

Case Report

# Effects of Prednisone on a Patient with Dysferlinopathy Assessed by Maximal Voluntary Isometric Contraction: Alternate-Day Low-Dose Administration for a 17-Year Period

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## Keywords

Dysferlinopathy · Limb-girdle muscular dystrophy type 2B · Prednisone · Alternate-day low-dose administration · Isometric muscle strength

## Abstract

Glucocorticoids are candidates for the pharmacological treatment of dysferlinopathy. Deflazacort, however, showed a worse effect on muscle strength than placebo. Alternate-day low-dose prednisone may have beneficial effects with fewer adverse effects. The outcomes for a female patient with dysferlinopathy (limb-girdle muscular dystrophy type 2B) were assessed by maximal voluntary isometric contraction (MVIC) using a newly devised chair and arm table with push-pull type strain gauges. Grip strength was also measured isometrically. Prednisone 15 mg was started orally at the age of 24 years and was taken every other day in the morning until 41 years of age. The MVIC of flexion of the knees and elbows increased gradually and significantly. The MVIC of extension of the knees and elbows increased to a lesser extent. Isometric grip strength showed no remarkable increase, but strength was sustained over 10 years. Muscle fiber types account for these differences. The beneficial effects of alternate-day prednisone treatment on dysferlinopathy are reported.

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## Introduction

Dysferlinopathy is an autosomal recessive disorder caused by mutations in the dysferlin (*DYSF*) gene and is most often characterized by two clinical phenotypes: Miyoshi distal myopathy (MM) and limb-girdle muscular dystrophy type 2B [1, 2]. Highly elevated serum creatine kinase (CK) and other muscle enzyme levels accompany the disorder.

No curative treatment for dysferlinopathy is currently known, including gene therapy [3, 4]. Therefore, it is a great concern for patients and their families to have access to any beneficial therapy to delay the progression of the disease or increase muscle strength. Dysferlin deficiency causes defective membrane repair and inflammatory responses [5, 6]. Thus, glucocorticoids and other immunosuppressive drugs have been candidates for the pharmacological treatment of dysferlinopathy. Deflazacort, however, has had rather worse effects on muscle strength than placebo [7]. Rituximab has been reported to increase handgrip muscle strength [8].

This report details the use of alternate-day prednisone therapy, which was chosen to minimize the side effects of the steroid, such as myopathy, hypertension, weight gain, osteoporosis, psychopathology, and others. The outcomes were assessed by maximal isometric muscle strength, physical findings, and biochemical studies.

## Case Report and Methods

A female patient was referred at the age of 14 years for the diagnosis of elevated serum CK. At this time, her manual muscle strength was in the normal range on the Medical Research Council Scale. She had previously been diagnosed with liver dysfunction because of elevated alanine and aspartate transaminases. At 20 years of age, she started to have difficulty ascending staircases. Two years later, a muscle biopsy of the right vastus lateralis was performed with her and her family's consent. DNA analysis was performed using peripheral blood leukocytes, also with consent.

To measure maximal voluntary isometric contraction (MVIC), a newly devised chair utilizing GT-30 (OG-Giken, Japan) and a position-adjustable arm table were used; each was equipped with a push-pull type strain gauge (Minebea U3B1-50k-B) connected to a switch selecting peak indicator. The repeatability of this gauge is 0.03% of the rated output. A muscle power receiving plate with a leather cushion and a pulling belt was screwed into the gauge (the transducer). This setup did not necessitate any change in the patient's sitting position during the measurements. During this study, the patient did not have any apparent joint contractures.

Knee flexion and extension were measured at 90° flexion with two belts on the thighs and a waist belt for restraint on a 12° tilted backrest. The distance from the knee joint axis to the lower pretibial site of the transducer was fixed at 0.375 m during the test. To distinguish static torque from isokinetic torque, "moment" was used and calculated by maximal peak value (kg) × 0.375 m × 9.8 N. Elbow flexion and extension were measured in a perpendicular position by putting the upper arm on the adjustable table with one restraint belt. The distance from the elbow joint axis to the transducer below the wrist joint was fixed at 0.245 m. Therefore, the moment value was equal to the maximal peak value (kg) × 0.245 m × 9.8 N. Pulling belts were used only for flexion of the joints. Measurements were performed successively three times with 2-min rest intervals.

Grip muscle power was measured isometrically in a horizontal position. Grip width was fixed at 5 cm during the test. Usually, the first value was recorded because of decreases following repetition. All measurements were performed by a single rater every time, which resulted in intrarater reliability coefficients of 0.97–0.98.

Clinical observation and laboratory examinations were performed for 27 years. After confirming the declines in MVIC of the extremities, an oral dose of 15 mg prednisone was started at the age of 24 years (0.25 mg/kg body weight) and was taken every other day in the morning, continuing until 41 years of age.

Graphical and statistical analyses were performed using Excel (2003) and PASW Statistics 18.

## Results

Histological examinations showed some variation in fiber caliber and an increase in endomysial connective tissue. Scattered necrotic fibers with phagocytosis were present. Immunohistochemistry showed positive dystrophin (C, N termini and Rod domain).

Three years later, after a dysferlin antibody (Novocastra) had become available, negative dysferlin staining was clarified. DNA analysis revealed compound heterozygous mutations, c.1939G>C in exon 18 and c.3746delG in exon 31, which caused stop codons.

Changes in serum CK since the first visit, after start of the treatment, and after cessation of prednisone are shown in [Figure 1](#). The maximal CK was 13,880 IU/L at the age of 18 years. After the start of prednisone, CK decreased from 4,751 IU/L to 3,060 IU/L 57 days later and then increased in a rebound-like fashion, followed by a gradual decrease as the disease progressed, as shown in [Figure 1](#). The isozyme of CK was 100% MM (total 6,309 IU/L) and LD isozymes showed a normal pattern (total 594 IU/L) just before prednisone was started. Ten months later, the isozymes of CK were MM: 98.6% and MB: 1.4% (total 6,829 IU/L), and the LD isozymes were LD1: 15.4%, LD2: 38.4%, LD3: 19.9%, LD4: 10.9%, and elevated LD5: 15.3% (total 360 IU/L). The latter was assessed to be an abnormal myopathic pattern.

The outcomes for muscles strength of the extremities are shown in [Figure 2](#). The MVIC of right knee flexion increased gradually from 7.11 to 13.20 N (+85.7%) on the 1,522nd day and then decreased gradually, passing the starting level on the 2,202nd day after prednisone treatment. The MVIC of left knee flexion showed a similar change (not shown). On the other hand, the MVIC of right knee extension increased to a lesser and shorter extent just after starting the steroid and then decreased exponentially. After cessation of the steroid, a slight but significant increase ( $p < 0.05$ ) was recorded on the right side of this right-handed patient, but not on the left side. The MVIC of right elbow flexion increased from 10.97 N to a maximum of 14.93 N (+37.0%) on the 1,200th day and sustained strength was observed until the 3,650th day. Left elbow flexion showed a similar change (not shown). On the other hand, the MVIC of right elbow extension showed a lesser and shorter increase after prednisone and then decreased gradually. Left elbow extension showed a similar but faster decrease (not shown). Right isometric grip strength showed no remarkable increase after the steroid but a sustainable tendency up to the 3,800th day. Left grip strength showed a greater tendency, as shown in [Figure 3](#).

Just before starting the steroid, body mass index (BMI) was 24.4, and 7 months later, a transient maximal BMI of 26.0 was observed. At approximately the time of peak MVIC of right knee flexion, the BMI was 23.1. There was no correlation between muscle strength and BMI.

No hyperlipidemia was observed during this study. Liver and renal functions remained normal.

## Discussion

Elevated serum CK reflects muscle fiber damage and damaged integrity of the sarcolemma. In this case, CK decreased after prednisone treatment for 87 days, while all muscle strength increased. Thereafter, individual changes in flexion and extension muscle power were observed. The strength of the flexor muscles of the knees and elbows increased significantly after the prednisone treatment. The strength of the extensors of the knees and elbows showed lesser increases and faster declines. These differences could be explained by fiber type differences. The catabolic effect of glucocorticoids is known to be more prominent in type II fibers. Rectus femoris muscles contain 61.9% type II and 38.1% type I fibers (means for the surface lateral head, deep lateral head, and medial head). Biceps femoris muscles contain 66.9% type I and 33.1% type II fibers. Biceps brachii muscles contain 46.4% type I and 53.6% type II fibers (means for surface and deep muscles), with almost equal proportions. Triceps muscles contain 32.6% type I and 67.4% type II fibers (means for surface and deep muscles).

Grip power is mainly generated by the flexor digitorum profundus, which contains 47.3% type I and 52.7% type II fibers. These fiber type proportions are from the data of human muscles reported by Johnson et al. [9]. The effect of prednisone on grip power has been beneficial. The patient has been working and using a computer keyboard even at 42 years of age. Prednisone seemed to increase muscle strength more in type I fibers. A megascore consisting of the muscle strength of both extensors and flexors combined might obscure changes in outcomes by any intervention. Right and left differences in grip power might be due to handedness and overuse damage to the diseased muscles, as observed in facioscapulohumeral muscular dystrophy or polymyositis (personal observation).

A positive correlation between annexin A1 and A2 and clinical severity in patients with dysferlin deficiency has been reported [10]. The glucocorticoid possibly increased annexin A1 and together with annexin A2 and A6 promoted the repair of the sarcolemmal tubular system [11, 12]. Intermittent glucocorticoid treatment enhanced muscle repair without eliciting muscle atrophy in mice [13]. Recently, prednisone provided once weekly was reported to have improved muscle function in the murine limb-girdle muscular dystrophy type 2B model [14].

This study is only one case report; however, the accurate estimation of muscle strength and alternate-day administration of the glucocorticoid for a 17-year period could elucidate its effect on dysferlinopathy. Additional similar trials in more cases are expected.

## Acknowledgments

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## Statement of Ethics

Informed consent was obtained from all individuals who participated in this study. This study was approved by the Committee of Research Ethics of our clinic.

## Disclosure Statement

The author has no conflict of interest to disclose.

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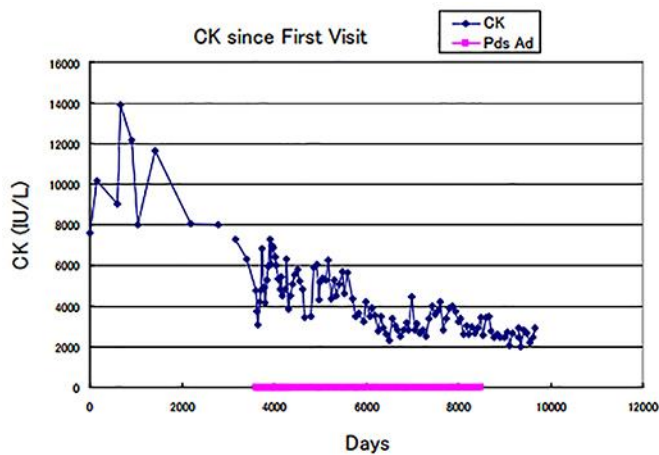


Fig. 1. CK values following the first visit and after the administration of prednisone.

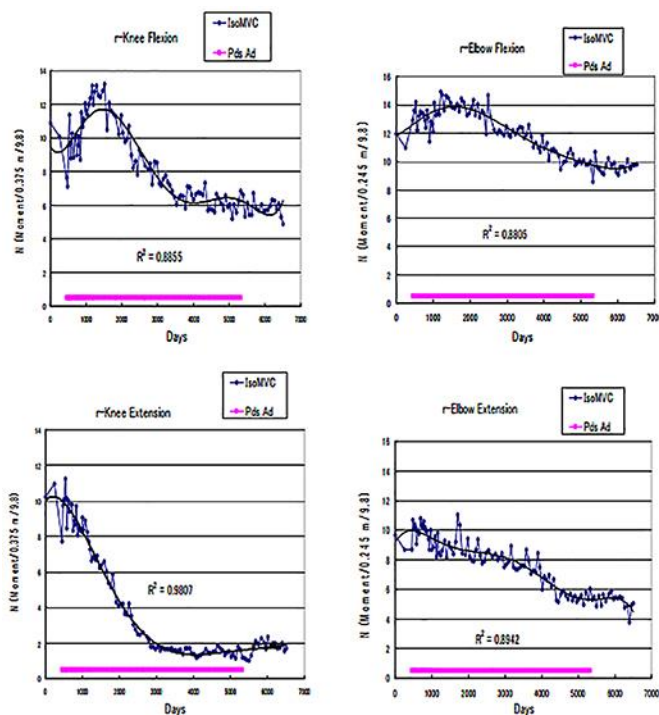
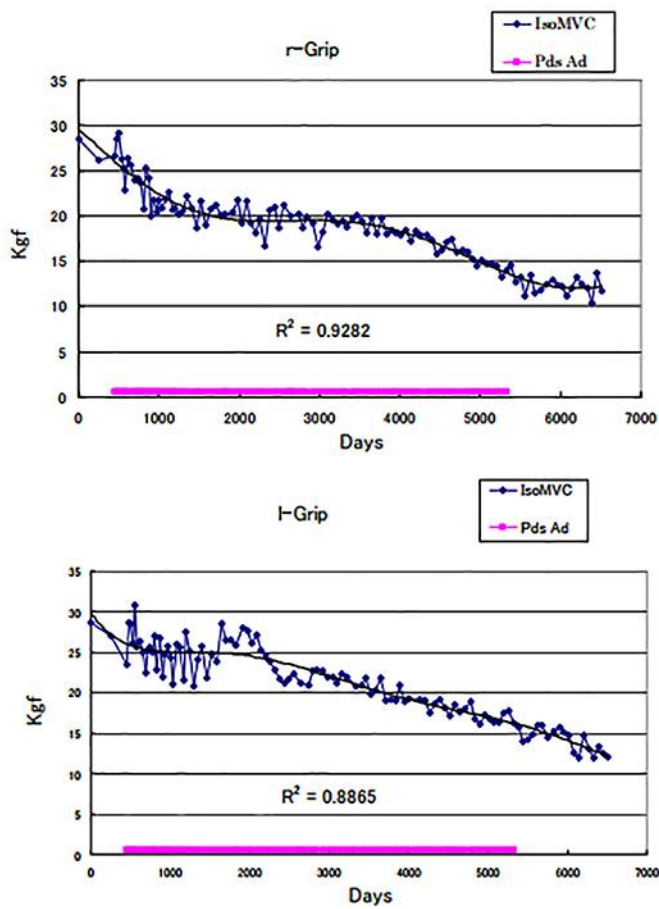


Fig. 2. Effects of prednisone on the extensors and flexors of the right knee and the right elbow. Regression lines were made by 6th-degree polynomial analyses.  $R^2$  values are shown in each graph.



**Fig. 3.** Effects of prednisone on right and left grip power. Regression lines were made by 6th-degree polynomial analyses.  $R^2$  values are shown in each graph.