Efficacy of resistance training in malnutrition-Inflammation complex syndrome of chronic kidney disease

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Abstract: protein malnutrition starts in the early stage of chronic kidney disease and increases steadily as kidney function declines. There is a connection between malnutrition and chronic inflammation in people with kidney disease. Eating problems may occur frequently in kidney disease patients, especially for those with end stage renal disease (ESRD) and on dialysis. Poor appetite results in a lack of calorie and protein intake. Over time, a condition called protein energy malnutrition (PEM) occurs. **Purpose**: The purpose of this study is to investigate the effectiveness of resistance training in malnutrition inflammation complex syndrome of chronic kidney disease. **Methods**: - forty patients with chronic kidney disease not on dialysis therapy from both sexes participated and completed the study. They ranged in age from 40 to 60 years. The patients were randomized into two groups of equal number. Group A: received resistance training with low protein diet, and Group B: received low protein diet regimen only. The evaluation procedures was in form of measurement of the level of serum C-reactive protein (mg/l), albumin (g/dl), creatinine (mg/dl), BMI (kg/m2) and isokinetic peak torque of quadriceps (Nm) at 90º/s pre-treatment and after three months post treatment. **Results**: - showed significant decrease in the level of serum (CRP) and significant increase in the level of serum albumin and in isokinetic peak torque of quadriceps in resistance training group versus controls ($p < 0.05$). **Conclusion**: - It could be concluded that resistance training can decrease inflammation and improve nutritional status and muscle strength in patients with chronic kidney disease.
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1. Introduction

Chronic kidney disease (CKD) refers to the progressive and irreversible decline in renal function and is defined as kidney damage for ≥3 months based on findings of abnormal structure or function or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for ≥3 months with or without evidence of kidney damage **[1].**

Patients with chronic kidney disease frequently present with chronic elevations in markers of inflammation, a condition that appears to be exacerbated by disease progression and onset of haemodialysis. Systemic inflammation is interlinked with malnutrition and muscle protein wasting and is implicated in a number of morbidities including cardiovascular disease the most common cause of mortality in this population **[2].**

The combined occurrence of protein-energy malnutrition and inflammation in kidney failure, referred to as malnutrition-inflammation complex syndrome **[3].** Causes of protein- energy malnutrition in patients with chronic kidney disease are not well understood. However contributing factors may include inadequate dietary intake, metabolic acidosis, insulin resistance, comorbid conditions, and inflammation **[4-5].** In CKD, chronic inflammation plays an important role in the disease process and high levels of CRP appear to accompany reduced renal function **[6].**

Within the predialysis CKD population the prevalence of inflammation is great and is an important indicator of patient health and outcome; high levels of CRP reflect a chronic inflammatory state associated with reduced serum albumin levels, inadequate response to erythropoietin replacement, and greater hospitalisation **[7].** In patients with kidney failure, inflammatory cytokine mediated catabolism is associated with hypoalbunminemia, **[8]** hypermetabolism, **[9]** and loss of body cell mass **[10].**

Since inflammation, malnutrition and protein-energy wasting are significant contributors to mortality in CKD patients, **[11]** any treatments which may positively influence these conditions should be explored. The concept of exercise as medicine is an area of increasing interest due to its wide range of diverse beneficial effects **[12].**

The purpose of this study is to further characterize whether resistance training would lead to reduction of systemic inflammation, measured by serum CRP and albumin levels. In addition the association between inflammatory markers and nutritional and functional parameters from the effect on muscle function.

2. Patients and Methods:

This study was carried out on forty patients (31males 9 females) with severe chronic kidney disease (median glomerular filtration rate [GFR]

27ml/min/1.73m^2) were recruited from the National Institute of Urology and Nephrology, Cairo, Egypt. Signed informed consent was obtained from each participant before enrollment in the study. The history and clinical examination were done for all patients. Subjects who fulfilled the following criteria were eligible for enrollment in the study; (1) age from 40-60 years old, (2) confirmation of the diagnosis of renal disease, (3) not on dialysis therapy, (4) serum creatinine level 1.5 – 5 mg/dl, (5) had blood hematologic test, urine analysis, and a treadmill stress test, (6) following a low protein diet of (0.6g /kg body weight /day). Patients were excluded if they had (1) Uncompensated congestive heart failure, (2) Recent myocardial infarction, (3) Cerebrovascular accidents within prior 6 months, (4) severe muscle weakness or interfering skeletal deformity, (5) History of repeated episodes of hypoglycemia, (6) malignant disorders, smokers, alcohols drinking, (7) active infection or inflammation. Reasons for early termination of the study included loss of greater than 25% of initial body weight, need for dialysis or transplantation, development of a serious condition requiring hospitalization.

After exclusion of the subjects who not fulfilled the inclusion criteria, the patients were randomized into two groups of equal number. Group (1): resistance training and low protein diet group. This group follow a resistance training program 3times/ week and a low protein diet (0.6g /kg body weight /day) for 3 months. Group (2): low protein diet group. This (0.6g /kg body weight /day) group follow a low protein diet regimen only (0.6g /kg body weight /day) for 3 months. Assessment was done before and after 12 weeks of treatment for all patients.

At the time of this study, Human Research Ethics committee had not been established in the faculty of physical therapy, but the study was approved by the departmental council.

2. Methods:

The resistance training program was performed by using Kettler multigym. Subjects did the exercise 3 times/week under supervision in the out clinic of Faculty of Physical Therapy, Cairo University, Each session lasted approximately 45 minutes and included a 5-minutewarm-up, 35-minute resistance training (knee extension/flexion and Latissimus pull down), and a 5-minute cool down. Subjects performed 3 sets of 8 repetitions for each exercise per training session. Each repetition consisted of a 2-count concentric (lifting) phase, a slight pause, and a 4-count eccentric (lowering) phase. There was a 1- to 2-count pause between repetitions and a 1- to 2-minute rest period between sets. Proper breathing technique was emphasized at all times to avoid an increase in thoracic pressure with fluid intake in between to avoid dehydration. Training intensity was at an intensity of 15-17 out of 20 at the RPE scale. Starting weights were determined from a three-repetition maximum (3RM) using weights that could be adjusted in 0.5–1 kg/week increments. A 3RM is the maximum weight that can be lifted three times with a proper technique. Training started at approximately 60% of 3RM for two sets of eight repetitions and was increased to three sets as tolerated or (60% of MHR). When patients could perform three sets successfully, the weight would be increased. Blood pressure and heart rate of the participants were monitored each 5 min during exercise. Training intensity was increased progressively as needed to ensure that target intensity was maintained as subjects got stronger and setting of workloads would become easier, assessed by subjects' self-perceived levels of exertion using a Rating of Perceived Exertion Scale. Cool-down exercises included 5to 8 stretching and flexibility exercises for the upper and lower body. Subjects were asked to follow low protein diet, (0.6 g/kg body weight/d) for 2 weeks before randomization and they continued on the low protein diet for an additional 12 weeks based on the Food Composition Tables for Egypt for kidney disease (National Nutrition Institute, Cairo, A.R.E). Subjects were counseled to reduce their habitual protein intake by eating food sources with less protein or reducing portions sizes of higher protein foods **[13].**

Control group. Subjects performed the same stretching and flexibility exercises as those used during cool- down in the exercise group. These exercises were used to ensure there would not be a physiological impact but provide contact time and socialization similar to those of the resistance training group.

All measures were obtained before (week 0) and 12 weeks after randomization, for systemic inflammation serum CRP levels were measured by means of immunoturbidimetric method **[14],** serum albumin concentrations were estimated by means of dye-binding end-point reaction using the Dialab automated centrifugal **[15]** and serum creatinine concentrations was measured by using Dialab automated centrifugal.

Body weight and height (without shoes) were measured on a TZ weight and height scale then Body mass index was determined from body weight and height as kg/m^2.

Muscle strength was determined by measuring isokinetic peak torque of quadriceps muscle (Nm) of dominant side using Biodex Isokinetic dynamometer (Biodex Corporation, Shirley, New York) at angular velocity of 90º/s. one advantage of isokinetic testing

is that it provides numerous objective parameters that can be used to evaluate and analyse a patient's or athlete's performance. Isokinetic testing data frequently used to analyse muscular performance include peak torque, time rate of torque development, total work, and mean power **[16].** The peak torque is used most often because of its high reliability **[17].** The measurements were carried out using Biodex isokinetic with the backrest reclined 5° from vertical, and straps fixing the trunk, waist, and distal thigh. The lateral femoral epicondyle was used as the body landmark for matching the rotation axes of the knee joint and the lever arm of the dynamometer. The dynamometer strap was then fastened around the leg 5 cm proximally to the medial malleolus. The subjects were positioned sitting at the machine and were asked to move their legs forwards using maximal effort against the accommodating resistance, patients performed five maximal leg extension repetition at 90 degree per second and 30 sec rest. 3RM testing was performed during resistance training program.

Statistical Analysis

All statistical measures were performed using the statistical package for social studies (SPSS) version 19 for windows. For each variable, the range, mean and standard deviation were calculated. Paired t- test was conducted for comparison between pre and post treatment mean values in each group and between pre and post treatment mean values between both groups. The level of significance was set at $p<0.05$ for all statistical tests.

3. Results

As shown in table (1), there were no statistical significant differences ($P>0.05$) observed between both groups concerning general characteristics.

Table (1): general characteristics of both groups

	Group (1), (n=20)	Group (2), (n=20)
Age (years)	50 ± 5.3	49.55± 4.43
Sex (female/male)	4/16	5/15

Resistance training group (group1)

Data represented in table (2) shows that twelve weeks of resistance training resulted in significant reduction in circulating CRP with percentage of 24.81% when compared with pre-treatment, improvement in serum albumin concentration by 4.43%, significant decrease in creatinine level ($P<0.0001$), significant increase in BMI by 0.28% ($P<0.0001$) and significant increase in the isokinetic peak torque of quadriceps with percentage of improvement 13.33% when compared with pre-treatment ($P<0.0001$).

Table (2): mean values of CRP, albumin, creatinine, BMI and isokinetic peak torque of quadriceps pre and post treatment for Group (1)

	Pre x□±SD	Post x□±SD	*P* - value
CRP	6.85±0.83	5.15±0.87	0.0001*
Albumin	3.38±0.28	3.53±0.26	0.0001*
creatinine	3.13±0.89	2.89±0.9	0.0001*
BMI	24.24±2.77	24.31±2.77	0.0001*
Quad.peak torque	49.03±6.99	55.57±6.95	0.0001*

X=mean, SD=Standard Deviation *P* -value=Probability level *highly significant ($P<0.05$).

Results of control group (group2)

As shown in table (3) the mean value, standard deviation and P value of CRP, albumin, creatinine, BMI and isokinetic peak torque of quadriceps pre and post treatment for group 2. The results showed significant differences pre and post treatment for group 2 as *p* value <0.05

Table (3):): mean values of CRP, albumin, creatinine, BMI and isokinetic peak torque of quadriceps pre and post treatment for Group (2)

	Pre x□±SD	Post x□±SD	*p* -value
CRP	6.49±0.66	7.84±0.64	0.0001*
Albumin	3.41±0.32	3.22±0.31	0.0001*
creatinine	3.19±0.8	2.77±0.82	0.0001*
BMI	24.87±2.72	23.75±2.74	0.0001*
Quad.peak torque	49.23±6.78	47.62±6.83	0.0001*

X=mean, SD=Standard Deviation P-value=Probability level *highly significant (P<0.05).

Comparison between resistance training group and control group

Table (4): comparative analysis of the mean differences of CRP, albumin, creatinine, BMI and isokinetic peak torque of quadriceps between both groups post treatment

	Group 1 x□±SD	Group 2 x□±SD	*P* -value
CRP	5.15±0.87	7.84±0.64	0.0001*
Albumin	3.53±0.26	3.22±0.31	0.002*
Creatinine	2.89±0.9	2.72±0.82	0.66
BMI	24.31±2.77	23.75±2.74	0.52
Quad.peak torque	55.57±6.95	47.62±6.83	0.001*

X=mean, SD=Standard Deviation P-value=Probability level *highly significant ($P<0.05$).

Comparative analysis of the mean differences of CRP, albumin, creatinine, BMI and isokinetic peak torque of quadriceps between both groups post-treatment as shown in Table (4).The results showed

that there were highly statistically significant differences between both groups at the end of the study with *P* value <0.05 except for creatinine and BMI.

4. Discussion:

The present study was designed to determine the effectiveness of resistance training in malnutrition inflammation complex syndrome of chronic kidney disease. Forty patients from both sexes had severe chronic kidney disease with median [GFR] 27ml/min/1.73m2, not on dialysis therapy, ranged in age between 40-60 years. Classified randomly into two groups of equal number. Group 1: twenty patients received resistance training program and low protein diet, Group 2: twenty patients received low protein diet only. Measurement of serum CRP, albumin, creatinine, and BMI and isokinetic peak torque of quadriceps pre -treatment and after three months post treatment, results showed that individuals undergoing resistance training program and consuming low protein diet for 12 weeks showed significant reduction in serum CRP, a concomitant increase in serum albumin concentration and a highly significant increase in isokinetic peak torque of quadriceps (Nm). Serum CRP concentrations reflect the activity of cytokine- mediated inflammatory processes and are approximately proportional to the extent of tissue injury **[18].**

Systemic inflammation has a role in malnutrition and protein-energy wasting, atherosclerosis, endocrine disorders, and depression **[19]** With regards to malnutrition and protein-energy wasting in CKD, these comorbidities are interlinked and share common aetiologies, yet the contribution of each aspect to poor outcome is not well defined. Therefore, "malnutrition-inflammation-cachexia syndrome" (MICS) has been suggested to denote the important contribution of these conditions to outcome in CKD **[20].** Despite smaller cohorts and a limited depth of literature, associations between inflammatory markers and physical fitness or activity levels in CKD patients correspond with findings from healthy populations. In a study of over 200 dialysis patients self-reported physical activity levels correlated inversely with CRP **[21].** These findings were supported in ESRD patients who wore SenseWear physical activity monitors for 7 days; circulating CRP >5 mg/L was associated with lower energy expenditure and steps walked than patients with lower concentrations of CRP **[22].** In contrast Zamojska and colleagues found no such relationships between CRP and steps walked **[23].**

A few studies have reported no changes in inflammatory cytokines that is, IL-6 **[24, 25]** and the acute phase protein CRP **[26–29],** and others have reported decreased levels of circulating CRP after training **[30–34].**

Also the results of this study come in agreement with Cheema and colleagues who reported an improvement in inflammatory status due to a reduction in CRP concentrations after 12 weeks of progressive resistance training **[32].** However, upon later analysis no changes in pro- or anti-inflammatory cytokines were reported in the same cohort (IL-1β, TNF-α, IL-6, IL-8, IL-10, and IL-12) although greatest muscular hypertrophic adaptations were associated with the greatest reductions in resting IL-6 levels **[25].**

Two studies from a single research group gave surprisingly large positive changes after a modest training programme. In two randomized controlled trails, 8 weeks of cycling for 10–30 minutes at intensity perceived to be "somewhat hard" produced over 80% reductions in circulating CRP and a 20% decline in serum leptin concentrations **[33, 34].**

Elsewhere, a couple of training studies found no alterations in IL-6 or CRP in predialysis patients **[35, 36].** Despite a large duration, a programme of supervised mixed aerobic and resistance training lasting 48 weeks improved aerobic capacity but did not alter concentrations of IL-6 or CRP **[35].**

Smith et al., reported that CRP levels have been reduced with progressive resistance exercise training in a randomized trial in 34 hemodialysis patients. The resistance training group performed two sets of 10 exercises with free weights, targeting all major muscle groups, 3 times per week, during routine HD. The limb containing the vascular access was exercised just before each treatment session, whereas all other training was performed during dialysis sessions. Log CRP significantly decreased in the resistance training group compared to the control group (f=4.426, *p* =0.047) **[37].**

In the presence of an inflammatory state, albumin synthesis is reduced, whereas that of acute – phase reactant proteins such as CRP is increased **[38].** The inverse relationship between serum albumin and CRP concentrations that we found is suggestive of the inflammatory process and consistent with the same observations by others **[39].** Findings by Kaysen *et al.*, **[40].** From a large cohort of patients with kidney failure on hemodialysis therapy provide a rational for protein and energy supplementation for optimal nutrition management. This study provides another therapeutic modality, resistance training with the potential to improve malnutrition inflammation complex syndrome. The efficacy of resistance training has been tested in a few studies of patients with earlier stages of chronic kidney disease, as well as in patients with kidney failure treated by hemodialysis [**41-44**]. These studies showed that

resistance training increases muscle mass, muscle strength and quality of life in individuals with kidney failure.

The results of this study show that resistance training program results in increase in muscle strength as manifested in increasing in the isokinetic peak torque of quadriceps muscle at 90º/sec with percentage of improvement (13.33%) when compared with control group (3.27%) which come in agreement with.

Headley *et al.* **[41],** reported on the results of a 12- week resistance training programme in a group of ten patients on haemodialysis. The programme consisted of two supervised training sessions per week during which, after a 5- to 10 minute warm up period, subjects performed eight to nine weight machine exercises designed to strengthen the whole body. At the end of training programme, the patients increased their peak torque of the leg extensors of the dominant leg at the 90º/sec velocity by 12.7 ± 3.6%, but there was 150º/sec or in grip strength in either hand. Patients improved on several physical performance tests after the training, including a 6-minute walk test, normal and maximum gait speed, and time to complete a sit- to- stand test 10 times. There were no complications or injuries related to the exercise training.

There are some limitations of this study. First the findings of the present study are based on single CRP measurements at each time point , however other inflammatory cytokines can be measured but are not clinically available as IL-6, second, the resistance training program prescribed in this study requires rigorous screening and interventions, therefore it may not be applicable to individuals with different stages of kidney disease, third, these findings may not apply to individuals with chronic renal insufficiency not consuming a low protein diet, fourth, small sample size, finally, limitations of the type of resistance exercise given to the female unlike the male cause of different muscle mass.

In conclusion, resistance training can reverse malnutrition-inflammation complex syndrome of chronic kidney disease. Although maintenance dialysis and kidney transplantation promote extended survival in kidney failure but may be less effective in improving muscle function and quality of life. The CKD population are frequently sedentary and present with chronic systemic inflammation, therefore, long term interventions of resistance training should be investigated further to improve health status.

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