A pilot study to relationship between urinary protein excretion and muscle strengthening in patients with acute onset renal disease

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ABSTRACT. Purpose: The purpose of this study was to investigate urine protein excretion and the effect of muscle strengthening in patients with renal disease. Subjects: Twenty-eight patients (18 to 87 years old) with acute onset renal disease were treated with steroids at the Hospital of Shiga University of Medical Science. Maximum quadriceps force was measured, and 20-minutessessions in resistance training were started. After 5 weeks, maximum quadriceps force was measured again. Results: Quadriceps force showed no significant difference between before and after intervention. There was negative correlation between mean urinary protein excretion and amount of change in quadriceps force over the 5 weeks (r=-0.40, p=0.038). Conclusions: We observed the patients with reduced urine protein excretion are tends to easier to obtain muscle strengthening. On the other hand, there is a possibility that the patients with increased urine protein excretion are hard to obtain muscle strengthening, during the intervention.

Key words: renal disease, urinary protein excretion, muscle strength

In Japan, approximately 13.3 million adults experience chronic kidney disease (CKD) according to a survey by the Japan Society of Nephrology1). Many patients show prolonged survival due to high healthcare standards in dialysis.

Patients with CKD and undergoing dialysis demonstrate decreased physical exercise2), and a comprehensive rehabilitation program, kidney rehabilitation, has been recommended in patients with disorders related to renal diseases and dialysis3). Accumulating evidence in kidney rehabilitation, suggests an improvement in malnutrition-inflammation complex syndrome4), promotion of assimilation of muscle protein5), improvement of quality of life6), and improvement of exercise capacity7). However, most of these studies included patients with stable CKD and regular dialysis, not acute cases. There is no clear guideline for acute cases, thus, there is a need for accumulating evidence of an effect of kidney rehabilitation on acute onset renal disease.

Resistance training is a common intervention approach to improve individual performance, and has been applied to kidney rehabilitation. Muscle strengthening by exercise load, has been demonstrated to affect protein anabolic hormones such as insulin-like growth factors (IGF-1)8), to suppress myostatin9), to affect assimilation of muscle protein, and to improve nervous system function. Muscle strengthening and an increase in muscle mass by exercise load has been shown to benefit elderly individuals as well9).

The excretion of urinary proteins can deplete raw materials for the assimilation of muscle protein, and steroid treatment in patients with acute onset renal disease may influence the excretion of these proteins. The deviation of urine protein excretion from normal should be considered to influence the assimilation of muscle protein in patients with renal disease. However, no studies have examined the relationship between urinary protein excretion and the effect of muscle strengthening.

In this study, we examined urinary protein excretion and the effect of muscle strengthening during five weeks of...
Patients were treated with only steroid treatment, 12 patients started rehabilitation after steroid treatment. Fourteen patients underwent renal biopsy, and then started steroid treatment. The remaining 5 patients with ANCA-associated glomerulonephritis. Twenty-three patients underwent renal biopsy and steroid treatment, and 1 patient was rapidly progressive mesangiocapillary glomerulonephritis. Twenty patients were nephrotic syndrome, 4 patients were suspected steroid psychosis and 3 patients were discharged at hospital admission. Of the remaining 28 patients, 1 patient was excluded as the value of mean urine protein excretion is less than 0.1 g/gCre above the ankle. The isometric quadriceps force was measured twice for 3 seconds after practicing once, and the greater value was calculated. After we measured the maximum quadriceps force, knee extension training with a load of 40-60% of the maximum quadriceps force, depending on the age of the patient, was performed using a dedicated machine (Leg Extension FS-50, PARAMOUNT, Los Angeles, USA). Subjects performed 1 set of 10 repetitions on machine training session at sitting position. Repetition consisted of a 2-count concentric (lifting) phase, a slight pause, and a 4-count eccentric (lowering) phase. The frequency of training was adjusted for medium or higher fatigue, and training occurred 5 days per week for 5 weeks. Patients worked for 20-minute sessions in resistance training, and measured maximum quadriceps force was measured initially and again after 5 weeks. Weight loss during intervention was primarily a decrease in moisture due to diuresis. The quadriceps force was not divided by body weight, but it was divided by the length of the lower limb (Nm).

For renal function, in addition to the basic information at hospital admission, urinary protein, albumin (Alb), Creatinine (Cre) and blood urea nitrogen (BUN) were monitored once every week during the 5 weeks from medical record, the value of mean urine protein excretion is the average amount of urine protein excretion of 5 weeks.

**Participants**

Twenty-eight patients (14 men; 18 to 87 years old) with acute onset renal disease received steroid treatment at the Hospital of Shiga University of Medical Science between March, 2015 and October, 2017. None of the patients were receiving dialysis treatment. Steroid treatment was started from 45-60 mg adjusted of patient age and weight. Rehabilitation started under the direction of the doctor, and for prevention of thrombosis and disuse syndrome. The doctor and physical therapist evaluated by direct monitoring and indirectly using blood test and urinalysis to ensure safety. Subjects are hospitalized, and were provided supervised meals by a nutritionist.

Baseline characteristics of the patients at hospital admission are shown in Table 1. Thirty two patients were enrolled in the study initially, but 1 patient was excluded as the value of mean urine protein excretion is less than 0.1 g/gCre above the ankle. The isometric quadriceps force was measured twice for 3 seconds after practicing once, and the greater value was calculated.

Statistical analysis was performed using IBM SPSS Statistics 22 (IBM, New York, USA). Results were considered statistically significant if 2-tailed P was less than 0.05.

**Table 1.** Baseline characteristics of the patients at hospitalization

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.0±21.5</td>
</tr>
<tr>
<td>Gender (Men, %)</td>
<td>14 (50%)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.1±8.5</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58.2±11.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.7±3.9</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.0 (0.7-1.3)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.0 (0.7-1.3)</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>21.7±10.3</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>2.1±0.8</td>
</tr>
<tr>
<td>Urinary protein (g/gCre)</td>
<td>6.3 (3.3-12.4)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>6.3 (3.3-12.4)</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.1 (0.03-0.5)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>0.1 (0.03-0.5)</td>
</tr>
</tbody>
</table>

Characteristics of the subjects are shown as mean±SD in the parametric data, and median in the non-parametric data.

Methods

**Participants**

Participants

Twenty-eight patients (14 men; 18 to 87 years old) with acute onset renal disease received steroid treatment at the Hospital of Shiga University of Medical Science between March, 2015 and October, 2017. None of the patients were receiving dialysis treatment. Steroid treatment was started from 45-60 mg adjusted of patient age and weight. Rehabilitation started under the direction of the doctor, and for prevention of thrombosis and disuse syndrome. The doctor and physical therapist evaluated by direct monitoring and indirectly using blood test and urinalysis to ensure safety. Subjects are hospitalized, and were provided supervised meals by a nutritionist.

Baseline characteristics of the patients at hospital admission are shown in Table 1. Thirty two patients were enrolled in the study initially, but 1 patient was excluded as suspected steroid psychosis and 3 patients were discharged prior to completing the study. Of the remaining 28 patients, 18 patients were nephrotic syndrome, 4 patients were ANCA-associated glomerulonephritis, 3 patients were systemic lupus erythematosus, 2 patients were mixed connective tissue disease and 1 patient were rapidly progressive glomerulonephritis. Twenty-three patients underwent renal biopsy, and then started steroid treatment. The remaining 5 patients started steroid treatment without biopsy. All patients started rehabilitation after steroid treatment. Fourteen patients were treated with only steroid treatment, 12 patients with steroid treatment and immunosuppressive therapy, 1 patient with steroid treatment and immunoadsorption therapy, and 1 patient with steroid treatment / immunosuppressive therapy / LDL apheresis. All patients lived independently.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the clinical research ethical committee of Hospital of Shiga University of Medical Science (approval number: 27-187) and informed consent was obtained from all patients enrolled in this study.

**Study Protocol**

Isometric quadriceps force was measured using an isometric dynamometer (Isoforce GT-310, OG Wellness Co., Okayama, Japan). During the assessment, the foot was not weight-bearing and the knee passively drawn into 60° flexion by gravity. A soft cuff, attached via an adjustable non-elastic metal cord to a load cell, was fitted with Velcro just above the ankle. The isometric quadriceps force was measured twice for 3 seconds after practicing once, and the greater value was calculated. Resistance training in elderly people can be effective even at a low load. After we measured the maximum quadriceps force, knee extension training with a load of 40-60% of the maximum quadriceps force, depending on the age of the patient, was performed using a dedicated machine (Leg Extension FS-50, PARAMOUNT, Los Angeles, USA). Subjects performed 1 set of 10 repetitions on machine training session at sitting position. Repetition consisted of a 2-count concentric (lifting) phase, a slight pause, and a 4-count eccentric (lowering) phase. The frequency of training was adjusted for medium or higher fatigue, and training occurred 5 days per week for 5 weeks. Patients worked for 20-minute sessions in resistance training, and measured maximum quadriceps force was measured initially and again after 5 weeks. Weight loss during intervention was primarily a decrease in moisture due to diuresis. The quadriceps force was not divided by body weight, but it was divided by the length of the lower limb (Nm).

**Statistical Analysis**

Statistical analysis was performed using IBM SPSS Statistics 22 (IBM, New York, USA). Results were considered statistically significant if 2-tailed P was less than 0.05. Data are shown as mean ± SD, except for non-normally distributed variables, which are shown as median.

Baseline comparisons between body weight and quad-
UPE and QF in renal disease

Figure 1. Five-week trend of urinary protein and albumin

<table>
<thead>
<tr>
<th>Table 2. Quadriceps force and body weight before and after intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before intervention</td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Quadriceps force (Nm)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
</tr>
</tbody>
</table>

Results

All cases completed the training, and no adverse events were observed. The average patient weight decreased during the study from 55.2± 9.6 kg at week 1 to 51.4 ± 8.0 kg at week 5, which was a significant decrease. On the other hand, quadriceps force was 92.3±30.3 Nm at week 1, and 98.3±33.6 Nm at week 5, which was not a significant difference (Table 2). There was no effect of age by ANCOVA (p=0.435). Urinary protein showed a significant decrease after 3 weeks compared to week 1, a significant decrease between the second and fourth weeks, and between the second and fifth weeks. Alb was significantly decreased in all the weeks after 3 weeks compared to the first week. And, Alb was significantly decreased between the second and fourth weeks, as well as between the second and fifth weeks (Fig. 1). Cre was not a significant difference. BUN was significantly decreased between the first and fifth weeks (Fig. 2). Finally, there was negative correlation between mean urinary protein excretion and the amount of change in quadriceps force (r=-0.40, p=0.038, Fig. 3).

Discussion

The patients enrolled in this study represented a wide range in age, and exercise load was decreased with age. In recent years, muscle strengthening in elderly people even at low exercise load has been demonstrated13), and we were able to provide the exercise load necessary for muscle strengthening throughout the intervention duration in this study. During the quadriceps resistance training for renal disease requiring steroid treatment (5 days per week for 5 weeks), no significant effect on quadriceps force was observed. Frequency and duration did not correlate in this study, thus, extreme care should be taken in interpreting these results. Binder et al14) demonstrated muscle strengthening effects in 22% of elderly people, and Castaneda et al15) demonstrated the effects of muscle strengthening in 28% of patients with CKD. Cheema et al16) reported a decrease in muscle attenuation represented by the extent of fat infiltr-


Iwai, et al.

Figure 2. Five-week trend of creatinine and blood urea nitrogen

![Graph showing creatinine and blood urea nitrogen trend over 5 weeks.](image)

* $p<0.05$ vs 1 week

Figure 3. Spearman’s correlation analysis between mean urinary protein excretion (mUPE) and amount of change in quadriceps force ($\Delta$ QF). $r = -0.40; p = 0.038$

![Graph showing correlation between urinary protein excretion and quadriceps force change.](image)

In regards to steroid myopathy, this possibility cannot be ruled out because all of the patients were treated with moderate to high doses of steroid throughout the intervention duration. However, confirming a diagnosis of steroid myopathy requires an invasive muscle biopsy, which is difficult to implement clinically all cases.

Insulin has an anti-hyperglycemic effect, is a protein anabolic hormone, and promotes the assimilation of muscle protein. On the other hand, with steroid treatment, glucocorticoid increases insulin resistance and increases blood sugar levels. Thus, insulin resistance may have inhibited muscle protein assimilation.

Fig. 1 and Fig. 2 shows repeated measures ANOVA. No increase of Cre and BUN were observed. Urine protein excretion showed a significant decrease throughout the intervention duration, as a recognized effect of steroid treatment. In addition, Alb showed a significant improvement, due to the decrease in urinary protein excretion. These findings suggest that the early intervention provide safety and may contribute to include patients with acute onset renal disease in rehabilitation. On the other hand, although urine protein excretion showed a decrease with time, throughout
the intervention duration, urine protein excretion deviation from normal was seen in many patients. In general, resistance training rapidly increases the assimilation of muscle protein, and its effects may persist for 48 hours after exercise\textsuperscript{19}. The accumulation of muscle protein by repeating this resistance training, can lead to muscle hypertrophy over the long term. Previous reports suggest that, the time required for muscle hypertrophy is 4 to 6 weeks\textsuperscript{19,20}, or 8 to 12 weeks or more\textsuperscript{21,22}. Thus, 5 weeks of intervention, as in the present study may not be sufficient to observe muscle hypertrophy.

Scanlon et al\textsuperscript{23} demonstrated increased myofibers prior to muscle hypertrophy with short-term resistance training. The assimilation of muscle protein acts shortly after exercise, and, even if muscle hypertrophy does not occur, it is possible to increase myofibers through resistance training. Therefore, Spearman’s rank correlation analysis was used to investigate the relationships between mean urinary protein excretion and amount of change in quadriceps force in during the intervention. Results demonstrated a negative correlation between mean urinary protein excretion and the change in quadriceps force.

Resistance training has been reported to promote the assimilation of muscle protein in patients with CKD\textsuperscript{6}, and was able to maintain quadriceps force despite adverse conditions to muscle strengthening. However, it is possible to urinary protein excretion depletes raw material leading to the inhibition of muscle protein assimilation. Therefore, it is possibility that the patients with increased urine protein excretion are hard to obtain muscle strengthening.

**Limitation**

As limitations of this study subject age varied widely and the exercise load was inconsistent between patients. In addition, sufficient muscle hypertrophy was not obtained during the training term, and was not consistent in disease. Also, the number of subjects in this study was a small.

**Conclusion**

We examined the relationship between urinary protein excretion and the effects of muscle strengthening in patients with acute onset renal disease. Our results showed that the patients with reduced urine protein excretion are tend to easier to obtain muscle strengthening. On the other hand, there is a possibility that the patients with increased urine protein excretion are hard to obtain muscle strengthening, during the intervention. Although the influence of steroid treatment could not be ruled out, the assimilation of muscle protein in exercise may be reduced by increased urinary protein excretion.

**Conflict of Interest:** Authors have no conflict of interest to disclose.

**Acknowledgments:** The authors acknowledge Prof. Toru Yamakado for advice, and thank the people who participated in the study.

**References**


