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ORIGINAL PAPER

Relation between myostatin levels and malnutrition and muscle wasting in hemodialysis patients

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Summary *Background and aim: Malnutrition is one of the most troublesome comorbidities among hemodialysis patients (HD). Myostatin (MSTN) belongs to the transforming growth factor-β superfamily. In HD patients, MSTN effects are not limited to skeletal muscle growth. The present study aimed to assess MSTN levels in HD patients and its relation to various clinical and biochemical parameters.*

Patients and methods: The present case control study included 60 patients on HD for at least three years. In addition, there were age and sex-matched healthy subjects who constitutes the control group. Nutritional status was evaluated using the malnutrition inflammation score (MIS). Muscle wasting in the present study was evaluated using the lean tissue index (LTI) as assessed by the body composition monitor (BCM). Rectus Femoris Muscle (RFM) thickness was also measured as indicator for nutritional status of patient.

Results: The present study included 60 HD patients, and age- and sex-matched healthy controls. Patients expressed significantly higher myostatin levels when compared to controls [median (IQR): 221.3 (153.5-688.2) versus 144.8 (97.0-281.7), p < 0.001]. According to MIS, patients were classified into those with no/mild malnutrition (n = 22) and others with moderate/severe malnutrition (n = 38). Comparison between the two subgroups revealed that the former group had significantly lower myostatin levels [167.7 (150.3-236.3) versus 341.7 (160.9-955.9), p = 0.004]. According to LTI, patients were classified into those with muscle wasting (n = 23) and others without muscle wasting (n = 37). Comparative analysis showed that patients in the former group had significantly higher myostatin levels [775.1 (325.1-2133.7) versus 161.8 (142.6-302.3), p < 0.001].

Conclusions: Myostatin seems to be a promising marker for identification of malnutrition and muscle wasting in HD patients.

KEY WORDS: *Hemodialysis; Malnutrition; Muscle wasting; Myostatin.*

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INTRODUCTION

Malnutrition is one of the most troublesome comorbidities among hemodialysis patients (HD) (1). Factors responsible for malnutrition in HD patients include dialysis factors (e.g. low dialysis adequacy, low quality dialysis membranes and techniques) and dietary factors (e.g. poor appetite and low diet quality) (2). Poor nutritional status in HD patients was linked to cognitive impairment (3), cardiac dysfunction (4), hospitalization and mortality (5). Assessment of the nutritional status in HD patients is of paramount importance for the sake of better quality of life and clinical outcomes. However, there is a lack of consensus regarding the gold standard indicators (6). Fortunately, our understanding of the pathological mechanisms involved in malnutrition and muscle wasting in HD patients has markedly improved over years. One of the significant achievements in this context is identification of *myostatin* (MSTN)/activin system and its transcriptional system (7). MSTN, also known as *growth development factor-8* (GDF-8) was discovered in 1997. It belongs to the transforming growth factor-ß superfamily.

The present study aimed to assess MSTN levels in HD patients and its relation to various clinical and biochemical parameters.

PATIENTS AND METHODS

The present case control study was conducted at *Al-Azhar University Hospitals, Cairo, Egypt*. The Research Ethics Committee of the *Faculty of Medicine, Al-Azhar University* (FMG-IRB).

approved the study protocol and written informed consent was obtained from all participants before enrollment in line with Helsinki Declaration.

The study included 60 HD patients who were undergoing hemodialysis for at least rhree years through mature arteriovenous fistula that was fashioned by vascular team in vas-

cular department. Patients were excluded if they had other neurological, gastrointestinal or endocrinal conditions with direct effect on the nutritional status or if they have associated malignant tumors. A Control group was selected from hospital staff. They were age and sex-matched healthy subjects who constitutes the control group. All participants were submitted to sophisticated history taking, thorough clinical assessment and examination of *arterio-venous fistula* (AVF) and standard laboratory investigations. All participants were subjected to Ultrasound measurement of rectus femoris muscle thickness by a high frequency linear transducer (*L12-4 Linear Active Probe*) connected to an ultrasound machine (*Philips Affinity 30, by: Singha's medical system India private limited, New Delhi*). The ultrasound probe was placed perpendicular to the long axis of the thigh on its anterior surface. The obtained B-mode cross sectional image was adjusted to visualize the rectus femoris muscle, the subcutaneous tissues and the femur. After identifying the muscle tissue, the maximum muscle thickness of the rectus femoris muscle was obtained by scanning the muscle through its length until its insertion into the patella. Nutritional status was evaluated using the *malnutrition inflammation score* (MIS) (8). Recent studies proved that MIS assessment in HD patients is well correlated with biochemical parameters (9) and showed better performance (10) and prognostic value (11).

Patients were divided into two groups according to their MIS values as mild (MIS < 6) and moderate/severe malnutrition (MIS ≥ 6). Muscle wasting in the present study was evaluated using the *lean tissue index* (LTI) as assessed by the *body composition monitor* (BCM). LTI was considered a reliable indicator of skeletal muscle mass (12). In HD patients, low LTI was related to poor prognosis (13). Patients with LTI < 10.0% of the normal reference range were considered to have muscle wasting (14). Kt/v was calculated by dialysis machine, and we take the results from the machines screen.

Control patients had controls had only measurement of myostatin.

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). Numerical variables were compared using t test or Mann-Whitney U t test, as appropriate while categorical variables were compared using chi-square test. Spearman's correlation coefficient was used to correlate numerical variables. Binary logistic regression analysis was used to identify predictors of the study outcomes. All statistical procedures were accomplished using SPSS (*Version 27, IBM Corporation, IL, USA*).

Results

The present study included 60 HD patients and age- and sex-matched healthy controls. Patients expressed signifi-

		Malnutrition		
	All patients n = 60	**No/mild n = 22**	**Moderate/severe n = 38**	**p value**
Age (years) mean ± SD	54.0 ± 7.9	49.5 ± 6.9	56.5 ± 7.4	0.001
Male/female n	29/31	13/9	16/22	0.21
BMI	24.4 ± 3.4	24.6 ± 2.9	24.3 ± 3.7	0.056
Comorbidities n (%)				
DM	23 (38.3)	9 (40.9)	14 (36.8)	0.76
HTN	31 (51.7)	13 (59.1)	18 (47.4)	0.38
IHD	17 (28.3)	7 (31.8)	10 (26.3)	0.65
COPD	11 (18.3)	4 (18.2)	7 (18.4)	0.98
HCV	9 (15.0)	3 (13.6)	6 (15.8)	0.82
HD duration (months)	47.0 (28.0-76.0)	45.5 (28.8-67.5)	49.5 (21.0-79.8)	0.84
Kt/V	1.3 ± 0.1	1.4 ± 0.1	1.3 ± 0.1	0.003
Laboratory findings mean ± SD/median (IQR)				
Hb (gm/dL)	9.8 ± 1.3	10.4 ± 0.3	9.5 ± 1.6	< 0.001
WBCs	5.4 ± 2.0	4.7 ± 1.8	5.9 ± 2.0	0.009
Platelets	188.0 ± 61.9	167.1 ± 63.1	200.3 ± 58.6	0.015
Creatinine (mg/dL)	8.2 ± 2.4	7.9 ± 2.0	8.4 ± 2.6	0.4
Urea (mg/dL)	110.0 ± 32.3	97.6 ± 30.1	117.1 ± 31.7	0.047
FBS (mg/dL)	119.6 ± 46.0	117.2 ± 44.2	120.9 ± 47.5	0.54
Albumin (gm/dL)	4.0 ± 0.4	4.2 ± 0.2	3.8 ± 0.4	< 0.001
Cholesterol (mg/dL)	158.4 ± 44.0	146.3 ± 34.6	165.5 ± 47.6	0.13
Triglycerides (mg/dL)	172.3 ± 114.5	131.8 ± 42.7	195.7 ± 135.4	0.026
Calcium (mg/dL)	8.9 ± 0.8	8.7 ± 0.8	8.9 ± 0.8	0.41
Phosphorus (mg/dL)	4.5 ± 1.5	4.2 ± 1.5	4.6 ± 1.4	0.51
Sodium	138.9 ± 4.8	140.1 ± 5.4	138.1 ± 4.3	0.017
Potassium	4.9 ± 0.6	4.8 ± 0.6	5.0 ± 0.6	0.033
PTH (pg/mL)	407.5 (191.8-895.0)	512.5 (233.0-897.8)	407.5 (187.0-897.8)	0.78
Uric acid (mg/dL)	5.8 ± 1.4	5.6 ± 1.7	5.9 ± 1.3	0.56
Ferritin (ng/mL)	829.4 (752.4-1689.0)	789.0 (370.8-1689.0)	1408.5 (752.4-1726.3)	0.21
hsCRP (mg/L)	111.2 (88.2-121.5)	89.5 (68.6-111.5)	113.9 (100.9-124.0)	< 0.001
Myostatin	221.3 (153.5-688.2)	167.7 (150.3-236.3)	341.7 (160.9-955.9)	0.004

Table 1.
Association between PPLA score and risk factors for kidney stones or stone recurrence.

	+ve n = 23	-ve n = 37	p value
Age (years) mean ± SD	58.3 ± 5.2	51.2 ± 8.2	< 0.001
Male/female n	9/14	20/17	0.26
BMI	23.5 ± 3.5	25.5 ± 0.7	0.12
Comorbidities n (%)			
DM	12 (52.2)	11 (29.7)	0.082
HTN	13 (56.5)	18 (48.7)	0.55
IHD	7 (30.4)	10 (27.0)	0.78
COPD	5 (21.7)	6 (16.2)	0.59
HCV	4 (17.4)	9 (24.3)	0.53
HD duration (months)	71.0 (42.0-101.0)	42.0 (24.0-57.0)	0.005
Kt/V	1.24 ± 0.12	1.37 ± 0.11	< 0.001
Laboratory findings mean ± SD/median (IQR)			
Hb (gm/dL)	8.7 ± 0.7	10.5 ± 1.2	< 0.001
WBCs	6.5 ± 1.8	4.8 ± 1.9	< 0.001
Platelets	220.3 ± 46.2	168.1 ± 62.2	< 0.001
Creatinine (mg/dL)	8.0 ± 1.7	8.3 ± 2.8	0.58
Urea (mg/dL)	120.7 ± 30.3	103.3 ± 32.1	0.041
FBS	124.3 ± 51.1	116.6 ± 42.9	0.53
Albumin (gm/dL)	3.7 ± 0.4	4.2 ± 0.3	<0.001
Cholesterol	177.9 ± 51.6	146.3 ± 33.9	0.006
Triglycerides	226.9 ± 158.5	138.4 ± 55.2	0.016
Calcium (mg/dL)	9.0 ± 0.8	8.8 ± 0.9	0.32
Phosphorus (mg/dL)	4.8 ± 1.5	4.3 ± 1.5	0.24
Sodium	137.1 ± 3.6	139.9 ± 5.1	0.026
Potassium	5.1 ± 0.5	4.8 ± 0.6	0.11
PTH (pg/mL)	338.0 (187.0-895.0)	420.0 (262.0-900.5)	0.84
Uric acid (mg/dL)	5.9 ± 0.9	5.7 ± 1.7	0.61
Ferritin (ng/mL)	825.5 (807.0-1603.0)	833.2 (531.6-1689.0)	0.41
hsCRP (mg/L)	113.6 (109.1-121.9)	100.6 (71.5-131.5)	< 0.001
Myostatin	775.1 (325.1-2133.7)	161.8 (142.6-302.3)	< 0.001

Table 2.
Comparison between hemodialysis patients with and without muscle wasting regarding clinical and laboratory findings.

cantly higher myostatin levels when compared to controls [median (IQR): 221.3 (153.5-688.2) *versus* 144.8 (97.0-281.7), p < 0.001]. According to MIS, patients were classified into those with no/mild malnutrition (n = 22) and others with moderate/severe malnutrition (n = 38).

Comparison between both subgroups revealed that subjects in the former group were significantly younger (49.5 ± 6.9 years *versus* 56.5 ± 7.4, p = 0.001) with higher Kt/V (1.4 ± 0.1 *versus* 1.3 ± 0.1, p = 0.003), higher hemoglobin levels (10.4 ± 0.3 gm/dl *versus* 9.5 ± 1.6, p < 0.001), higher albumin levels (4.2 ± 0.2 gm/dl *versus* 3.8 ± 0.4), lower triglycerides levels (131.8 ± 42.7 mg/dL *versus* 195.7 ± 135.4, p = 0.026), lower hsCRP [89.5 (68.6-111.5) mg/dL *versus* 113.9 (100.9-124.0), p < 0.001] and lower myostatin levels [167.7 (150.3-236.3) *versus* 341.7 (160.9-955.9), p = 0.004] (Table 1). According to LTI, patients were classified into those with muscle wasting (n = 23) and others without muscle wasting (n = 37). Comparative analysis showed that patients in the former group are significantly older (58.3 ± 5.2 years *versus* 51.2 ± 8.2, p < 0.001) with longer HD duration [71.0 (42.0-101.0) months *versus* 42.0 (24.0-57.0), p = 0.005], lower Kt/V (1.24 ± 0.12 *versus* 1.37 ± 0.11, p < 0.001), lower hemoglobin (8.7 ± 0.7 gm/dL *versus* 10.5 ± 1.2, p < 0.001), lower albumin (3.7 ± 0.4 gm/dL *versus* 4.2 ± 0.3, p < 0.001), higher cholesterol (177.9 ± 51.6 mg/dL versus 146.3 ± 33.9, p = 0.006) and higher triglycerides (226.9 ± 158.5 mg/dL *versus* 138.4 ± 55.2, p = 0.016). They also showed significantly lower RFM thickness (0.8 +/_ 0.2 *versus* 1.4 +/- 0.3 cm p 0.001). and significantly higher hsCRP [113.6 (109.1-121.9) mg/dL *versus* 100.6 (71.5-131.5), p < 0.001] and myostatin 775.1 (325.1-2133.7) *versus* 161.8 (142.6-302.3), p < 0.001] levels (Table 2). Comparison between patients with low (< median) and high (≥ median) myostatin levels identified that patients with high myostatin levels were significantly older (57.6 ± 6.4 years *versus* 50.3 ± 7.8, p < 0.001) with lower albumin levels (3.8 ± 0.4 *versus* 4.1 ± 0.3 gm/dL, p = 0.003) and higher hsCRP levels [113.7 (101.8-122.6) mg/dL *versus* 101.3 (72.0-116.2), p = 0.005] (Table 3). Correlation analysis recognized significant

	Myostatin levels		
	Low n = 30	High n = 30	p value
Age (years) mean ± SD	50.3 ± 7.8	57.6 ± 6.4	< 0.001
Male/female n	12/18	17/13	0.2
BMI	23.9 ± 3.0	25.0 ± 3.8	0.22
Comorbidities n (%)			
DM	10 (33.3)	13 (43.3)	0.43
HTN	18 (60.0)	13 (43.3)	0.2
IHD	9 (30.0)	8 (26.7)	0.77
COPD	7 (23.3)	4 (13.3)	0.32
HCV	6 (20.0)	3 (10.0)	0.28
HD duration (months)			
Kt/V	1.34 ± 0.13	1.3 ± 0.14	0.28
Laboratory findings mean ± SD/median (IQR)			
Hb (gm/dL)	10.1 ± 1.3	9.5 ± 1.3	0.059
WBCs	5.2 ± 2.0	5.7 ± 2.0	0.32
Platelets	182.1 ± 60.5	194.1 ± 63.7	0.46
Creatinine (mg/dL)	8.3 ± 2.1	8.1 ± 2.7	0.87
Urea (mg/dL)	110.1 ± 29.5	109.8 ± 35.4	0.97
FBS	126.8 ± 52.0	112.4 ± 38.5	0.23
Albumin (gm/dL)	4.1 ± 0.3	3.8 ± 0.4	0.003
Cholesterol	155.4 ± 40.2	161.5 ± 47.9	0.59
Triglycerides	137.1 ± 55.2	207.5 ± 145.1	0.018
Calcium (mg/dL)	8.8 ± 0.9	8.9 ± 0.8	0.59
Phosphorus (mg/dL)	4.4 ± 1.5	4.6 ± 1.4	0.51
Sodium	138.7 ± 4.8	139.0 ± 4.8	0.79
Potassium	5.0 ± 0.7	4.9 ± 0.5	0.58
PTH (pg/mL)	311.5 (195.3-897.8)	687.0 (187.0-906.3)	0.32
Uric acid (mg/dL)	5.7 ± 1.4	5.9 ± 1.5	0.66
Ferritin (ng/mL)	1374.0 (370.8-1835.8)	825.5 (752.4-1689.0)	0.75
hsCRP (mg/L)	101.3 (72.0-116.2)	113.7 (101.8-122.6)	0.005

Table 3.
Comparison between hemodialysis patients with low and high myostatin levels regarding clinical and laboratory findings.

Table 4.
Correlation between myostatin levels and clinical and laboratory findings in the studied patients.

	Myostatin levels	
	r	p
Age	0.47	<0.001
BMI	0.16	0.22
HD duration	-0.03	0.85
Kt/V	-0.21	0.11
Hb	-0.29	0.027
WBCs	0.17	0.19
Platelets	0.22	0.09
Creatinine	0.13	0.3
Urea	0.08	0.52
FBS	-0.22	0.098
Albumin	-0.37	0.004
Cholesterol	0.14	0.29
Triglycerides	0.26	0.041
Calcium	-0.06	0.66
Phosphorus	0.24	0.031
Sodium	-0.07	0.58
Potassium	-0.03	0.83
PTH	0.24	0.06
Uric acid	0.18	0.17
Ferritin	-0.03	0.84
hsCRP	0.38	0.003

K = clearance of a solute (ml/min).
t = time (min. or hr.).
v = volume of distribution of a solute (ml or liter).

linear correlation between myostatin levels and age (r = 0.47, p < 0.001), hemoglobin (r = -0.29, p = 0.027) albumin (r = -0.37, p = 0.004) and hsCRP (r = 0.38, p = 0.003) (Table 4). ROC curve analysis showed good performance of myostatin levels in identification of moderate/severe malnutrition [AUC (95%CI): 0.72 (0.6-0.85)] (Figure 1) and muscle wasting [AUC (95% CI: 0.83 (0.72-0.94)] (Figure 2).

Figure 1.
Performance of myostatin levels in identification of moderate/severe malnutrition.

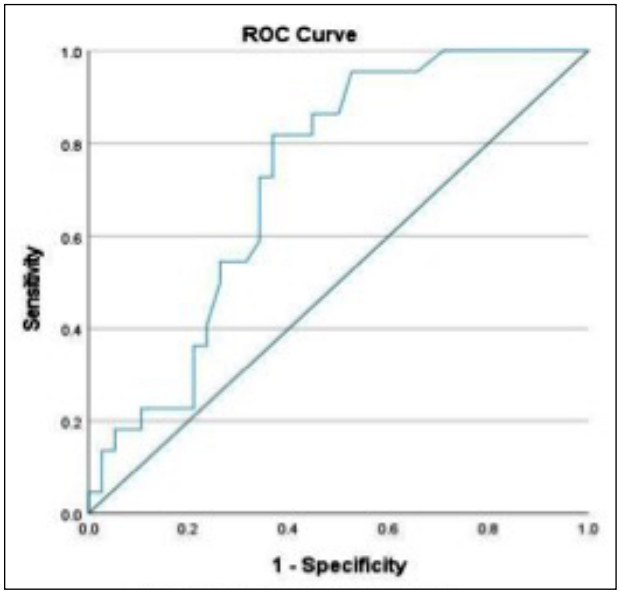
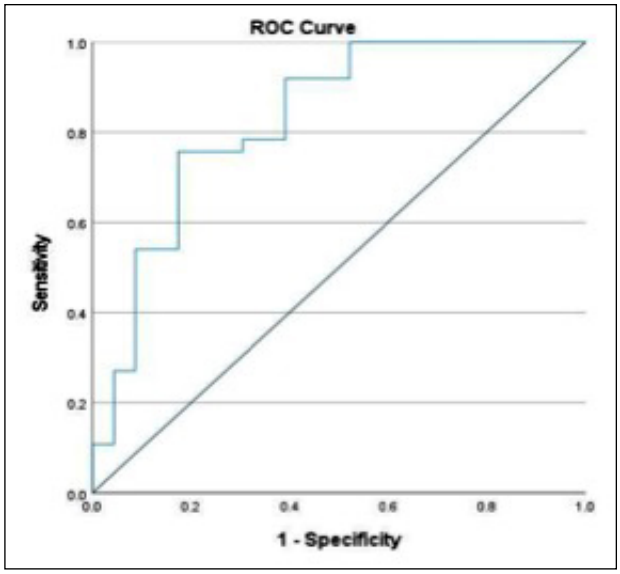


Figure 2.
Performance of myostatin levels in identification of muscle wasting.



Discussion

Patients suffering from *chronic kidney disease* (CKD), mainly those undergoing *hemodialysis* (HD), often present malnutrition and muscle wasting, which directly correlate with morbidity and mortality (15).

In CKD patients, an up-regulation of Myostatin gene expression in skeletal muscle has been found, which was related to IL-6 expression, suggesting a link between MSTN and microinflammation (16). Moreover, it has also been recently described that uremic toxins may accelerate muscle atrophy, by inducing Myostatin expression (17). Myostatin is secreted by the skeletal myocytes into the bloodstream to act back on the secretory cells limiting their proliferation (18). Its actions on the muscular system are mediated through activation of the ubiquitin-proteasome system resulting in inhibition of satellite muscle cell proliferation and differentiation with induction of proteolytic muscle cells (19).

In HD patients, MSTN effects are not limited to skeletal muscle growth. They are also linked to insulin resistance, inflammation and cardiovascular morbidity (20). However, studies assessing MSTN in HD patients are scarce and their results are inconsistent, with some studies (21) showing that patients have MSTN levels comparable to healthy controls and others reporting higher levels of MSTN in the studied patients (22). The present study detected significantly higher myostatin levels in patients under maintenance HD as compared to healthy controls. In addition, we noted higher myostatin expression in HD patients with moderate/severe malnutrition in contrast to their counterparts with no/mild malnutrition. Moreover, those with muscle wasting showed significantly higher myostatin levels in contradiction to their peers without muscle wasting. Our conclusions are supported by previous studies.

The study of *Koyun et al.* (23), also noted significantly higher myostatin levels in HD patients as compared to controls. In addition, the study of *Delanaye et al.* (24),

reported significant association between muscle mass and myostatin levels. They also noted a significant association between myostatin levels and mortality. The present study also identified a significant correlation between myostatin levels and patients age in accordance with the study of *Han et al*. (25). Likewise, the study of *Yasar et al*. (26), on renal transplantation, hemodialysis and peritoneal dialysis patients showed that myostatin levels were highest in HD patients. Furthermore, they revealed that myostatin was negatively correlated with handgrip strength (HGS, albumin, estimated glomerular filtration rate, and Kt/V. However, myostatin had no correlation with inflammatory markers or appendicular skeletal muscle index. Moreover, the study of *Bataille et al*. (27), found that myostatin together with activin were increased in patients with CKD without increased production attributing this increase to the impaired renal clearance. Similar conclusions were also reported by the study of *Widajanti et al.* (28), on elderly HD patients. In contrast to our findings, the study of *Lee et al*. (29), concluded that lower myostatin levels were associated with lower muscle mass. In addition, *Esposito et al.* (21), found no significant differences between HD patients and healthy controls regarding myostatin levels. They also recognized a positive correlation between myostatin levels and patients' age and muscle mass.

Conclusions

The results of the present study suggest that myostatin may be a promising marker for identification of malnutrition and muscle wasting in hemodialysis patients. It shows significant association with poor hemodialysis adequacy, anemia and inflammatory marker.

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