The Egyptian Journal of Hospital Medicine (January 2023) Vol. 90, Page 194-199

# Study of the Relationship between Insulin-Like Growth Factor 1, Myostatin and Muscle Status in a sample of Egyptian Patients on Hemodialysis

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## ABSTRACT

**Background:** Sarcopenia is a common occurrence in people receiving hemodialysis. For hemodialysis patients, early sarcopenia identification is essential since it can be treated with nutritional strategies and exercise. Measurement of muscle mass and strength requires specialised equipment and takes time. Biomarkers are required to assist sarcopenia screening and follow-up. Serum creatinine (SCr), which is impacted by residual renal function and the type of dialysis being used, has been found to be the best biomarker too far for measuring muscle function in hemodialysis patients. In the general population, new biomarkers relating to muscle function have appeared. The aim of the current study is to evaluate the ability of insulin-like growth factor 1(IGF-1) and myostatin to assess muscle status in hemodialysis patients.
**Patients and Methods:** A case control study was conducted on 30 apparently healthy individuals as a control group (Group A) and 30 Egyptian patients on hemodialysis (HD) with muscle wasting Group (B) recruited from Ain Shams University Hospital.
**Results:** On comparing the studied groups, there were significant differences in the characteristics and parameters between the HD patients and healthy control subjects reflect the sarcopenia and malnutrition status in our HD patients. IGF-1 levels were found to be negatively correlated with sarcopenia status in HD patients according to correlation analyses (p 0.05). On the other hand, in HD patients, myostatin levels were p/ositively correlated with the presence of sarcopenia (all p 0.05). **Conclusion:** Our findings showed that in individuals undergoing HD, IGF-1 and myostatin levels linked with the presence of sarcopenia. To verify these findings, however, additional research is required.
**Keywords:** Insulin-Like Growth Factor 1, Myostatin and muscle status, Hemodialysis.

## INTRODUCTION

Sarcopenia is a common sign in patients with chronic kidney disease (CKD), particularly those receiving hemodialysis (HD) for end-stage renal disease [(1)]. Muscle mass, strength, and function loss is a chronic condition that raises the risk of cardiovascular disease, morbidity, and mortality. It also encourages sedentary behavior and a lower quality of life [(2)].

Sarcopenia may result from a number of reasons, such as an anabolic/catabolic imbalance. IGF-1 is a hormone that promotes growth, differentiation, and maintenance of skeletal muscle [(3)].

The transforming growth factor (TGF) superfamily member myostatin, which acts as a catabolic factor and a negative regulator of muscle growth, is the alternative [(4)]. Myostatin levels were shown to be elevated and inversely linked with muscle atrophy in chronic illnesses [(5)]. IGF1 levels were discovered to be lower, which caused a decline in muscle protein synthesis and concomitant muscle protein breakdown, aggravating catabolic disorders such end-stage chronic renal disease [(6)].

The aim of the current study was to evaluate the relationship between Insulin-Like Growth Factor 1 and myostatin and Muscle status (strength and mass) in a sample of Egyptian patients on Hemodialysis.

## PATIENTS AND METHODS

A case control study that was conducted on 60 subjects divided into 2 groups matched for age and sex**:**

**Group A (Control)** that included 30 apparently healthy individuals.

**Group B (Patients)** that included 30 patients on hemodialysis (3 sessions per week) having muscle wasting recruited from the Hemodialysis unit at Ain Shams university Hospitals throughout six months.

**Inclusion Criteria:** Adult (>18 years), both sex (male and female) and patients with maintained HD for at least 6 months.

**Exclusion Criteria:** Patients with acute diseases, such as infections or immunological disorders, patients with history of primary muscle diseases and patients with history of cerebrovascular stroke.

**Study Procedures:**

**All patients in this study were subjected to the following:**

1. **Full medical history taking** including (age, dialysis vintage (the duration since the first day of dialysis), body mass index (weight and height).
2. **Full clinical examination** (pulse, blood pressure and muscle status tests as below)**.**
3. **Laboratory parameters including:** (A) Complete blood count, kidney function test (Urea and Creatinine), serum sodium, potassium, phosphate, Calcium and albumin were taken from the patients' medical records. (B) Myostatin levels and IGF-1 levels were measured using the Rayto tool with Enzyme-linked Immunosorbent Assay (ELISA) method before HD (USA).



Received: 12/07/2022
Accepted: 15/09/2022

4. **Malntition and sarcopenia parameters:**
   a. **Malnutrition-Inflammation Score (MIS)** was employed to evaluate the state of the diet. Ten factors are included in it: altered end-dialysis dry weight, nutritional intake, co-morbidities, functional ability, gastrointestinal symptoms, BMI, loss of subcutaneous fat, decreased fat storage or/and evidence of sarcopenia (as determined by SGA), serum albumin, and total iron-binding capacity. Each item has four severity levels, ranging from 0 (normal) to 3. (severely abnormal). As a result, the MIS score can be between 0 and 30, with a higher value indicating more severe malnutrition and inflammation. A rating of 5 or higher denotes malnutrition [(7)].
   b. **Muscle function tests:** Before the HD session began, two trained assessors conducted all functional evaluations in a quiet setting while adhering to a predetermined protocol. These evaluations included the dynamometer handgrip strength (HGS), the 6 minute walking test (6MWT), and the Fatigue Severity Scale (FSS).
      - Using a Jamar hand dynamometer, the HGS was assessed on the non-fistula arm, taking into account the greatest HGS value after three trials (with a one-minute break in between trials) [(8)].
      - 6MWT was carried out in accordance with the recommendations of the American Thoracic Society. Under medical supervision, the respondents were instructed to walk for 6 minutes at their usual daily speed down a 30-meter corridor. The total distance covered during the test was recorded in m, with a 1 m accuracy [(9)].
      - The FSS, a 9-item self-report questionnaire with a 1–7 scale, was used to evaluate muscular tiredness. A score more than 36 was deemed abnormal and should be included. The total score ranged from 9 to 63 [(10)].

**Ethical consent:**

**An approval of the study was obtained from Ain Shams University Academic and Ethical Committee. Written informed consent of all the participants was obtained. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.**

***Statistical Analysis***

Data collected and encoded using Microsoft Excel software. Data were then imported into Statistical Package for Social Sciences (SPSS version 20.0) software for analysis. According to the type of data, qualitative represented as numbers and percentages, while quantitative data represented by mean and SD. Chi-square test ($\chi 2$) and Fisher's exact test to calculate difference between two or more groups of qualitative variables. Independent samples t-test was used to compare between two independent groups of normally distributed variables. Pearson correlation analysis was utilized. For the ordinal variables, the Spearman correlation analysis was used. Binary logistic regression and multiple linear regressions were used to examine the interactions between numerous components. P-value was set at $\leq 0.05$ for significant results.

**RESULTS**

*Group B* (HD patients) had significantly lower weight and BMI (P-value <0.001*) but higher systolic blood pressure (P-value =0.01*) than *Group A* (healthy controls) (**Table 1**).

**Table (1): Comparison between Group A (no. =30) and Group B (no. =30) regarding demographic data.**

| Variable | | Group A (healthy controls) | Group B (HD patients) | t-test | P-value |
|---|---|---|---|---|---|
| Age (yrs) | Range<br>Mean ±SD | 22 – 75<br>58.4 ± 12.689 | 20 – 76<br>55.333 ± 14.93 | 0.857 | 0.395 |
| Weight (Kg) | Range<br>Mean ±SD | 53.32 – 88.62<br>75.971 ± 9.017 | 43.49 – 80.24<br>61.81 ± 8.759 | 6.17 | <0.001* |
| Height (m) | Range<br>Mean ±SD | 1.5 – 1.79<br>1.684 ± 0.064 | 1.55 – 1.8<br>1.686 ± 0.067 | -0.138 | 0.89 |
| BMI (kg/m2) | Range<br>Mean ±SD | 21.1 – 31.4<br>26.847 ± 3.374 | 18.1 – 26.5<br>21.463 ± 2.555 | 6.967 | <0.001* |
| SBP (mm/Hg) | Mean ±SD | 123.333 ± 8.339 | 133 ± 18.364 | -2.625 | 0.011* |
| DBP (mm/Hg) | Mean ±SD | 78.167 ± 5.49 | 78.667 ± 10.25 | -0.236 | 0.815 |
| Pulse (min) | Mean ±SD | 77.467 ± 7.633 | 77.633 ± 10.5 | -0.07 | 0.944 |

Group B (HD patients) had significantly lower Hb, Ca and IGF1 (**P-value** <0.001*) but significantly higher PO4, S.Creat, urea and myostatin **(P-value** <0.001*) than Group A (healthy controls) (**Table 2**).

**Table (2): Comparison between Group A (no. =30) and Group B (no. =30) regarding Laboratory data.**

| Laboratory investigations | | Group | | t-Test | |
|---|---|---|---|---|---|
| | | **Group A** (healthy controls) | **Group B** (HD patients) | **T** | **P-value** |
| Hemoglobin (g/dL) | Mean ± SD | 12.303 ± 0.701 | 10.007 ± 1.206 | 9.02 | <0.001* |
| Calcium (mg/dL) | Mean ± SD | 9.773 ± 0.61 | 8.627 ± 0.694 | 6.797 | <0.001* |
| Phosphorus (mg/dL) | Mean ± SD | 3.9 ± 0.288 | 5.18 ± 0.511 | -11.958 | <0.001* |
| Na (mEq/l) | Mean ± SD | 134.667 ± 2.294 | 135.433 ± 2.909 | -1.133 | 0.262 |
| K (mEq/L) | Mean ± SD | 4.307 ± 0.463 | 4.2 ± 0.492 | 0.865 | 0.391 |
| Serum Albumin (g/dL) | Mean ± SD | 3.737 ± 0.378 | 3.67 ± 0.399 | 0.664 | 0.509 |
| Serum creatinine (mg/dL) | Mean ± SD | 1.032 ± 0.268 | 9.059 ± 2.238 | -19.507 | <0.001* |
| Serum urea (mg/dL) | Mean ± SD | 24.477 ± 5.472 | 124.803 ± 0.219 | -17.352 | <0.001* |
| Myostatin (pg/mL) | Mean ± SD | 1247.53 ± 86.87 | 770.00 ± 83.71 | -10.476 | <0.001* |
| IGF-1 (mg/L) | Mean ± SD | 370.933 ± 9.772 | 137.6 ± 9.528 | 9.892 | <0.001* |

Group B (HD patients) had significantly lower HGS and 6MWT (**P-value** <0.001*), but significantly higher MIS and FSC **(P-value** <0.001*) than Group A (healthy controls) (**Table 3**).

**Table (3): Comparison between Group A (no. =30) and Group B (no. =30) regarding Malnutrition and sarcopenia parameters.**

| Malnutrition and sarcopenia parameters | | Group | | T-Test | |
|---|---|---|---|---|---|
| | | **Group A** (healthy controls) | **Group B** | **T** | **P-value** |
| Malnutrition-Inflammation Score | Range<br>Mean ± SD | 0 – 18<br>9.3 ± 2.231 | 10 – 30<br>20.3 ± 4.911 | -7.506 | <0.001* |
| Handgrip strength | Range<br>Mean ± SD | 18 – 44<br>31.1 ± 7.321 | 13 – 31<br>20.5 ± 5.101 | 5.96 | <0.001* |
| 6 min walking test | Range<br>Mean ± SD | 504 – 667<br>574.533 ± 40.852 | 427 – 574<br>504.8 ± 40.318 | 6.654 | <0.001* |
| Fatigue Severity Scale | Range<br>Mean ± SD | 9 – 42<br>24 ± 5.562 | 33 – 59<br>45.6 ± 8.177 | -8.964 | <0.001* |

Myostatin was negatively correlated with IGF-1 P-value<0.001*, BMI P-value 0.799 Serum Albumin P-value 0.021* and HGS P-value 0.572. Myostatin was positively correlated with age, dialysis vintage, MIS and FSS (P-value<0.001* in all) (**Table 4**).

**Table (4): Myostatin Correlation with other variables.**

| Group B | Myostatin (pg/mL) | |
|---|---|---|
| | **r** | **P-value** |
| IGF-1 (mg/L) | **-0.957** | **<0.001*** |
| Age(yrs) | **0.822** | **<0.001*** |
| Weight (Kg) | 0.084 | 0.661 |
| Height (m) | 0.055 | 0.771 |
| BMI(kg/m2) | -0.049 | 0.799 |
| Dialysis vintage (Years) | **0.598** | **<0.001*** |
| Calcium (mg/dL) | 0.303 | 0.104 |
| Phosphorus (mg/dL) | **0.437** | **0.016*** |
| Na (mEq/l) | -0.153 | 0.420 |
| K (mEq/L) | **-0.406** | **0.026*** |
| Serum Albumin (g/dL) | **-0.419** | **0.021*** |
| Serum creatinine (mg/dL) | **0.363** | **0.048*** |
| Serum urea (mg/dL) | 0.111 | 0.561 |
| Malnutrition-Inflammation Score | **0.554** | **0.001*** |
| Handgrip strength | -0.107 | 0.572 |
| 6 min walking test | 0.036 | 0.849 |
| Fatigue Severity Scale | **0.604** | **<0.001*** |

Myostatin levels showed negative significant correlation with IGF1 levels (**Table 5**).

**Table (5): Multivariate Regression analysis between Myostatin and other variables.**

| Group B | Unstandardized Coefficients | | Standardized Coefficients | t-test | P-value |
|---|---|---|---|---|---|
| | B | Std. Error | Beta | | |
| IGF-1 (mg/L) | -16.380 | 1.916 | -0.768 | -8.550 | <0.001* |
| Age (years) | 10.306 | 3.063 | 0.244 | 3.365 | 0.003* |
| Dialysis vintage (Years) | 14.947 | 7.132 | 0.118 | 2.096 | 0.049* |
| Phosphorus (mg/dL) | 28.846 | 58.573 | 0.023 | 0.492 | 0.628 |
| K (mEq/L) | 78.315 | 66.548 | 0.061 | 1.177 | 0.253 |
| Serum Albumin (g/dL) | -39.003 | 77.969 | -0.025 | -0.500 | 0.622 |
| Serum creatinine (mg/dL) | 13.042 | 14.377 | 0.046 | 0.907 | 0.375 |
| Malnutrition-Inflammation Score | -6.732 | 6.219 | -0.064 | -1.083 | 0.292 |
| Fatigue Severity Scale | -2.265 | 4.528 | -0.029 | -0.500 | 0.622 |
| **Dependent Variable: Myostatin (pg/mL)** | | | | | |

IGF1 showed negative correlation with myostatin, age, serum creatinine, dialysis vintage, MIS and FSS (**all p <0.001**), 6MWT (**p = 0.8**) and positive correlation with albumin (**p <0.001**) and HGS (**p = 0.7**) (**Table 6**).

**Table (6): Correlation between IGF-1 and other parameters.**

| Group B | IGF-1 (mg/L) | |
|---|---|---|
| | r | P-value |
| Myostatin (pg/mL) | **-0.957** | **<0.001*** |
| Age(years) | **-0.721** | **<0.001*** |
| BMI(kg/m2) | 0.068 | 0.721 |
| Dialysis vintage (Years) | **-0.498** | **0.005*** |
| Calcium (mg/dL) | -0.292 | 0.117 |
| Phosphorus (mg/dL) | **-0.405** | **0.027*** |
| Na (mEq/l) | 0.175 | 0.356 |
| K (mEq/L) | **0.526** | **0.003*** |
| Serum Albumin (g/dL) | **0.404** | **0.027*** |
| Serum creatinine (mg/dL) | **-0.410** | **0.024*** |
| Malnutrition-Inflammation Score | **-0.524** | **0.003*** |
| Handgrip strength | 0.066 | 0.727 |
| 6 min walking test | -0.047 | 0.806 |
| Fatigue Severity Scale | **-0.646** | **<0.001*** |

IGF1 levels showed highly significant negative correlation with myostatin (**Table 7**).

**Table (7): Multivariate regression analysis between IGF-1 levels and other variables.**

| Group B | Unstandardized Coefficients | | Standardized Coefficients | t-test | P-value |
|---|---|---|---|---|---|
| | B | Std. Error | Beta | | |
| Myostatin (pg/mL) | -0.048 | 0.006 | -0.822 | -8.550 | <0.001* |
| Age(years) | 0.295 | 0.197 | 0.109 | 1.502 | 0.149 |
| Dialysis vintage (Years) | 0.613 | 0.403 | 0.103 | 1.518 | 0.145 |
| Serum Albumin (g/dL) | 0.036 | 4.244 | 0.000 | 0.008 | 0.993 |
| Serum creatinine (mg/dL) | -0.008 | 0.794 | -0.001 | -0.010 | 0.992 |
| Malnutrition-Inflammation Score | -0.284 | 0.340 | -0.057 | -0.835 | 0.414 |
| Fatigue Severity Scale | -0.254 | 0.240 | -0.070 | -1.058 | 0.303 |
| **Dependent Variable: IGF-F-1 (mg/L)** | | | | | |

## DISCUSSION

Patients with end-stage renal disease (ESRD) can benefit from hemodialysis, a life-saving replacement therapy. Although HD can help patients with ESRD maintain and even improve their quality of life, it also raises the risk of serious complications such as cardiovascular disease, a tendency to bleed easily, renal osteodystrophy, gonadal dysfunction, protein malnutrition, insulin resistance, immunodeficiency, anemia, and muscle wasting [(11)].

Despite tremendous advances in the treatment of HD-related comorbidities, muscle atrophy remains a prominent concern. Muscle wasting is defined as accidental body weight loss that can be separated into loss of lean body mass and loss of fat mass. It has been found as a common and critical concern with CKD. It affects patient mortality rates, daily activities, quality of life, immunity function, and the amount of hospital days spent [(12)].

Previous research has revealed that HD patients with a large body mass had a better chance of survival, and persons on maintenance HD had more severe muscle wasting than CKD patients prior to dialysis. As a result, early detection and treatment of muscle wasting are critical for CKD patients to enhance their quality of life and prognosis [(13)].

Serum creatinine (SCr), which is modified by residual renal function and dialysis type, is currently the best biomarker for evaluating muscular function in hemodialysis patients. In the general population, there are novel biomarkers for muscle function [(14)].

Myostatin (Mstn), a member of the Transforming Growth Factor (TGF) class, is predominantly expressed in skeletal muscle cells but is also found in macrophages, arteries, and cardiomyocytes. Several studies have demonstrated that Myostatin is more commonly expressed in atrophic muscle and chronic diseases, and that it limits protein synthesis and muscular development in skeletal muscle. These inhibitory effects have been studied in both laboratory and clinical settings[(15)].

Insulin-like growth factor 1 (IGF-1) is a hormone with a chemical structure similar to insulin. It is vital for childhood growth, and it also has anabolic effects on adults. It stimulates the Akt/mTOR pathway, which in turn causes protein synthesis and muscle creation. On the other hand, myostatin and activin A are both obstructing the akt/mTOR pathway [(15)].

This study was a case control study conducted on 30 apparently healthy individuals as a control group and 30 patients on hemodialysis with muscle wasting attending hemodialysis unit at Ain Shams University Hospital to study the relationship between insulin like growth factor-1, Myostatin and muscle status in a sample of Egyptian patients on hemodialysis.

On comparing the studied groups; *Group B* (HD patients with muscle wasting) showed significantly lower weight and BMI; (61.81 ± 8.76 VS 75.971 ± 9.017) kg and (21.463 ± 2.55 VS 26.847 ± 3.374) respectively, significantly lower HGS and 6MWT; (20.5 ± 5.309 VS 31.1 ± 8.168) and (504.8 ± 40.318 VS 574.533 ± 40.852) respectively and significantly higher MIS and FSS; (20.3 ± 5.943 VS 9.3 ± 5.396) and (45.6 ± 8.177 VS 24 ± 10.359) respectively, with (**all p <0.001**) than in *Group A* (healthy control ) which would represent the sarcopenia and malnutrition status in our HD patients.

*Group B* (HD patients with muscle wasting) also showed higher levels of myostatin than in *Group A* (healthy control); (2770.00 ± 692.71 VS 1247.53 ± 486.87) pg/ml with p-value <0.001. while Myostatin levels showed positive significant correlation with age, dialysis vintage, MIS and FSS (P-value <0.001* in all), which agrees with **Han *et al.*[(16)]** and supports the hypothesis of myostain cascade; the signaling pathway that is possibly involved in muscle atrophy and cachexia as the transforming growth factor-B superfamily member; myostatin is primarily expressed in skeletal muscle and has the effect of limiting muscle growth causing muscle atrophy and cachexia when its level increases in chronic diseases and with aging [(17)]. In contrast to our finding, **Esposito *et al.*[(18)]** found no significant difference in myostatin levels between HD patients and healthy controls. He attributed this finding to the variety of myostatin measurement assays used, the different study design (crossover vs. observational), and the small number of patients included in his study.

Meanwhile, IGF1 showed significantly lower levels in *Group B* (HD patients with muscle wasting) than in the control group ; (137.6 ± 29.528 VS 370.933 ± 125.77) with p-value <0.001. IGF1 also showed negative correlation with age, serum creatinine, dialysis vintage, MIS, FSS (all p <0.001), 6MWT (p =0.8) and positively correlated with albumin (p <0.001) and HGS (p =0.7).

This was comparable to the findings of **Bian *et al.*** [(19)]. They found that IGF-1 levels were lower in the sarcopenia group compared to the non-sarcopenia group (all p <0.001), and that there was a positive link with the appendicular skeletal muscle mass index (ASM index) (p <0.05). **Shimohata *et al.* [(5)], Esposito *et al.* [(15)],** and **Delanaye *et al.* [(20)]** have similarly discovered a connection between IGF-1 levels and muscular hypertrophy and strength in patients with HD. IGF-1 has been shown to activate a number of anabolic and compensatory pathways, increasing skeletal muscle protein synthesis and preventing muscle loss, thus counteracting sarcopenia [(21)], and alterations in IGF-1 signalling in skeletal muscle can have a significant impact on myofiber size and function [(22)].

So to summarize; our results showed significantly higher levels of myostatin versus lower levels of IGF1 in our HD patients and myostatin had a significant positive correlation with MIS and FSS while IGF1 had a significant negative correlation with MIS and FSS. Our results also showed a highly significant negative

correlation between IGF1 and myostatin which agree with various previous studies [5,15,16,20], and demonstrate that IGF-1 is a key anabolic hormone for the growth, differentiation, and maintenance of skeletal muscle [24]. The transforming growth factor (TGF) superfamily member myostatin, which works as a catabolic factor and a negative regulator of muscle growth, is the alternative [24]. Myostatin levels and muscle atrophy are inversely associated in chronic circumstances [5]. Decreased muscle protein synthesis and concomitant muscle protein breakdown are catabolic conditions brought on by insulin resistance and low insulin levels [25].

In conclusion, our findings showed that myostatin and IGF-1 can be employed as biomarkers of muscle condition in HD patients. To verify these findings, however, additional longitudinal research and examinations of larger groups are required.

**Conflict of interest:** The authors declare no conflict of interest.

**Sources of funding:** This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**Author contribution:** Authors contributed equally in the study.

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