p = 0.03$] with lower BMI (23.8 ± 3.8 vs. 26.3 ± 3.5 kg/m^2, $p < 0.001$) and longer HD duration (82.2 ± 42.1 vs. 64.8 ± 36.9 months, $p = 0.031$) (Table 1).

Moreover, it was noted that DD group had significantly higher frequency of patients with moderate/severe malnutrition (81.4% vs. 45.6%, $p = 0.005$), lower Hb levels (9.6 ± 1.5 vs. 10.3 ± 1.4 gm/dL, $p = 0.011$), lower albumin levels (3.4 ± 0.4 vs. 4.1 ± 0.5 gm/dL, $p < 0.001$) and higher hsCRP levels [median (IQR) 113.6 (90.9–130.4) vs. 91.1 (50.9–105.6) mg/dL, $p < 0.001$] as compared to patients without DD (Table 1).

Binary logistic regression analysis identified HD duration [OR (95% CI) 0.98 (0.97–0.99)], moderate/severe malnutrition [OR (95% CI) 3.67 (1.45–9.28)], Hb levels [OR (95% CI) 1.44 (1.08–1.91)] and albumin levels [OR (95% CI) 31.3 (7.98–123.0)] as significant predictors of DD in univariate analysis. However, in multivariate

Table 1 Clinical and laboratory findings in the studied patients (n = 100)

	All patients N = 100	**Diaphragmatic dysfunction + ve n = 43**	**Diaphragmatic dysfunction −ve n = 57**	***p* value**
Age (years) mean ± SD	60.7 ± 8.7	60.5 ± 9.1	60.9 ± 8.5	0.83
Male/female n (%)	55 (55.0)/45 (45.0)	29 (67.4)/14 (32.6)	26 (45.6)/31(54.4)	0.03
BMI (Kg/m^2)	25.2 ± 3.8	23.8 ± 3.8	26.3 ± 3.5	< 0.001
Comorbidities n (%)				
HTN	54 (54.0)	22 (51.2)	32 (56.1)	0.62
DM	41 (41.0)	18 (41.9)	23 (40.4)	0.88
RA	15 (15.0)	6 (14.0)	9 (15.8)	0.8
SLE	8 (8.0)	5 (11.6)	3 (5.3)	0.25
HD duration (months) mean ± SD	72.4 ± 40.0	82.2 ± 42.1	64.8 ± 36.9	0.031
Malnutrition n (%)				
No/Mild	34 (34.0)	8 (18.6)	31 (54.4)	0.005
Moderate/severe	66 (66.0)	35 (81.4)	26 (45.6)	
Laboratory findings mean ± SD/median (IQR)				
Hb (gm/dL)	10.0 ± 1.5	9.6 ± 1.5	10.3 ± 1.4	0.011
WBCs (× 10^3/mL)	6.1 ± 2.0	6.4 ± 2.0	5.8 ± 1.9	0.09
Platelets (× 10^3/mL)	196.7 ± 58.5	190.4 ± 65.0	201.5 ± 53.2	0.35
Creatinine (mg/dL)	7.8 ± 2.5	7.5 ± 2.4	8.0 ± 2.5	0.31
Urea (mg/dL)	112.7 ± 32.1	115.2 ± 33.0	110.8 ± 31.6	0.5
FBS (mg/dL)	125.3 ± 46.7	127.6 ± 49.2	123.6 ± 45.1	0.67
Albumin (gm/dL)	3.8 ± 0.6	3.4 ± 0.4	4.1 ± 0.5	< 0.001
Cholesterol (mg/dL)	171.5 ± 48.2	183.4 ± 52.9	162.5 ± 42.6	0.031
Triglycerides (mg/dL)	181.8 ± 107.4	194.7 ± 113.1	172.0 ± 102.8	0.29
Calcium (mg/dL)	8.8 ± 0.8	8.4 ± 0.8	9.0 ± 0.7	< 0.001
Phosphorus (mg/dL)	4.5 ± 1.2	4.2 ± 1.1	4.7 ± 1.3	0.067
Sodium (mEq/L)	136.2 ± 5.7	133.0 ± 5.2	138.6 ± 4.8	< 0.001
Potassium (mEq/L)	4.7 ± 0.6	4.4 ± 0.6	4.7 ± 1.3	< 0.001
iPTH (pg/mL)	366.5 (187.0–909.8)	395.0 (206.0–904.0)	338.0 (175.0–930.0)	0.79
Uric acid (mg/dL)	5.9 ± 1.3	6.0 ± 1.4	5.8 ± 1.2	0.61
hsCRP (mg/L)	100.6 (75.9–116.6)	113.6 (90.9–130.4)	91.1 (50.9–105.6)	< 0.001

BMI Body mass index, *DM* Diabetes mellitus, *FBS* Fasting blood sugar, *Hb* Hemoglobin, *HD* Hemodialysis, *hsCRP* High-sensitivity C-reactive protein, *HTN* Hypertension, *iPTH* Intact parathyroid hormone, *RA* Rheumatoid arthritis, *SLE* Systemic lupus erythematosus, *WBCs* White blood cells analysis, only albumin levels [OR (95% CI) 43.2 (6.91–270.7)] remained significant (Table 2).

While no significant differences were found between patients receiving study interventions at baseline, patients submitted to IS training showed significant improvement of diaphragmatic excursion measurements as compared to the standard care group (Table 3).

Table 3 Effect of incentive spirometry exercise on diaphragmatic functions in the studied patients

	Incentive spirometry N = 22	Standard Care N = 21	*p* value
Diaphragmatic excursion (cm)			
Rt tidal			
Baseline	1.20 ± 0.26	1.26 ± 0.22	0.62
8 weeks	1.9 ± 0.24	1.61 ± 0.22	0.04
p value	< 0.001	0.21	–
Change	0.72 ± 0.33	0.36 ± 0.16	< 0.001
Rt deep			
Baseline	4.41 ± 0.55	4.23 ± 0.25	0.37
8 weeks	5.21 ± 0.53	4.54 ± 0.21	< 0.001
p value	< 0.001	0.64	–
Change	0.81 ± 0.48	0.30 ± 0.18	< 0.001
Rt sniff			
Baseline	2.11 ± 0.29	2.19 ± 0.27	0.55
8 weeks	2.71 ± 0.37	2.27 ± 0.23	0.006
p value	< 0.001	0.17	–
Change	0.6 ± 0.36	0.07 ± 0.15	< 0.001
Diaphragmatic thickness mm			
Rt tidal insp			
Baseline	2.69 ± 0.31	2.79 ± 0.14	0.23
8 weeks	2.78 ± 0.28	2.89 ± 0.11	0.14
p value	0.2	0.23	–
Change	0.09 ± 0.3	0.11 ± 0.06	0.77
Rt tidal Exp			
Baseline	1.79 ± 0.20	1.67 ± 0.22	0.18
8 weeks	1.69 ± 0.20	1.72 ± 0.24	0.71
p value	0.092	0.41	–
Change	0.09 ± 0.24	0.05 ± 0.07	0.2

Discussion

The present study found that DD as assessed by ultrasound imaging is highly prevalent in maintenance HD patients. Also, we found an association between DD, and male sex, HD duration, moderate-to-severe malnutrition, lower hemoglobin and albumin levels and high hsCRP levels. Our conclusions are supported by the few studies that assessed DD in HD patients through different designs and protocols.

In their case control study, Wang et al. [5] found that HD patients had lower diaphragmatic thickness, thickening fraction and excursion as compared to healthy controls. However, they didn't report the prevalence of DD in the studied patients nor assessed the relation between DD and other HD parameters. In another work, Zheng et al. [6] documented DD in 44.9% of the studied HD patients, a figure that is close to that found by the present study. However, patients included in their work included—among others—patients with previous cardiovascular events and congestive heart failure. These conditions may affect the performance of diaphragmatic tests irrespective of the hemodialysis parameters (Fig. 1).

Also, the study of Yuenyongchaiwat et al. [4] noted that HD patients exhibited significantly impaired respiratory muscles strength parameters in comparison to healthy controls. They added that this impairment is related to HD duration in harmony with our conclusions.

DD is HD patients may be explained by multiple factors. As shown by the present study and other studies [19], malnutrition is quite prevalent in HD patients. Malnutrition was also linked to reduced diaphragmatic thickness and function in many populations [19–21] probably due to increased proteolysis and reduced protein synthesis [22, 23] mediated by autocrine/paracrine [24] or inflammatory [25] pathways.

The persistent proinflammatory state related to HD is another suggested contributor to DD. Multiple reports identified impaired diaphragmatic functions in patients with proinflammatory conditions [26–28].

Table 2 Predictors of diaphragmatic dysfunction in the studied patients

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
HD duration	0.98	0.97–0.99	0.037	1.0	0.99–1.02	0.74
Malnutrition	3.67	1.45–9.28	0.006	0.79	0.23–2.67	0.7
Hb	1.44	1.08–1.91	0.013	0.92	0.6–1.39	0.69
Albumin	31.3	7.98–123.0	< 0.001	43.2	6.91–270.7	< 0.001
hsCRP	0.98	0.96–0.99	0.001	0.99	0.98–1.02	0.95

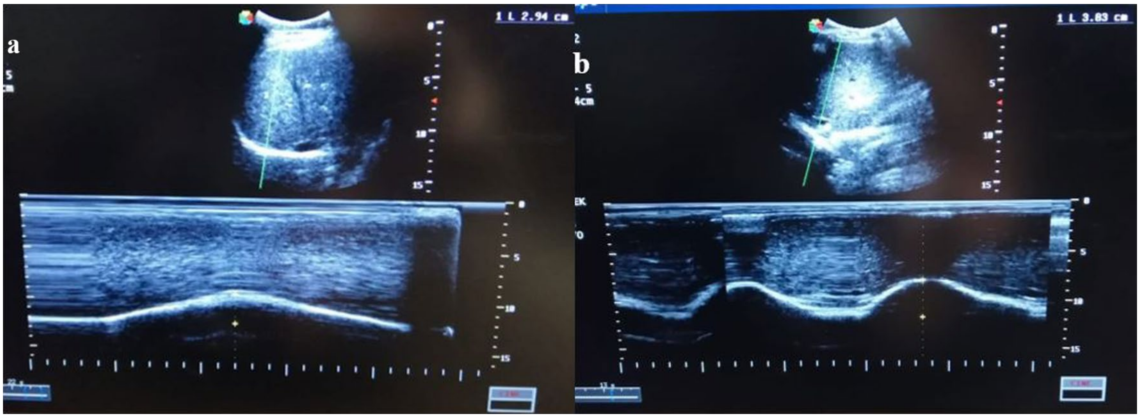

Fig. 1 **a** Baseline right tidal diaphragmatic excursion in one patient of the study. **b** Right tidal diaphragmatic excursion 8 weeks after incentive spirometry training in same patient of the study

Patients with DD in the present study were subsequently advanced to a clinical experiment where they were randomized to receive IS of standard care for DD. Patients in the IS arm showed significant improvement of diaphragmatic excursion after 8-week training protocol.

Interestingly, no corresponding improvement was noted regarding diaphragmatic thickness. This is probably attributed to the muscle wasting commonly seen in this population. In fact, some studies reported that HD patients failed to gain muscle mass after exercise while others identified improved muscle mass in response to exercise protocols as shown by one systematic review [29].

The positive impact of IS in HD patients is probably attributed to improved pulmonary functions and blood gases as suggested by previous studies. In one study, IS proved to be effective in improving arterial blood gases, pulmonary functions tests and diaphragmatic excursion in chronic obstructive pulmonary disease patients [30]. In diabetic patients, it was reported that IS improved all cardiopulmonary functions, functional capacity and event glycemic control [31]. Similar findings were recognized in stroke patients where flow-oriented IS outperformed volume oriented IS and diaphragmatic breathing [14]. Also, the study of Ribeiro et al. [32] concluded that use of IS in Parkinson's disease was associated with markedly improved pulmonary functions. In conclusion, DD is commonly encountered in HD patients. Probable risk factors include longer HD duration and low albumin levels. Use of IS can improve diaphragmatic excursion in affected patients. However, these conclusions are limited by the fact that this is a single-center study. Moreover, the long-term effects of IS training on HD patients' health outcomes and quality of life wasn't studied. It's also recommended to assess the relation between sarcopenia and frailty commonly seen in HD patients and DD.

Acknowledgements
We heartfully thank all patients participating in the study.

Author contributions
All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding
The research is self-funded from the authors.

Availability of data and materials
Data of this research will be available upon reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the ethical committee of Al-Azhar University Faculty of Medicine (Approval No. 202008330).

Consent for publication
Informed consent was obtained from all individuals included in this study.

Competing interests
The authors declare that they have no competing interests.

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Received: 27 June 2023 Accepted: 7 December 2023
Published online: 18 December 2023

References

1. Sahathevan S, Khor BH, Ng HM, et al. Understanding development of malnutrition in hemodialysis patients: a narrative review. Nutrients. 2020;12(10):3147. https://doi.org/10.3390/nu12103147.
2. Slee A, McKeaveney C, Adamson G, et al. Estimating the prevalence of muscle wasting, weakness, and sarcopenia in hemodialysis patients. J Ren Nutr. 2020;30(4):313–21. https://doi.org/10.1053/j.jrn.2019.09.004.
3. Ricoy J, Rodríguez-Núñez N, Álvarez-Dobaño JM, et al. Diaphragmatic dysfunction. Pulmonology. 2019;25(4):223–35. https://doi.org/10.1016/j.pulmoe.2018.10.008.
4. Yuenyongchaiwat K, Vasinsarunkul P, Phongsukree P, et al. Duration of hemodialysis associated with cardio-respiratory dysfunction and breathlessness: a multicenter study. PeerJ. 2020;4(8):e10333. https://doi.org/10.7717/peerj.10333.
5. Wang B, Yin Q, Wang YY, et al. Diaphragmatic dysfunction associates with dyspnoea, fatigue, and hiccup in haemodialysis patients: a cross-sectional study. Sci Rep. 2019;9(1):19382. https://doi.org/10.1038/s41598-019-56035-4.
6. Zheng J, Yin Q, Wang SY, et al. Ultrasound-assessed diaphragm dysfunction predicts clinical outcomes in hemodialysis patients. Sci Rep. 2022;12(1):16550. https://doi.org/10.1038/s41598-022-20450-x.
7. Laghi FA Jr, Saad M, Shaikh H. Ultrasound and non-ultrasound imaging techniques in the assessment of diaphragmatic dysfunction. BMC Pulm Med. 2021;21(1):85. https://doi.org/10.1186/s12890-021-01441-6.
8. Dass C, Dako F, Simpson S, et al. Sonographic evaluation of diaphragmatic dysfunction: technique, interpretation, and clinical applications. J Thorac Imaging. 2019;34:W131–40.
9. Windisch W, Schönhofer B, Magnet FS, et al. Diagnosis and treatment of diaphragmatic dysfunction. Pneumologie. 2016;70(7):454–61. https://doi.org/10.1055/s-0042-106694.
10. Eltorai AEM, Szabo AL, Antoci V Jr, et al. Clinical effectiveness of incentive spirometry for the prevention of postoperative pulmonary complications. Respir Care. 2018;63(3):347–52.
11. Kotta PA, Ali JM. Incentive spirometry for prevention of postoperative pulmonary complications after thoracic surgery. Respir Care. 2021;66(2):327–33.
12. Sullivan KA, Churchill IF, Hylton DA, et al. Use of incentive spirometry in adults following cardiac, thoracic, and upper abdominal surgery to prevent post-operative pulmonary complications: a systematic review and meta-analysis. Respiration. 2021;100(11):1114–27.
13. Chang PC, Chen PH, Chang TH, et al. Incentive spirometry is an effective strategy to improve the quality of postoperative care in the patients undergoing pulmonary resection: a systematic review and meta-analysis. Asian J Surg. 2022;S1015–9584(22):01588–93. https://doi.org/10.1016/j.asjsur.2022.11.030.
14. Shetty N, Samuel SR, Alaparthi GK, et al. Comparison of diaphragmatic breathing exercises, volume, and flow-oriented incentive spirometry on respiratory function in stroke subjects: a non-randomized study. Ann Neurosci. 2020;27(3–4):232–41. https://doi.org/10.1177/0972753121990193.
15. Kalantar-Zadeh K, Kopple JD, Block G, et al. A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. Am J Kidney Dis. 2001;38(6):1251–63. https://doi.org/10.1053/ajkd.2001.29222.
16. Bobbia X, Clément A, Claret PG, et al. Diaphragmatic excursion measurement in emergency patients with acute dyspnea: toward a new diagnostic tool? Am J Emerg Med. 2016;34(8):1653–7. https://doi.org/10.1016/j.ajem.2016.05.055.
17. Boussuges A, Gole Y, Blanc P. Diaphragmatic motion studied by m-mode ultrasonography: methods, reproducibility, and normal values. Chest. 2009;135:391–400.
18. Kim WY, Suh HJ, Hong SB, et al. Diaphragm dysfunction assessed by ultrasonography: influence on weaning from mechanical ventilation. Crit Care Med. 2011;39:2627–30.
19. Güngör Ş, Doğan A. Diaphragm thickness by ultrasound in pediatric patients with primary malnutrition. Eur J Pediatr. 2023;182(7):3347–54.
20. Hart N, Tounian P, Clément A, et al. Nutritional status is an important predictor of diaphragm strength in young patients with cystic fibrosis. Am J Clin Nutr. 2004;80(5):1201–6.
21. You Y, Chen M, Chen X, Yu W. Diaphragm thickness on computed tomography for nutritional assessment and hospital stay prediction in critical COVID-19. Asia Pac J Clin Nutr. 2022;31(1):33–40.
22. Lewis MI, Bodine SC, Kamangar N, et al. Effect of severe short-term malnutrition on diaphragm muscle signal transduction pathways influencing protein turnover. J Appl Physiol 1985. 2006;100(6):1799–806.
23. Bando JM, Fournier M, Da X, et al. Effects of malnutrition with or without eicosapentaenoic acid on proteolytic pathways in diaphragm. Respir Physiol Neurobiol. 2012;180(1):14–24.
24. Lewis MI, Li H, Huang ZS, et al. Influence of varying degrees of malnutrition on IGF-I expression in the rat diaphragm. J Appl Physiol 1985. 2003;95(2):555–62.
25. Lewis MI, Da X, Li H, et al. Tumor necrosis factor-alpha and malnutrition-induced inhibition of diaphragm fiber growth in young rats. J Appl Physiol 1985. 2005;99(5):1649–57.
26. Soilemezi E, Savvidou S, Sotiriou P, et al. Tissue doppler imaging of the diaphragm in healthy subjects and critically Ill patients. Am J Respir Crit Care Med. 2020;202(7):1005–12.
27. Spiesshoefer J, Orwat S, Henke C, et al. Inspiratory muscle dysfunction and restrictive lung function impairment in congenital heart disease: association with immune inflammatory response and exercise intolerance. Int J Cardiol. 2020;1(318):45–51.
28. Chen Y, Liu Y, Han M, et al. Quantification of diaphragmatic dynamic dysfunction in septic patients by bedside ultrasound. Sci Rep. 2022;12(1):17336.
29. Bakaloudi DR, Siargkas A, Poulia KA, et al. The effect of exercise on nutritional status and body composition in hemodialysis: a systematic review. Nutrients. 2020;12(10):3071.
30. El-Koa AA, Eid HA, Abd Elrahman SR, et al. Value of incentive spirometry in routine management of COPD patients and its effect on diaphragmatic function. Egypt J Bronchol. 2023;17:8.
31. Aweto HA, Obikeh EO, Tella BA. Effects of incentive spirometry on cardiopulmonary parameters, functional capacity and glycemic control in patients with type 2 diabetes. Hong Kong Physiother J. 2020;40(2):121–32. https://doi.org/10.1142/S1013702520500110.
32. Ribeiro R, Brandão D, Noronha J, et al. Breath-stacking and incentive spirometry in Parkinson's disease: randomized crossover clinical trial. Respir Physiol Neurobiol. 2018;255:11–6. https://doi.org/10.1016/j.resp.2018.04.011.

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