

## CASE REPORT

# Case report of an exercise training and nutritional intervention plan in a patient with A350P mutation in DES gene

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**Abstract**

Performing a supplementation intervention with creatine and protein, in conjunction with low-intensity endurance and resistance exercise is safe and has a positive effect on the quality of life in a patient with desminopathy.

**KEYWORDS**

creatine, desmin, desminopathy, exercise, neuromuscular disease

## 1 | INTRODUCTION

We present the case of a patient with muscular dystrophy—desminopathy—who underwent for 24 weeks on a supervised exercise and protein/creatine supplementation intervention. The results of the present case show that the interventions were safe and had a positive effect on muscle mass and quality of life.

Desminopathy is a neuromuscular disease caused by a mutation of DES, the gene encoding the intermediate filament desmin.<sup>1</sup> Desmin primarily functions to provide structure within the sarcomere by connecting the contractile apparatus to the plasma membrane, nucleus and mitochondrial membranes of cardiac and skeletal muscle.<sup>2-4</sup> Recently, 67 different mutations of DES gene were described of which arginine 350 proline (A350P) was the most common.<sup>5</sup> This mutation affects both cardiac and skeletal muscle and usually presents as weakness in the appendicular leg muscles before spreading proximally leading.<sup>1</sup> The normal progression of the disease is increasing weakness resulting in paresis and wheelchair dependence.

To date, there are no treatments available for desminopathies; however, the application of exercise and nutritional

strategies to minimize the progression of this disease and the secondary pathologies associated with it (ie, insulin resistance, cardiovascular risk due to physical inactivity), could provide significant value for these patients. There is substantial evidence supporting the use of exercise and nutrition to improve quality of life in people with Duchenne muscular dystrophy.<sup>6,7</sup> However, in patients with desminopathy, it is not clear whether these strategies are beneficial or accelerate the progression of the disease. Thus, the present case study aimed to identify whether an exercise and nutritional regimen would be beneficial in a patient with the A350P mutation in DES gene.

## 2 | CASE PRESENTATION

A 49-year-old male of German descent diagnosed in 2006 with desminopathy—with confirmation of a A350P mutation of the DES gene—was referred with the following symptoms: (a) muscular weakness in lower extremities, which were more severe in the left leg; (b) muscular weakness in upper left extremity (shoulder and shoulder girdle); and (c) recurrent falls every 2-3 months.

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The patient moved with the help of a cane and while walking presented a mix of slippage and waddling. Postural evaluation revealed anteversion of head, neck, and pelvis accompanied by hyperkyphosis of the dorsal column. Muscle strength testing<sup>8</sup> revealed lower extremity muscle weakness, whereas upper extremity strength was normal.

The patient was consuming the following drugs: metformin hydrochloride (500 mg); clonazepam (5 mg); olmesartan medoxomil (20 mg); escitalopram oxalate (10 mg); acetylsalicylic acid (100 mg); eszopiclone (3 mg); and allopurinol (100 mg), at presentation and throughout the intervention.

The intervention consisted of a 6-month nutritional program and an exercise program for the final 3 months of the study. The purpose of the case study was to first determine whether exercise was safe, and second whether an exercise and nutritional supplementation plan could attenuate the progressive loss of muscle mass and improve quality of life of the patient.

## 2.1 | Nutritional intervention

Prior to the intervention, the amount and macronutrient content of the patient's diet was assessed. The initial assessment determined that he consumed ~3.0 g/kg/d of carbohydrate, ~0.5 g/kg/d of fat, and ~1.5 g/kg/d of protein. Protein intake of the patient was within current recommendations for his age; however, we sought to increase protein in the diet, as it has recently been suggested that ill patients should consume between 2.0 and 2.5 g/kg/d of protein.<sup>9</sup> In addition, 3 grams/day creatine monohydrate (GNC) was added to the diet in an effort to increase lean mass and muscle strength, since this is beneficial in patients with muscular dystrophy.<sup>10</sup>

Beyond the basic changes to the diet, the patient consumed 31 g of casein (MuscleTech Platinum, Bryan, TX, USA) 3 times per week before going to sleep. In addition, the patient was supplemented with 22 g of whey protein (Dymatize ISO

100) and 2 g of leucine (Leucine complex, GNC) after each exercise bout.

## 2.2 | Exercise intervention

The exercise intervention was divided in two parts: acute and chronic (Table 1). Acute exercises were performed to determine whether endurance or low-intensity resistance exercises would lead to significant muscle damage. The chronic exercise intervention was designed after no significant increase in creatine kinase was detected following the acute interventions. The supervised exercise program was performed for 12 weeks and consisted of two different exercise protocols performed on separate days: (a) arm ergometer at 60% of maximal heart rate (HR) for 30 minutes, including a 5 minutes warm up and a 5 minutes cool down (Figure 1); and (b) blood flow restricted (50 mm Hg) resistance exercises: bicep curl, pull down, pull up, quadricep isometric, and hip abduction and adduction (Figure 2) (Table 1), involving 1 set of 30 repetitions and 3 sets of 15 repetitions with a 30-second break between sets. During each exercise bout, the patient wore a Polar V800 HR monitor (Kempele) and was asked before the end of each exercise session to estimate the intensity of the training session utilizing the Borg rating of perceived exertion scale.<sup>11</sup>

## 2.3 | Blood measurements

Blood sampling was performed at Clinica UC-CHRISTUS for analysis of metabolic and inflammatory markers, including triglycerides (TG), total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), insulin, and glucose.

Blood creatine kinase (CK) levels were measured in the Ciencias del Deporte y Movimiento laboratory at the Universidad Finis Terrae) using a spectrophotometer (Reflotron<sup>®</sup> Plus, Roche Diagnostics).

**TABLE 1** Acute and chronic exercise, rating of perceived exertion (RPE), heart rate (HR), and blood creatine kinase (CK) levels

| Type of exercise                                   | Time | RPE    | HR     | CK (U/L) |           |           |
|--|------|--------|--------|----------|-----------|-----------|
|  |      |        |        | Pre      | Post 20 m | Post 24 h |
| Cycle ergometer                                    | 30   | 15     | 109    | 113      | 117       | 66        |
| Arm ergometer                                      | 30   | 15     | 101    | 102      | 107       | 103       |
| Blood flow (50 mm Hg) restricted UE and LE         | 60   | 14     | 86     | 97       | 86        | 69        |
| Treadmill (2 km/h)                                 | 20   | 12     | 95     | 93       | 103       | 105       |
| Treadmill (3 km/h)                                 | 20   | 16     | 110    |          |           |           |
| Chronic arm ergometer                              | 30   | 15 ± 1 | 93 ± 3 | –        | –         | –         |
| Chronic blood flow (50 mm Hg) restricted UE and LE | 60   | 13 ± 1 | 95 ± 4 | –        | –         | –         |

Abbreviations: LE, lower extremity; UE, upper extremity.

## 2.4 | Body composition

Body composition was measured at Clinica MEDS with a dual-energy X-ray absorptiometry (DXA, Hologic Discovery Wi). Waist circumference was measured in the laboratory.

## 2.5 | Timed up and go test

To assess the clinical mobility, the patient performed the timed up and go test.<sup>12</sup>

## 2.6 | Questionnaires

A series of questionnaires were completed by the patient to assess quality of life and independence including: (a) WHO quality of life-BREF (WHOQOL-BREF) (World Health Organization); (b) functional independence measure (FIM)<sup>13</sup>; and (c) multidimensional assessment of fatigue (MAF)<sup>14</sup>

## 2.7 | Creatine kinase

Baseline blood creatine kinase (CK) levels were normal and CK level remained unaltered both 20 minutes and 24 hours after an



**FIGURE 1** Image of arm cycle ergometer exercise

acute bout of cycle ergometry, arm ergometry, treadmill exercise, and blood flow-restricted strength training (Table 1).

## 3 | RESULTS

### 3.1 | Body composition

After the 24-week intervention, there was a 1.7 kg reduction in body mass, mostly due to a reduction in fat mass from 49.5 to 48 kg (Table 2). Fat-free mass only decreased 0.1 kg, whereas waist circumference was decreased by 2 cm (Table 2).

### 3.2 | Blood analyses

Total cholesterol decreased 17 mg/dL after the intervention, mainly due to a reduction in HDL-c (11 mg/dl). There were no changes in HOMA-IR and TG in blood (Table 2).

### 3.3 | Timed up and go test

After the intervention, there was a 6.6% improvement in time to perform the timed up and go test (Figure 3). Despite this positive result, the patient remained at the same level of classification (ie, over 20 seconds).

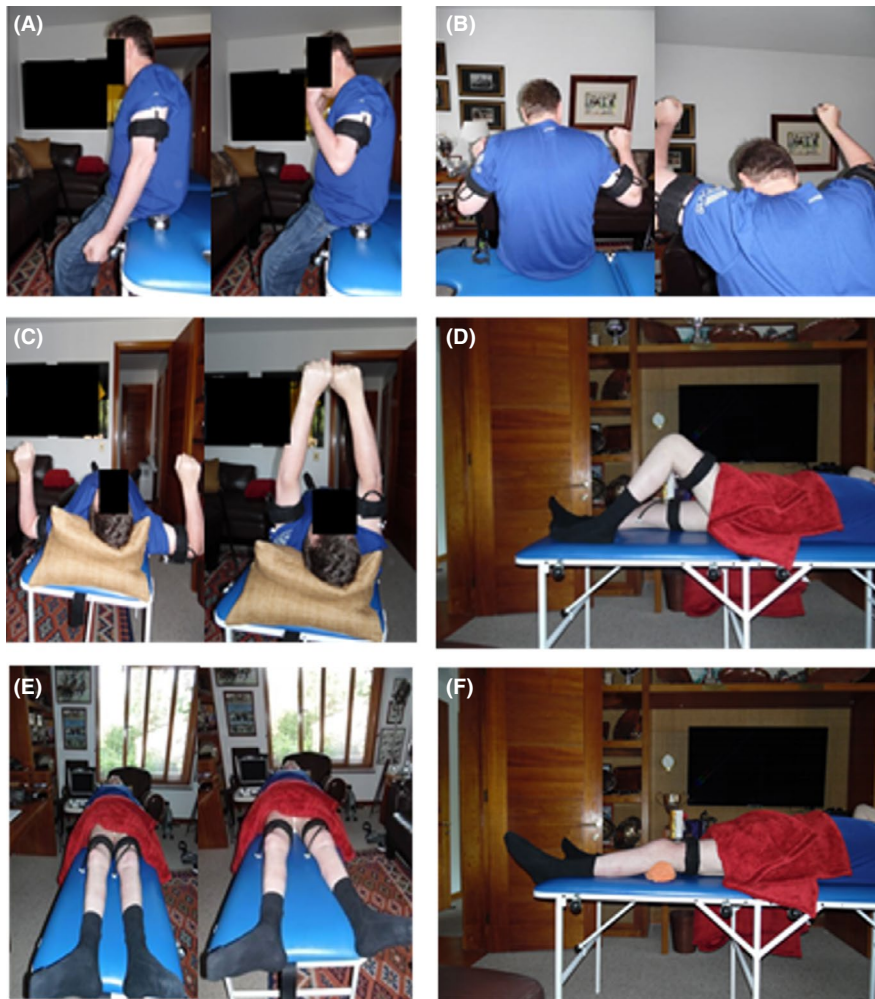
### 3.4 | Quality of life questionnaires

In the abbreviated version of quality of life questionnaire, the patient improved their score by 25% (Figure 4A). In addition, there was a 24% decrease in fatigue sensation (Figure 4B) and a 5.3% increase in functional independence test (Figure 4C).

## 4 | DISCUSSION

The results of the present case study revealed that acute and chronic low-intensity exercises were viable and safe in a patient with desminopathy (A350P mutation). In addition, the combination of a long-term exercise training and nutritional supplementation plan improved quality of life, physical function, and sensation of fatigue.

To date, it is not clear whether physical activity is beneficial or harmful in people with desminopathy. To our knowledge, this is the first report to provide evidence that acute exercise did not induce muscle damage in a patient with A350P mutation in DES gene. An indirect marker of muscle injury (blood CK levels) was normal at baseline and not affected by low-intensity endurance or resistance



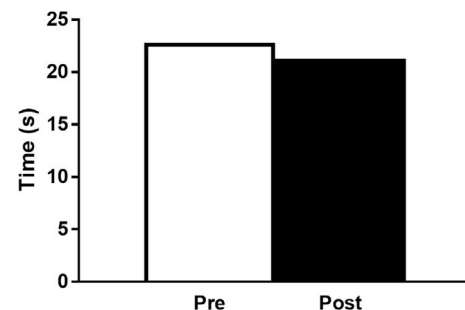
**FIGURE 2** Images of blood flow restricted exercises. Bicep curl (A); pull down (B); pull up (C); quadricep isometric (D, F); and hip abduction and adduction (E)

**TABLE 2** Body composition and blood measures

| Subject characteristics   | PRE  | POST |
|---------------------------|------|------|
| Body mass (kg)            | 94   | 92.3 |
| Fat mass (kg)             | 49.5 | 48   |
| Fat-free mass (kg)        | 41.2 | 41.1 |
| Waist circumference (cm)  | 116  | 114  |
| Total cholesterol (mg/dL) | 193  | 176  |
| Triglycerides (mg/dL)     | 295  | 294  |
| HDL-c (mg/dL)             | 38   | 27   |
| LDL-c (mg/dL)             | 96   | 90   |
| HOMA-IR                   | 7.2  | 7.4  |

Abbreviations: HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment-insulin resistance; LDL-c, low-density lipoprotein cholesterol.

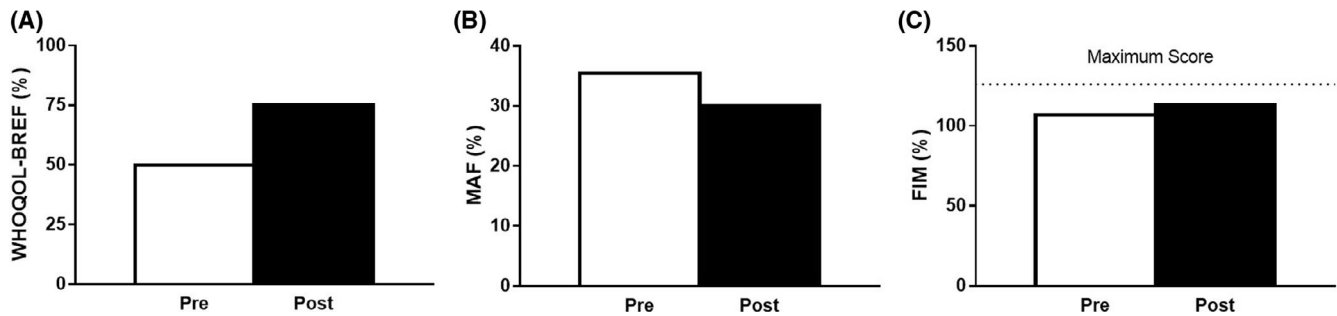
exercise. In support of the hypothesis that exercise did not induce muscle injury, neither body weight supported nor impact exercise (walking of the treadmill at 3km/h) induced an increase in CK. These results are similar to previous studies performed in patients with other muscular dystrophies where assisted cycling and arm ergometer exercises were shown to be safe.<sup>15-18</sup>



**FIGURE 3** Time (s) to perform timed up and go test

The patient of the present study is in an advanced stage of his disease. At presentation, he walked with the help of a cane and for longer distances used a wheelchair. Thus, a second goal of this case study was to improve the quality of life through a targeted and evidence-based exercise and nutritional plan. Despite not demonstrating significant improvements in cardiovascular function and body composition, disease progression was minimized, and quality of life was improved. In fact, this protocol yielded a 25% decrease in fatigue and improved functional independence, similar to previous studies in patients with other myopathies.<sup>19,20</sup> All





**FIGURE 4** World Health Organization Quality of Life-BREF (WHOQOL-BREF) (A); multidimensional assessment of fatigue (MAF) (B); and functional independence measure (FIM) (C)

together these results provide evidence that low-intensity exercise training in combination with a nutritional intervention plan is beneficial and, therefore, should be recommended to slow the progression and severity of this desminopathy.

A major limitation of the present report is that there were no measurements performed to test the independent effects of the nutritional plan after the first three months of the intervention; therefore, it was not clear whether the improvements reported by the patient were due to exercise, the nutrition intervention or a combination of both interventions. Further, it remains to be elucidated whether other exercise protocols (ie, higher intensity exercises) are well tolerated by these patients. Lastly, it is not clear whether training the legs through treadmill exercise or cycle ergometry would recruit more muscle mass and better improve functional results such as timed up and go test. Future studies should assess the independent effects of nutritional supplements and exercise and the specific exercise used on progression of the disease, function, and quality of life.

In conclusion, this case report demonstrates that low-intensity exercises are safe, even in advanced stages of desminopathy. In addition, this study proved that a nutritional intervention (protein and creatine supplementation) in combination with exercise training minimized progression of the disease, improved body composition, and quality of life. Therefore, we suggest that low-intensity exercise, greater dietary protein, and creatine monohydrate should be recommended in patients with desminopathy.

#### ACKNOWLEDGMENTS

The research was made possible by a generous gift from Family Bertin Barbe.

#### CONFLICT OF INTEREST

None declared.

#### AUTHOR CONTRIBUTIONS

CM: contributed to the conception of the study, analyzed and interpreted the data, wrote the first draft of the manuscript, and approved the final version of the manuscript. SJ-V: analyzed and interpreted the data, wrote the first draft of the

manuscript and approved the final version of the manuscript. KB: contributed to the conception of the study, and approved the final version of the manuscript. HZ-F: contributed to the conception of the study, analyzed and interpreted the data, wrote the first draft of the manuscript, and approved the final version of the manuscript.

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**How to cite this article:** Monje C, Jannas-Vela S, Baar K, Zbinden-Foncea H. Case report of an exercise training and nutritional intervention plan in a patient with A350P mutation in DES gene. *Clin Case Rep.* 2020;8:283–288. <https://doi.org/10.1002/ccr3.2607>