**ORIGINAL ARTICLE**

# Male dialysis patients are subject to a higher rate of muscle wasting and weakness than female counterparts

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**Background.** Gender has been shown to have an effect on muscle size, strength and performance. However, in patients on dialysis treatment it is not known whether gender plays a role in the degree of muscle wasting and weakness. Preliminary data have shown that male patients are more affected than female counterparts. We sought to determine whether the muscles of the lower leg are differentially affected in males and females with ESRD.
**Material and Methods.** Six healthy female controls (F-CON) were compared to 24 female dialysis patients (F-RFP) and 13 male controls (M-CON) compared to 27 male dialysis patients for measurements in muscle cross sectional area (CSA) and composition by MRI, isometric leg muscle strength, body composition by DEXA, physical activity by a 3D-accelerometry and physical performance using functional tests. The data were normalized for baseline differences between males and females by dividing the variables for each subject by the mean values of the sex-specific control group. ANOVA was performed to detect statistical differences.
**Results.** Muscle size in M-RPF group was reduced 13% more than in F-RFP group (p=0.01). Muscle strength was also reduced in M-RFP 5% more than the F-RFP group (p=0.01). Intramuscular fat content was similar in all groups. On the other hand, F-RFP group had 20% more reduction in gait speed than M-RFP group (p=0.01). A similar reduction in physical activity levels, lean body mass and total body fat was found in both dialysis groups. Testosterone concentration was highly correlated with muscle size in M-RFP group (R=0.554, p=0.001).
**Conclusions.** Male patients have a greater reduction in muscle size and strength than female dialysis patients while female patients have a greater reduction in gait speed. Hormonal changes may be a reason for those differences.
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Gender has been shown also to have an effect in muscle size, strength and performance[1]. Healthy males have 30% more muscle mass than females, when gender and activity levels were matched[2].

Renal failure is a catabolic disease and has been shown to be associated with atrophy in skeletal muscle in patients with end-stage renal disease (ESRD)[3,4]. Muscle atrophy in this population has been linked to poor performance of physical tasks required for activities of daily living[5]. While inactivity may explain a significant degree of the observed atrophy in ESRD, other factors appear to be important as well.

Uremic myopathy[6], inactivity[7], hyperparathyroidism, vitamin D deficiency[8], acidosis[9] or malnutrition[10] could all contribute to atrophy among dialysis patients. In addition, the dialysis treatment per se may be a catabolic event[11]. It has been suggested that dialysis subjects lose approximately 7g of protein per dialysis session, which could translate to a loss of 2 kg of lean mass over one year[12]. All of the aforementioned reasons could have an effect on skeletal muscles of all dialysis patients.

However, it is not known whether gender plays a role in the degree of muscle wasting and weakness usually found in dialysis patients. Subsequent analysis on the muscle biopsy data from Sakkas et al[3], (unpublished observations) showed that muscle fiber area from male patients is affected by 11.5% more compared to female patients. Therefore, we sought to determine whether muscle function of the whole lower leg has been differentially affected in males and females on dialysis treatment.

## Research Design and Methods

### *Study Patients*

Fifty-one dialysis patients were recruited from the University of California, San Francisco-affiliated dialysis units. Entry criteria for dialysis subjects included receipt of chronic hemodialysis for three months or more with adequate dialysis delivery (Kt/V = 1.2). Patients were excluded if they had reasons for being in a catabolic state such as HIV infection, known malignancy, or infection requiring intravenous antibiotics within 2 months prior to enrollment. Nineteen healthy control patients (CON) who reported no known kidney disease, diabetes mellitus or other catabolic diseases were recruited from the community. Within the fifty one dialysis patients, 11 males and 14 females were diabetic without any neuropathic alterations or evidence of neuropathy. Dialysis and CON patients were required to be sedentary, defined as participation in no routine exercise or fitness-related activities within two months of study enrollment.

All patients gave informed consent for study participation. The study was approved by the Committee on Human Research at the University of California San Francisco and the Research and Development Committee of the San Francisco VA Medical Center.

### *Clinical Measurements*

Patients were studied on two separate days in the Magnetic Resonance Unit and in the Nephrology division at the San Francisco VA Medical Center, and in the General Clinical Research Center at San Francisco General Hospital. Height and weight were recorded with patients wearing only a hospital gown, and body mass index was calculated as weight in kg divided by the square of height in meters. Dialysis patients were weighed following a dialysis session. Routine monthly laboratory results were recorded for dialysis patients and single-pool Kt/V calculated from pre- and post-dialysis BUN measurements.

### *Magnetic Resonance Imaging*

Magnetic resonance images (MRI) were obtained on the day after a dialysis session. Proton $T_1$-weighted MRI was used to visualize the cross-sectional area (CSA) of the lower leg muscles using a 1.5 T whole body Siemens Magnetom Vision system (TR = 510 ms, TE = 14 ms, FoV = 210 $mm^2$, slices = 33, thickness = 4 mm), using a 31-cm-diameter extremity coil, as performed previously[13]. The MRI parameters were selected to optimize differences in signal intensity between contractile (muscle) and non-contractile (e.g., fat or extramyocellular lipid) tissue. Data were acquired with the patient in a supine position. The right leg was studied except in cases where there was hardware or previous injury that appeared to distort the anatomy of the right leg (three dialysis patients and three control patients).

### *Muscle and Fat Measurements*

A customized software program written in IDL (Interactive Data Language Research Systems, Inc., Boulder, CO) allowed for the separate quantitation of muscle (contractile), fat (non-contractile), and miscellaneous (connective tissue, muscle fascia) components of the total cross sectional area of the muscle compartment of the lower leg (excluding the subcutaneous adipose tissue (SAT) and bones (Figure 1)[7, 13]. This software has been described in detail elsewhere[7]. Subcutaneous adipose tissue was quantified as the area below the skin and above the muscle fascias on the same MRI slice used to quantify muscle size and % of muscle content.

### *Muscle Strength*

Isometric maximum voluntary contraction (MVC) was recorded from the dorsiflexor tibialis anterior (TA) muscle with patients in a seated position[9,10]. The leg was fixed with the knee extended, and the foot was held firmly against a foot platform with an adjustable Velcro strap across the metatarsal heads. Force output was measured with a non-magnetic force transducer (West Coast Research, Los Angeles, CA) that was attached beneath the foot platform. The signal from the force transducer was amplified, converted to a digital signal and displayed using Labview Software (National Instruments, Austin, TX). Three MVCs (3-5 sec each) were performed with two minutes of rest between contractions.

### *Physical activity and Physical performance*

The TriTrac-R3D accelerometer (Professional Products, Madison WI, USA,) was used to measure physical activity in all subjects for seven days, and an average daily activity level was calculated. This method has been described and validated elsewhere[4, 14]. Gait speed was assessed on a non-dialysis day. Subjects were timed while walking 20 feet (609.6 cm) at their usual pace and as fast as they could. For each measure, two trials were performed, and the faster of the two was recorded to the nearest 10th of a second[15].

### *Body Composition*

Body composition was measured using a Lunar model DPX dual energy x-ray absorptiometry (DEXA) (Madison, WI) after a dialysis session. Briefly, this instrument scans with x-ray sources that produce dual energy photon beams. This technique has been widely used to estimate the proportion of lean and fat tissue as well as bone density[16].

### *Statistical Analysis*

Group data are presented as mean ± standard deviation. Differences between the four groups were examined using a one-way ANOVA test, with the Fisher's Protected Least Significant Difference post-hoc analysis. Activity levels were used as a covariate in the analysis. Statistical significance for all analyses was established when a 2-tailed p-value was less than 0.05. The data were normalized for baseline differences between males and females by dividing the variables for each subject by the mean values of the sex-specific control group. All analyses were performed using STATISTICA software (StatSoft Inc., Tulsa, OK, USA).

## Results

### *Patients*

The characteristics of the study population are presented in Table 1. Briefly, thirteen healthy male subjects (13M/6F) were recruited as the M-CON group and six healthy female subjects were recruited as the F-CON group. On the other hand, twenty seven dialysis male subjects comprised the M-RFP group and twenty four dialysis female subjects comprised the F-RFP group. The dialysis-related parameters showed satisfactory dialysis dosing [17]. The RFP groups were well-nourished and had corrected anemia prior to the study.

### *Muscle properties*

The results of the MRI analysis are presented in Table 2. Muscle size in the lower leg area was reduced by 13% more in the male dialysis patients compared to the female counterparts. However, when muscle percentage was calculated for a given muscle area, both patient groups were similarly affected. A similar pattern was found when extramyocellular lipids (EMCL) and SAT were calculated, with both patient groups being similarly affected Muscle strength was reduced 5% more in the M-RFP group compared to the F-RFP group. Specific strength (MVC/CSA) was 13 % more reduced in the F-RFP group compared to the M-RFP.

### *Body composition*

The increase in EMCL content in the muscle compartments in the RFP group compared with the CON group was not associated with an increased SAT in the lower leg (Table 2) or with overall adiposity, either estimated with BMI or measured with DEXA (Table 1). There were no significant differences in the levels of "miscellaneous" tissue (muscle fascia, connective tissue) (shown as red color in Fig 1) measured in the lower leg muscle compartments of the three study groups, which were approximately 5% of the total cross-sectional area (data not shown).

### *Physical activity and Physical performance*

Both M- & F-RFP groups had a similar reduction in physical activity levels (Table 3). However, the F-RFP group demonstrated 20% more reduction in normal gait speed and 10% more reduction in fast gait speed compared with the M-RFP group (Table 3).

### *Hormonal assessment*

Data are presented in Table 4. Testosterone levels in male dialysis patients were highly correlated with muscle size (R=0.554, p=0.001) (Figure 2).

**Table 1.** *Characteristics of the study population.*

| Variable | M-CON (n=13) | F-CON (n=6) | M-RFP (n=27) | F-RFP (n=24) | P value |
|---|---|---|---|---|---|
| Age (years) | 52 ± 12 | 58 ± 16 | 55 ± 11 | 59 ± 16 | NS |
| Race Caucasian | 8 | 2 | 1 | 1 | |
| African American | 3 | 2 | 17 | 15 | |
| Asian/Pacific Islander | 2 | 2 | 7 | 6 | |
| Other | 0 | 0 | 2 | 2 | |
| BMI ($kg/m^2$) | 24.7 ± 3 | 23.2 ± 4 | 25.8 ± 6 | 25.9 ± 6 | NS |
| Months of Dialysis | N/A | N/A | 36 ± 28 | 37 ± 34 | NS |
| LBM (Kg) (DEXA) | 55 ± 9 | 39 ± 3 | 52 ± 8 | 39 ± 7 | NS |
| Total Fat (Kg) (DEXA) | 17 ± 6 | 20 ± 8 | 18 ± 9 | 23 ± 14 | NS |
| BUN pre-dialysis (mg/dl) | N/A | N/A | 60 ± 16 | 61 ± 17 | NS |
| Hemoglobin (mg/dl) | N/A | N/A | 11.9 ± 2 | 11.8 ±1 | NS |
| Kt/V | N/A | N/A | 1.5 ± 0.3 | 1.5 ± 0.3 | NS |
| Albumin (mg/dl) | N/A | N/A | 3.7 ± 0.5 | 3.8 ± 0.5 | NS |
| PTH (ng/dl) | N/A | N/A | 320 ± 224 | 445 ±482 | NS |
| Cholesterol (mg/dl) | N/A | N/A | 141 ± 35 | 161 ± 34 | NS |
| LDH (mg/dl) | N/A | N/A | 167 ± 25 | 198 ± 54 | 0.03 |
| Triglycerides (mg/dl) | N/A | N/A | 144± 90 | 146 ± 73 | NS |

Data are Mean ± SD. Abbreviations are: N/A, Not Applicable, BMI, Body Mass Index; LBM, Lean Body Mass; HbA1c, Glycosylated hemoglobin; BUN, Blood Urea Nitrogen; Kt/V, Dialysis Dose; PTH, Parathyroid Hormone; LDH, Low Density Lipoprotein.

## Discussion

This cross sectional study demonstrates that male dialysis patients are prone to a higher degree of muscle wasting and lower muscle strength compared to their female counterparts. Differences in specific strength can explain the paradox that female dialysis patients with less muscle wasting have slower gait speed in both normal and fast walking tests than males. Endogenous production as well as the removal of various anabolic hormones may have a pivotal role on the preservation of muscle size and function in renal failure patients.

Both dialysis groups manifested significant muscle atrophy compared to their respective healthy sedentary control group; however, the M-RFP group was more affected by the uremic toxicity compared to the F-RFP group. Circulation of various anabolic and catabolic hormones could have an effect on the preservation of muscle size. The hemodialysis process has an effect on the removal of various hormones. It is well known that hypogonadism is frequent in dialysis patients[18]. In our study, testosterone levels were highly correlated with muscle size in M-RFP and poorly with F-RFP (Figure 2). It is conceivable to believe that male patients are more sensitive to small changes in anabolic hormones such as testosterone compared to female patients that have 10 times less the amount of the male patients. For example it is very clear from Figure 2 that a reduction of 200 ng/dl of testosterone could have an effect in muscle size by 1-3 $cm^2$ in males but a comparatively very small effect in female patients.

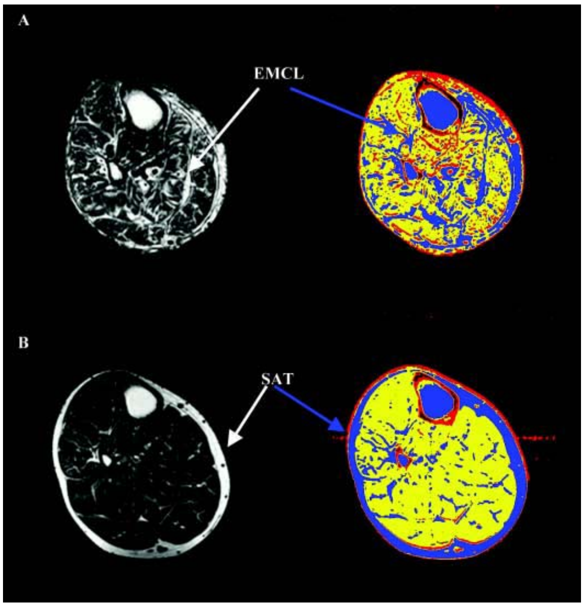


**Figure 1.** *Total lower leg muscles CSA from a two renal failure patient with (Panel A) and without fat infiltration (Panel B).*

*Colours indicate tissue of different signal intensity. Blue color denotes tissue with high signal intensity like fat, yellow denotes tissue with low signal intensity like muscle, and red shows miscellaneous tissue with very low signal intensity like connective tissue and fascia. SAT forms a rim around the exterior of the major muscle compartments, while EMCL refers to fat that can be seen within the muscle compartments. Abbreviations: EMCL; Extramyocellular Lipids, SAT; Subcutaneous Adipose Tissue, CSA; Cross Sectional Area.*

The reduction in gait speed observed in the F-RFP group was an unexpected observation. Since the M-RFP group demonstrated an increased muscle wasting (13% more than the F-RFP group), it was expected that those subjects would be the most affected in terms of muscle function and that they would have a slower gait speed. Surprisingly, however, F-RFP patients had 20% more reduction in gait speed compared to the M-RFP. This paradox could be explained by the observed changes in "specific strength". Specific strength is the ratio of force produced per muscle over the cross sectional area of this muscle, and represents the force produced per unit of muscle mass (MVC/CSA). Muscle atrophy and gender differences do not alter specific strength per se. Alterations in muscle properties like contractile proteins due to atrophy or hypertrophy, have an effect of muscle size. On the other hand, size and strength are closely related making the final recipient of those changes the muscle strength[19, 13]. Changes in specific strength reflect

**Table 2.** *Lower leg muscle properties. Data were normalized according to the control values.*

| **Variables** | **M-CON** (n=13) | F-CON (n=6) | M-RFP (n=27) | F-RFP (n=24) | P value |
|---|---|---|---|---|---|
| Muscle CSA | 0.99 ± 0.1 | 1.02 ± .02 | 0.83 ± 0.2 | 0.99 ± 0.2 | a |
| Muscle % of the total CSA | 0.99 ± .05 | 0.98 ± .07 | 0.94 ± .08 | 0.93 ± .08 | NS |
| EMCL CSA | 1.07 ±0.7 | 1.16 ± 0.8 | 1.38 ± 0.9 | 1.62 ± 0.9 | NS |
| Lower leg SAT | 0.97 ± 0.4 | 1.01 ± 0.2 | 0.79± 0.4 | 0.80 ± .04 | NS |
| Muscle Strength MVC | 1.03 ± 0.2 | 0.97 ± 0.2 | 0.69± 0.2 | 0.68 ± 0.2 | a, b |
| Specific Strength (MVC/CSA) | 1.03 ± 0.2 | 0.90 ± 0.1 | 0.85± 0.2 | 0.63 ± 0.2 | a, b |

Data are Mean ± SD. Abbreviations are: CSA, cross-sectional area; EMCL, extramyocellular lipids, SAT; subcutaneous adipose tissue, MVC; maximum voluntary contraction . Statistics: [a]M-CON vs. M-RFP, P<0.01; [b]F-CON vs. F-RFP, P<0.01

**Table 3.** *Functional tests. Data were normalized according to the control values.*

| Variables | M-CON (n=13) | F-CON (n=6) | M-RFP (n=27) | F-RFP (n=24) | P value |
|---|---|---|---|---|---|
| Physical activity | 1.0 ± 0.7 | 1.0 ± 0.2 | 0.3 ± 0.2 | 0.3 ± 0.2 | 0.001 [a, b] |
| Normal gait speed | 1.0 ± 0.2 | 1.0 ± 0.1 | 0.8 ± 0.1 | 0.6 ± 0.3 | 0.001 [a, b] |
| Fast gait speed | 1.0 ± 0.3 | 1.0 ± 0.2 | 0.7 ± 0.2 | 0.6 ± 0.2 | 0.001 [a, b] |

Data are Mean ± SD. Statistics: [a], M-CON vs. M-RFP; P<0.01, [b], F-CON vs. F-RFP; P<0.01

**Table 4.** *Hormonal assessment.*

| Variables | M-RFP (n=27) | F-RFP (n=24) | P value |
|---|---|---|---|
| Testosterone (ng/dl) | 489± 242 | 42 ± 44 | 0.001 |
| FSH (ng/dl) | 12 ±13 | 75 ± 77 | 0.001 |
| Leptin (ng/dl) | 15 ± 21 | 26 ± 29 | NS |

Data are Mean ± SD. Abbreviations: FSH, Follicle Stimulated Hormone

alterations of myopathic origins. In simple words, those muscles are unable to recruit or "utilize" all their fibers due to structural or other unknown alterations[13]. In our study, the F-RFP group showed a 13% more reduction in specific strength compared to M-RFP group. In other words, female patients may have preserved more muscle mass compared to their male counterparts, but they seem unable to use/recruit their preserved muscle for simple functions like walking. Lower gait speed has been associated with greater risk of falling in elderly populations[20]. Alterations in muscle function could be translated to a further reduction in physical activity, reduction in quality of life and generally deterioration of the health status of the patient.

The increased intramuscular fat (EMCL) deposition found in both male and female patients could be related to diabetes (Sakkas unpublished data), inactivity [7] or obesity [21]. In our study, both male and female patients had similar levels of inactivity, obesity and both groups contained diabetic patients (11M/14F). Therefore the reason that the two groups were similarly affected in terms of EMCL, could be related to the lack of differences in obesity, inactivity or diabetic status.

There was a limitation in this study that needs to be addressed. The F-CON group was composed of only six female subjects. Although, it would be preferable to have a larger number of subjects in order to give a wider distribution in our control group, the distribution of those six subjects was very normal making our study valid.

To our knowledge, this is the first study to show that male dialysis patients are prone to a higher degree of

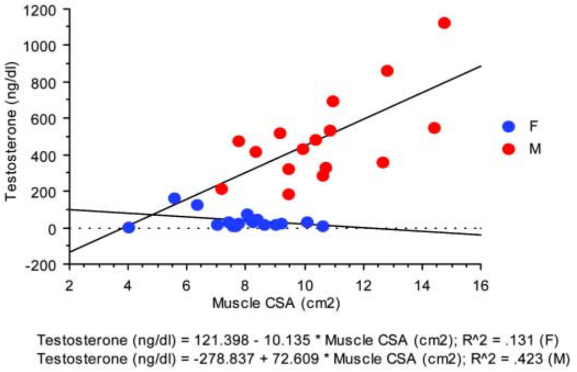


**Figure 2.** *Testosterone levels are correlated with muscle size in M-RFP group.*

muscle wasting and muscle weakness compared to female counterparts. On the other hand, female dialysis patients appeared to have altered specific strength, implying gender specific myopathic alterations. Future studies of interventions to improve muscle quality and function in the renal failure population need to consider that gender may affect patients in more complex ways than by a simple effect in muscle size.

**Περίληψη**

***Σακκάς ΓΚ, Στεφανίδης Ι, Λιακόπουλος Β, Johansen KL.* Οι άνδρες υπό αιμοκάθαρση υφίστανται μεγαλύτερο βαθμό απώλειας μυικής μάζας και έχουν μεγαλύτερη αδυναμία συγκριτικά με τις γυναίκες.**
***Ιπποκράτεια 8(4): 155-160***

**Εισαγωγή.** Είναι γνωστό ότι υπάρχουν σημαντικές διαφορές μεταξύ ανδρών και γυναικών που αφορούν στο μέγεθος των μυών, στη δύναμη αλλά και στη μυϊκή απόδοση. Ωστόσο, δεν είναι γνωστό εάν το φύλο παίζει σημαντικό ρόλο στο βαθμό της μείωσης της μυϊκής μάζας και δύναμης που πολύ συχνά συναντάμε στους ασθενείς με χρόνια νεφρική ανεπάρκεια (ΧΝΑ). Προκαταρκτικές μελέτες έχουν δείξει ότι οι επιπτώσεις αυτές της ΧΝΑ είναι περισσότερο έντονες στους άνδρες ασθενείς από ότι στις γυναίκες. Σκοπός αυτής της μελέτης είναι να εξετάσουμε εις βάθος εάν πραγματικά οι μύες των κάτω άκρων επηρεάζονται διαφορετικά ανάλογα με το φύλο του ασθενούς.
**Ασθενείς - Μέθοδοι.** ΄Εξι υγιείς γυναίκες (F-CON) που χρησιμοποιήθηκαν ως μάρτυρες συγκρίθηκαν με 24 γυναίκες ασθενείς με ΧΝΑ (F-RFP) και αντίστοιχα 13 υγιείς άνδρες (M-CON) συγκρίθηκαν με 27 άνδρες ασθενείς με ΧΝΑ (M-RFP), σε μετρήσεις που αφορούν: μέγεθος και σύσταση μυϊκού ιστού με χρήση μαγνητικού τομογράφου (MRI), σύσταση σωματικού βάρους με χρήση DEXA, επίπεδα φυσικής δραστηριότητας με το σύστημα 3D accelerometry και επίπεδα λειτουργικής κινητικότητας με διάφορες λειτουργικές δοκιμασίες. Τα δεδομένα είναι εκφρασμένα σε ποσοστό επί των αντίστοιχων αποτελεσμάτων των υγιών μαρτύρων του ίδιου φύλου για κάθε περίπτωση.
**Αποτελέσματα.** Το μέγεθος των μυών στην M-RPF ομάδα ήταν μειωμένο κατά 13% περισσότερο σε σχέση με τα αντίστοιχα αποτελέσματα στην F-RPF ομάδα (p=0.01). Η μυϊκή δύναμη ήταν επίσης μειωμένη στη M-RPF ομάδα κατά 5% περισσότερο σε σχέση με την αντίστοιχη F-RPF (p=0.01). Τα επίπεδα λιπώδους διήθησης στους μύες των ασθενών δεν βρέθηκαν να διαφέρουν μεταξύ των ομάδων. Διαφορές όμως βρέθηκαν στην ταχύτητα βαδίσματος, με την F-RPF ομάδα να είναι 20% περισσότερο επηρεασμένη σε σχέση με την M-RPF. Παρόμοιες μεταβολές παρατηρήθηκαν στα επίπεδα φυσικής δραστηριότητας και τη συνολική άλιπη και λιπώδη σωματική μάζα μεταξύ των δύο ομάδων ασθενών. Τέλος, σημαντική συσχέτιση βρέθηκε ανάμεσα στα επίπεδα τεστοστερόνης στο αίμα και τη μυϊκή μάζα στην M-RPF ομάδα (R=0.554, p=0.001).
**Συμπεράσματα.** Στους άνδρες ασθενείς με ΧΝΑ παρα-

τηρήθηκε μεγαλύτερη μείωση στα επίπεδα μυϊκής μάζας και δύναμης σε σχέση με τις γυναίκες ασθενείς, οι οποίες παρουσίασαν σημαντικά μειωμένη ταχύτητα βαδίσματος. Οι διαφορές αυτές είναι πιθανό να οφείλονται στα διαφορετικά επίπεδα ορμονών των δύο φύλων.

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