

CASE REPORT

Effectiveness and Safety of Rehabilitation for Pediatric Patients with Nephrotic Syndrome in the Acute Phase: A Case Study

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Background: Exercise therapy for patients with pediatric nephrotic syndrome is necessary to improve physical function to maintain the patient's activities of daily life and school life while managing the risk of relapse; however, few studies have examined exercise therapy in the acute phase of the syndrome. This case study aimed to evaluate the efficacy and safety of exercise therapy in a patient with acute pediatric nephrotic syndrome being treated with steroids. **Case:** The patient was a 10-year-old boy diagnosed with primary nephrotic syndrome. Prednisolone (50 mg) was started on the 3rd day of hospitalization. Exercise therapy (moderate-intensity, 40 min, five times a week) was started on the 15th day. The urine protein/creatinine ratio from the 15th day (at the start of rehabilitation) to discharge decreased from 1.1 to 0.4, with no recurrence of nephrotic syndrome. At the initial, middle, and final evaluations, respectively, the grip strength was 10.1, 8.9, and 8.3 kg; the knee extension strength was 0.38, 0.46, and 0.45 kgf/kg; the sit-up test results were 18, 18, and 15 times; the side-step test results were 34, 36, and 31 times; the sit-and-reach test results were 22.9, 24.5, and 23.8 cm; and the 6-min walk test results were 420, 490, and 520 m. Leg muscle strength and exercise tolerance improved, but upper limb strength, trunk muscle strength, and agility decreased. **Discussion:** Moderate-intensity exercises may be effective and safe for pediatric patients with nephrotic syndrome in the acute phase. Exercise therapy may be beneficial to improve physical function and prevent decline during hospitalization in pediatric nephrotic syndrome patients.

Key Words: acute phase; exercise therapy; pediatric nephrotic syndrome; physical function

INTRODUCTION

Treatment for pediatric nephrotic syndrome requires a multidisciplinary approach that includes medication, diet, and exercise therapy. Nephrotic syndrome, the most frequent pediatric renal disease, is characterized by proteinuria, hypoalbuminemia, and edema and is idiopathic in approximately 90% of cases. About 80% of idiopathic nephrotic syndrome patients achieve remission with a standard treatment protocol of glucocorticoids (steroids).¹⁾ However, steroids have

various side effects, especially a decline in physical function due to steroid myopathy.²⁾ Rehabilitation with a focus on exercise therapy is recommended as a treatment for steroid myopathy.³⁾ Furthermore, approximately 30–70% of patients with pediatric nephrotic syndrome experience relapse.¹⁾ Exercise therapy for pediatric nephrotic syndrome is necessary to maintain and improve physical function to maintain the patient's activities of daily life and school life while managing the risk of relapse.

The efficacy and safety of exercise therapy in pediatric

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patients with nephrotic syndrome in the acute phase have not been thoroughly investigated. The Guidelines for Renal Rehabilitation⁴⁾ recommend that patients with nephrotic syndrome should not be subjected to excessive rest or exercise restriction. In addition, previous studies have reported the efficacy and safety of exercise therapy in patients with nephrotic syndrome in remission⁵⁾ and in adults.⁶⁾ However, there are few reports on pediatric patients with nephrotic syndrome in the acute phase. Moreover, some previous studies have reported cases of recurrence of nephrotic syndrome due to exercise overload.⁷⁾ Because it is essential for pediatric nephrotic syndrome patients to perform sports and activities in school and in daily living, appropriate exercise therapy and instruction must be investigated to maintain physical function.

Moderate-intensity aerobic exercise, resistance training, and balance training may be safe and effective in pediatric patients with nephrotic syndrome in the acute phase. A previous study reported that exercise therapy in patients with conservative chronic kidney disease (CKD) resulted in no significant difference in proteinuria and a significant improvement in estimated glomerular filtration rate (eGFR).⁸⁾ Moreover, moderate-intensity aerobic exercise and resistance training in adult patients with nephrotic syndrome in the acute phase did not exacerbate nephrotic syndrome.⁹⁾ However, the efficacy and safety of moderate-intensity aerobic exercise, resistance training, and balance training for pediatric nephrotic syndrome patients in the acute phase have not been investigated.

The purpose of this case study was to evaluate the efficacy and safety of exercise therapy for acute pediatric nephrotic syndrome. If exercise therapy for pediatric nephrotic patients on acute steroid therapy does not worsen renal function and improves physical function, this would help inform the care of pediatric nephrotic patients.

CASE

Patient Information

The patient was a 10-year-old boy who presented with eyelid edema on awaking the day before admission. He attended a local hospital, which confirmed proteinuria 3+, and he was referred to our hospital for admission. Based on the patient's weight gain of approximately 3 kg, mild anorexia, and clinical examination, he was diagnosed with primary nephrotic syndrome and was admitted to the hospital. He had no medical history and was on no medication. Before admission, he lived with his mother and sister, and his father

worked away. He played basketball three times a week as a club activity. Written consent was obtained from the patient and his parents for publication of this case report.

Clinical Findings on Admission

Physical examination revealed the following: height 134.6 cm, weight 27.2 kg; blood pressure (BP) 122/66 mmHg; heart rate (HR) 93/min, and oxygen saturation 99%. Blood chemistry showed total protein 4.0 g/dl, serum albumin (Alb) 1.2 g/dl, blood urea nitrogen (BUN) 16 mg/dl, creatinine (Cr) 0.46 mg/dl, Na 139 mEq/l, white blood cell count 4460/ μ l, *C-reactive protein* 0.1 mg/dL, and hematocrit 38.7%. Urine testing showed a urine protein level of 1189 mg/dL and a urine creatinine level of 185.8 mg/dL, resulting in a urine protein/creatinine ratio (UP/Cr) of 6.4. A cardiothoracic ratio of 48.7 was assessed on chest radiography, with no iliopsoas image. Abdominal ultrasonography showed slight renal hyperintensity and ascites.

Progress after Admission

Prednisolone (PSL) was started at 50 mg (2 mg/kg/day) on the 3rd day. After admission, weight and edema decreased, whereas systolic BP remained in the 120–130 mmHg range, and 2 mg enalapril maleate was started on the 5th day. UP/Cr was below 2.0,¹⁾ the definition of nephrotic syndrome in pediatric patients, after the 12th day. Therefore, the effects of PSL treatment were evident, and renal function was expected to improve, so rehabilitation was started on the 15th day. The patient was independent in all activities of daily living at the start of rehabilitation.

Assessment of Physical Function

Physical function was evaluated on days 15, 29, and 51 of hospitalization. Measurements included grip strength, knee extension strength, the sit-up test, side-step test, sit-and-reach test, and 6-min walk test (6 MWT).

Grip strength was measured using a Smedley digital hand dynamometer with the patient in a standing posture. Measurements were made twice, alternately on the right and left sides, and the average of the highest value on each side was used. Knee extension strength was measured using a hand-held dynamometer (μ -tas F1, ANIMA, Tokyo, Japan) in a sitting square, with the hip and knee at 90° flexion.¹⁰⁾ The sit-up, side-step, and sit-and-reach tests were performed according to the method described in the new fitness test recommended by the Ministry of Education of Japan.¹¹⁾ In the sit-up test, a test of trunk muscle strength, the number of times both elbows touched both thighs in 30 s was counted

with the patient starting from a supine position with both arms folded in front of the chest and both knees held at 90°. The side-step test, an agility test, was measured using three lines drawn at intervals of 100 cm as the measurement area; the patient stands straddling the center line and, at the “start” signal, side-steps until crossing or touching one sideline, then returns to the center line and side-steps again until crossing or touching the opposite line. The measurement time was 20 s, and the number of times the center line was crossed was recorded. The sit-and-reach test, as a flexibility test, was measured by placing both legs in the flexibility box, and with both arms stretched out at shoulder width, the box was pulled forward with both hands to assume a long-sitting posture. The patient slowly bends forward and moves the slider on the box straight ahead as far as possible, taking care to keep the hands one above the other and not to bend the knees. The distance the slider was moved by the outstretched clasped hands when bending forward was measured. The 6 MWT was measured by walking as fast as possible along a marked indoor corridor and recording the total distance traveled after 6 min according to the methodology of the American Thoracic Society.¹²⁾

Evaluation of Renal Function

Alb, BUN, eGFR, and UP/Cr were obtained from medical records. UP/Cr was examined to evaluate the safety of rehabilitation. The measurement period was from the 19th day, just after the start of weekly rehabilitation, to the 54th day, the day of discharge.

Method of Exercise Therapy Intervention

Resistance training, balance exercise, and aerobic exercise therapy were administered for 40 min, five times a week. For resistance exercise, calf raises and squats were performed as 2–3 sets of 20 repetitions, and for balance exercise, 2–3 sets of standing on one leg for 1 min on each side were performed. Aerobic exercise was performed on a bicycle ergometer for 20 min at an intensity of 60% of the peak work rate (peak WR) calculated in the exercise tolerance test, and the Borg scale and heart rate were monitored and adjusted accordingly. Systolic BP, diastolic BP, and HR before and after rehabilitation during hospitalization were measured, and the average values were calculated. Karvonen’s formula determined the percentage of the HR during aerobic exercise to the maximum HR measured in the exercise tolerance test. The exercise tolerance test was performed only once as an initial evaluation using a bicycle ergometer to measure peak WR. The protocol of the exercise load test was a 3-min warm

up followed by a multistep incremental load of 10 W/min at 50 rpm. Improving balance, muscle strength, and exercise tolerance are important for maintaining athletic performance in basketball, the patient’s preferred sport. Therefore, balance training was included in the exercise program for this patient.

Progress of Treatment after the Start of Exercise Therapy

After the start of exercise therapy, the patient was steroid resistant. A renal biopsy was performed on the 34th day, and the patient was diagnosed with minimal change nephrotic syndrome. Subsequently, steroid pulse therapy was administered twice for three days, from 41st to 43rd and 48th to 50th day. No adverse events were observed before or after renal biopsy or steroid pulse therapy. The PSL dose was reduced to 25 mg on the 43rd day. The blood glucose level before breakfast was 142 mg/dl on day 49, indicating steroid-induced hyperglycemia, but this had decreased to normal levels on day 54. The patient was discharged home on the 54th day, and PSL 25 mg and an angiotensin-converting enzyme inhibitor 2 mg were administered. After discharge from the hospital, the patient was treated with pulse steroid therapy once a month, and cyclosporine A was considered after 4–6 months, depending on the response to pulse steroid therapy. The amount of energy provided by the patient’s diet was increased from 2000 to 2300 kcal from the 25th day.

Progress of Rehabilitation

From the 15th to the 33rd day, resistance exercise, balance exercise, and aerobic exercise were performed on the lower limbs. Bed rest was ordered until a renal biopsy was performed on the 34th; on the 35th day, based on the biopsy findings, the patient was released from bed rest. From the 36th day onward, bedside exercises for the lower limbs and gait training in the ward were performed. The amount of exercise was gradually increased. During steroid pulse therapy, exercise therapy was administered in the afternoon after the steroid pulse. During the 43rd–53rd day, lower limb resistance exercise, balance exercise, and aerobic exercise were resumed.

RESULTS

The UP/Cr, BUN, eGFR, and Alb levels during admission are shown in **Figs. 1–2**. The UP/Cr from the 15th day (at the start of rehabilitation) to discharge decreased from 1.1 to 0.4. UP/Cr levels indicated no recurrence of nephrotic

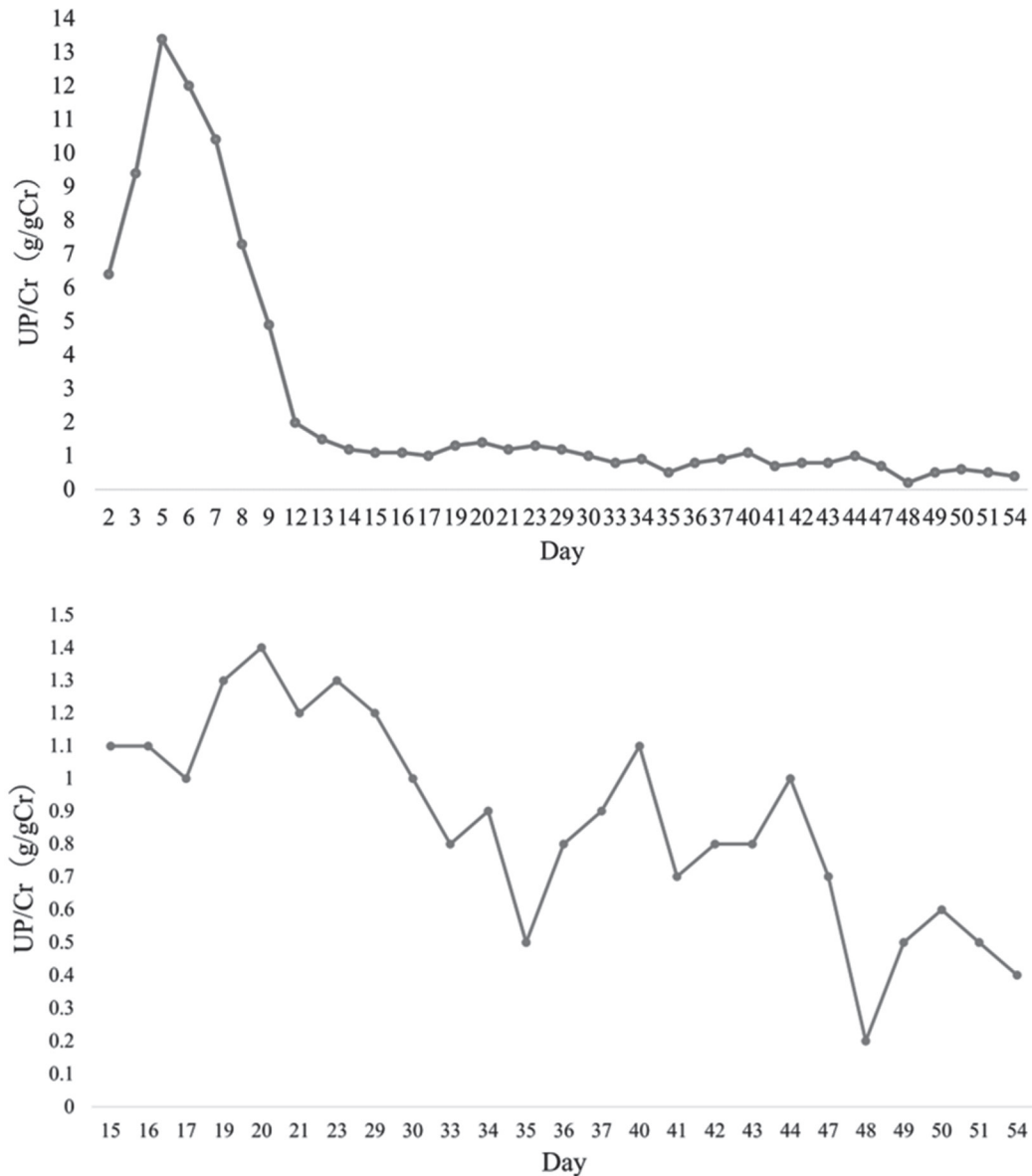


Fig. 1. Changes in UP/Cr during hospitalization and rehabilitation intervention.

syndrome, but the patient remained in partial remission, not complete remission. Laboratory parameters on the 19th day (closest to the start of rehabilitation) and at the time of discharge showed BUN from 14 to 18 mg/dl, eGFR from 167.0 to 159.7 ml/min/1.73 m², and Alb from 2.2 to 3.7 g/dl. Over this period, BUN and eGFR showed no change, but Alb levels increased. Furthermore, no adverse events were observed during rehabilitation intervention during hospitalization.

The course of treatment and rehabilitation during admission are shown in **Fig. 3**, and the results of the changes in physical function are shown in **Table 1**. At the initial, middle, and final evaluations, respectively, grip strength was 10.1, 8.9, and 8.3 kg; knee extension strength was 0.38, 0.46, and

0.45 kgf/kg; the sit-up test results were 18, 18, and 15 times; the side-step test results were 34, 36, and 31 times; the sit-and-reach test results were 22.9, 24.5, and 23.8 cm; and the 6-min walk test results were 420, 490, and 520 m. Leg muscle strength and exercise tolerance improved, but upper limb strength, trunk muscle strength, and agility decreased. The mean SBP was 106±7.7 mmHg, DBP was 72±10.6 mmHg, and HR was 91±6.8/min before exercise. After exercise, SBP was 120±11.3 mmHg, DBP was 87±8.2 mmHg, and HR was 125±7.2/min. No exercises at an intensity exceeding the reference value¹³⁾ were observed in terms of BP. The exercise intensity (k of Karvonen's formula) for maximum heart rate was 0.56±0.12.

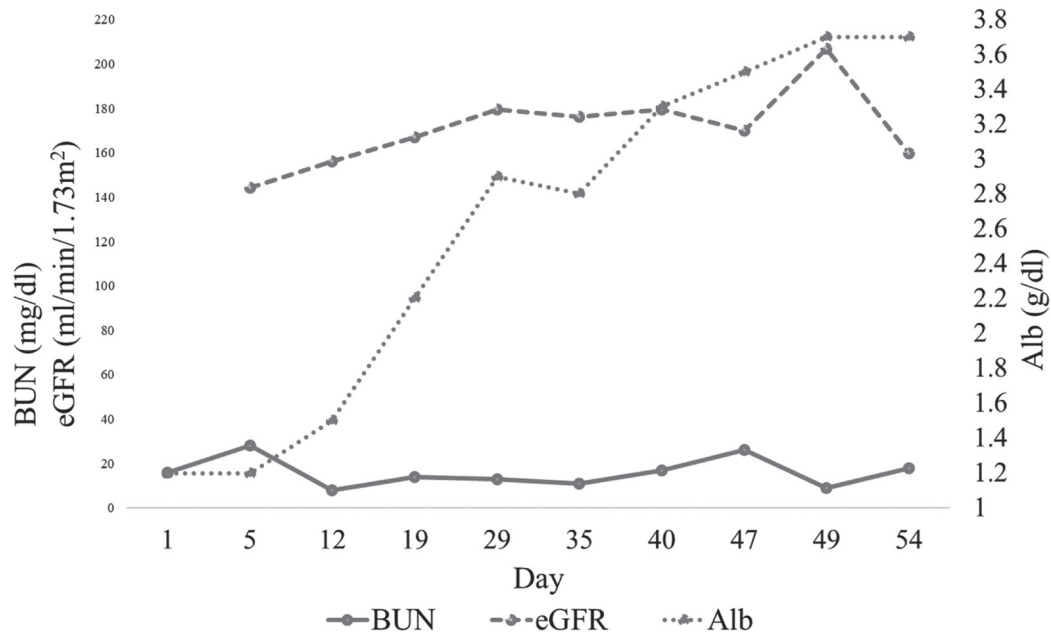


Fig. 2. Changes in BUN, eGFR, and Alb during hospitalization and rehabilitation intervention.

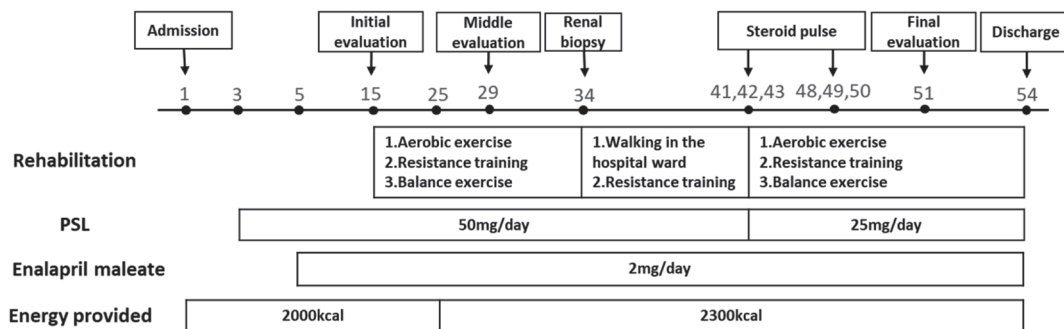


Fig. 3. The course of treatment and rehabilitation during hospitalization.

Table 1 . Physical function evaluation results

	Initial evaluation 15th day	Middle evaluation 29th day	Final evaluation 51st day
Grip (kg)	10.1	8.9	8.3
Knee extension strength (kgf/kg)	0.38	0.46	0.45
Sit-up test (times)	18	18	15
Side-step test (times)	34	36	31
Sit-and-reach test (cm)	22.9	24.5	23.8
6-min walk test (m)	420	490	520

DISCUSSION

To the best of our knowledge, this study is the first to report that exercise therapy for pediatric patients with acute nephrotic syndrome improves leg muscle strength and

exercise tolerance without relapse of nephrotic syndrome. The exercise therapy program based on resistance training, balance training, and moderate aerobic exercise was shown to be effective in improving leg muscle strength and exercise tolerance and was safe in the long term for this patient.

However, the effects of the exercise therapy program on the upper limb strength, trunk muscle strength, and agility and the short-term effects on proteinuria and renal function in this patient were not clear. The current results suggest that exercise therapy may help prevent the deterioration of physical function due to disuse syndrome and steroid myopathy during hospitalization.

The decline in physical function in pediatric patients with renal disease is an important problem. Pediatric patients with renal disease have a longer disease duration than adults, and physical and mental development can be affected by resistance to insulin and growth hormone, renal anemia, hypotrophy, increased protein catabolism, and inflammatory cytokines.¹⁴⁾ Moreover, pediatric patients with renal disease reportedly have lower muscle mass¹⁵⁾ and poorer physical function than healthy children.¹⁶⁾ Furthermore, pediatric patients with acute nephrotic syndrome are expected to be at high risk of physical function decline due to hospitalization-induced disuse syndrome and the side effects of steroids. According to a survey by the Ministry of Education, Culture, Sports, Science and Technology, the average physical function values for 10-year-old Japanese boys are 17.5 kg for grip strength, 20.8 times for the sit-up test, 44.4 times for the side-step test, and 34.1 cm for the sit-and-reach test.¹⁷⁾ The results of the initial evaluation of the current patient were 10.1 kg for grip strength, 18 times for the sit-up test, 34 times for the side-step test, and 22.9 cm for the sit-and-reach test, which were lower than the average values for 10-year-old boys. Such a decline in physical function may affect the quality of life (QOL) and school life after discharge. It is important to prevent physical function decline in pediatric nephrotic syndrome patients by providing exercise therapy early after hospitalization. However, few studies have investigated the efficacy and safety of exercise therapy in pediatric nephrotic syndrome patients in the acute phase.

Investigations into the safety of exercise therapy for pediatric patients with nephrotic syndrome in the acute phase have generated inconsistent results. Rest and exercise restriction have long been the mainstay of treatment for patients with CKD. This is because short-term exercise may transiently increase urinary protein and decrease GFR,^{18,19)} and there is concern that blood flow to the kidneys might be reduced. Furthermore, cases of recurrence due to sports have been reported in pediatric nephrotic syndrome patients.⁷⁾ The Guidelines for Renal Rehabilitation⁴⁾ recommend an exercise intensity of 40–60% of maximal oxygen uptake or anaerobic threshold (AT), and exercise with an intensity exceeding this may increase the risk of recurrence of nephrotic syndrome.²⁰⁾

In some previous studies of exercise therapy in CKD patients, the intensity of aerobic exercise was set at 50–60% of peak VO_2 in pre-dialysis CKD patients²¹⁾ or just before the AT⁹⁾ in adult patients with nephrotic syndrome in the acute phase. The Guidelines for Renal Rehabilitation recommend that exercise therapy for pediatric nephrotic syndrome patients be performed according to the stage of the disease, such as remission.⁴⁾ A previous study reported that exercise therapy in pre-dialysis CKD patients did not significantly increase urinary protein and significantly improved eGFR,⁸⁾ and exercise-induced changes in proteinuria and GFR were transient and did not exacerbate renal function in pediatric CKD patients.²²⁾ In animal studies, long-term aerobic exercise is assumed to increase renal blood flow and protect the kidneys by increasing nitric oxide through an increase in nitric oxide synthase and decreasing oxidative stress through a decrease in reactive oxygen species.²³⁾ Our patient could perform exercise without affecting UP/Cr, BUN, or eGFR. The BP did not exceed the criteria for discontinuation of rehabilitation¹³⁾ (SBP on exercise rises by more than 40 mmHg or DBP rises by more than 20 mmHg), and HR was also below moderate intensity during all exercises. However, this study did not assess proteinuria or renal function immediately before and after exercise, so the short-term effect of exercise on renal function was unclear. Therefore, this case study suggests that exercise therapy might be safe, at least concerning recurrence during the rehabilitation intervention period (approximately 6 weeks). In the future, it will be necessary to investigate proteinuria and renal function pre- and post-exercise therapy by establishing a control group and a control period.

In the current patient, leg muscle strength and exercise tolerance were maintained or improved at the interim and final evaluations compared with the initial evaluation. Previous studies have reported a 6–8% (0.4–0.6%/day) decrease in muscle mass after 2 weeks of bed rest.²⁴⁾ Furthermore, steroids significantly reduce muscle mass.²⁾ The current patient may also have experienced muscle loss due to bed rest and steroids for approximately 2 weeks from admission to the start of rehabilitation. However, the exercise therapy improved exercise tolerance in this study, supporting a previous study on the effectiveness of exercise therapy in pediatric renal disease patients²⁵⁾ and in adult patients with nephrotic syndrome taking steroids in the acute stage of the disease who were not in remission.⁶⁾

The main effects of resistance training include muscle hypertrophy, increased muscle strength, increased number of capillaries per fiber, and increased citrate synthase activity.^{26, 27)} Resistance training in pediatric patients with

nephrotic syndrome in the acute phase may improve muscle strength and exercise tolerance by increasing muscle mass, blood flow to muscles, and mitochondrial function. Furthermore, previous studies have reported that steroid myopathy selectively causes atrophy of type II fibers.²⁸⁾ Resistance training may reduce the atrophy of type II fibers characteristic of steroid myopathy because it mobilizes more type II fibers. The main effects of aerobic exercise are increased maximal oxygen uptake, increased cardiac output, and improved vascular endothelial function.^{26,29)} Furthermore, a previous study reported that treadmill exercise five times a week for 5 weeks in rats with glucocorticoid-induced muscle disease induced changes from type II to type I fibers in the moderate exercise group.³⁰⁾ Aerobic exercise for pediatric nephrotic syndrome patients may improve exercise tolerance by improving oxygen supply and utilization and by preventing atrophy of type I fibers. This case study suggests that moderate aerobic exercise, resistance training, and balance training may maintain and improve leg muscle strength and exercise tolerance, leading to improvement of disuse syndrome and prevention of steroid myopathy. However, under the current regimen, the upper limb and trunk muscle strengths and agility decreased. The grip strength for muscular strength of the upper limbs, the sit-up test for trunk muscle strength, and the side-step test for agility are all considered movements that mainly mobilize type II fibers because these movements require strong instantaneous force. The side-step test also evaluates the ability to change direction and start and stop quickly.³¹⁾ The resistance training in this case study was focused on the lower extremities, and training of the upper limbs, trunk, and agility was not conducted. Therefore, the current exercise therapy program did not prevent muscle weakness in type II fibers other than in the lower limbs and may not have improved the subitems such as upper limb strength, trunk muscle strength, and agility. In the future, we suggest that exercise therapy should include training for the whole body, not just the legs. Furthermore, we suggest other detailed muscle strength assessments and skeletal muscle mass assessments to investigate the effects of steroid myopathy.

This case study has some limitations. First, it was difficult to measure peak VO_2 and AT because an exercise tolerance test could not be performed using an expiratory gas analyzer. Second, skeletal muscle mass and steroid myopathy could not be evaluated, so the effect of exercise therapy on skeletal muscle was not clearly elucidated. Third, renal function and proteinuria immediately after exercise therapy were not evaluated, so the short-term safety of exercise was not

investigated.

An exercise therapy program based on resistance training, balance training, and moderate aerobic exercise was shown to be effective in improving leg muscle strength and exercise tolerance and was safe in the long term for the current patient. These results suggest that it may be important to provide exercise therapy to pediatric nephrotic syndrome patients to prevent decline and improve physical function during hospitalization. Furthermore, resistance training of the upper limbs and trunk and agility training should also be incorporated into the exercise therapy program.

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CONFLICTS OF INTEREST

The authors declare that no conflicts of interest exist.

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