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The Use of D-Ribose in Chronic Fatigue Syndrome and Fibromyalgia: A Pilot Study

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ABSTRACT

Objectives: Fibromyalgia (FMS) and chronic fatigue syndrome (CFS) are debilitating syndromes that are often associated with impaired cellular energy metabolism. As D-ribose has been shown to increase cellular energy synthesis in heart and skeletal muscle, this open-label uncontrolled pilot study was done to evaluate if D-ribose could improve symptoms in fibromyalgia and/or chronic fatigue syndrome patients.

Design: Forty-one (41) patients with a diagnosis of FMS and/or CFS were given D-ribose, a naturally occurring pentose carbohydrate, at a dose of 5 g t.i.d. for a total of 280 g. All patients completed questionnaires containing discrete visual analog scales and a global assessment pre– and post–D-ribose administration.

Results: D-ribose, which was well-tolerated, resulted in a significant improvement in all five visual analog scale (VAS) categories: energy; sleep; mental clarity; pain intensity; and well-being, as well as an improvement in patients' global assessment. Approximately 66% of patients experienced significant improvement while on D-ribose, with an average increase in energy on the VAS of 45% and an average improvement in overall well-being of 30% ($p < 0.0001$).

Conclusions: D-ribose significantly reduced clinical symptoms in patients suffering from fibromyalgia and chronic fatigue syndrome.

INTRODUCTION

Fibromyalgia (FMS), which currently affects an estimated 3 to 6 million Americans,[1,2] and chronic fatigue syndrome (CFS) are disabling syndromes that often coexist. Patients suffering with these syndromes commonly report severe persistent fatigue, diffuse migratory pain, cognitive dysfunction, and disordered sleep.

Many of the clinical symptoms found in FMS/CFS may be related to a decrease in tissue energy levels with altered energy metabolism. Previous reports claim that abnormal muscular energy metabolism frequently can be reflected in pain because of chronic muscle shortening,[3] postexertional fatigue, and low exercise tolerance associated with decreased cardiac output and stroke volumes.[4] In addition, it has been postulated that decreased energy production in these syndromes also may result in hypothalamic dysfunction, which can be reflected clinically as disordered sleep, hormonal imbalances, and autonomic dysfunctions.[5] Causes and mechanisms for this mitochondrial dysfunction are unknown; however, an alteration in muscle adenine nucleotide metabolism is found, mainly in lower adenosine triphosphate (ATP) levels and depleted energy reserves.[6,7]

D-Ribose, a naturally occurring pentose carbohydrate, is a key structural component in the DNA, RNA, ATP, FADH, coenzyme-A, and NADH needed by the mitochondria to maintain cellular energy homeostasis. Supplemental doses of D-ribose in patients with congestive heart failure and ischemic heart disease have shown a significant improvement in diastolic dysfunction, physical function, exercise tolerance, and quality of life.[8] D-Ribose has also been reported to be effective in restoring tissue energy levels following intense exercise[9] and in an isolated case report of a patient with FMS.[10] Because of the known energy and functional

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benefits of D-ribose, an open-label uncontrolled pilot study was performed to assess whether D-ribose would decrease symptoms in patients suffering from FMS and CFS.

MATERIALS AND METHODS

Patient enrollment

Forty-one (41) adult patients, diagnosed by their physicians as having FMS (by ACR Criteria) and/or CFS (by CDC criteria), were found eligible for this study. In addition, patients also had to be without known severe medication or nutrient sensitivities, and not have taken D-ribose in the past. Recruitment of patients was through the FMS and CFS e-mail newsletter associated with the Annapolis Research Center and the www.Vitality101.com web site. Readers with an established diagnosis of FMS or CFS were informed about the nature of the study and were invited to participate if they satisfied the entrance criteria. All patients were thoroughly informed about D-ribose, its potential benefits, and possible adverse side-effects and gave informed consent. The protocol is consistent with the principles of the Declaration of Helsinki. Except for a free container of D-ribose, patients received no compensation.

Design of study

A 280-g container of D-ribose (CORvalen, Valen Labs, Minneapolis, MN) and a questionnaire (outcome measures) were mailed to each subject once the patient was enrolled. Each patient was instructed to take one scoop (5-g) of D-ribose three times per day (t.i.d.) mixed with food, water, or another beverage until the container was empty and then to return the container and questionnaires in a prepaid envelope. They were instructed to stay on their current treatment regimen and not change dosing or add or delete any treatments during the study.

Outcome measures

Subjective outcome measures were assessed using discrete Visual Analog Scale questions (DVAS) pre- and postintervention. Measured DVAS parameters were energy levels, sleep disturbances, mental clarity, pain, and an overall sense of well-being.

Patients were asked to individually rate each of these five areas on a 1 to 10 scale as shown below:

A. How is your energy?
1 2 3 4 5 6 7 8 9 10
1 = near dead and 10 = excellent
B. How is your sleep?
1 2 3 4 5 6 7 8 9 10
1 = no sleep and 10 = 8 hours of sleep a night without waking
C. How is your mental clarity?
1 2 3 4 5 6 7 8 9 10
1 = brain dead and 10 = good clarity
D. How bad is your pain?
1 2 3 4 5 6 7 8 9 10
1 = very severe pain and 10 = pain free
E. How is your overall sense of well-being?
1 3 4 5 6 7 8 9 10
1 = near dead and 10 = excellent

Compliance was addressed in each patient by asking how many doses were missed and noting how long it took to finish the 280-g container, as well as by weighing the received container at the completion of the study. Each patient was asked if any adverse side effects occurred while on D-ribose. Finally, each patient commented on his or her overall subjective feeling while taking D-ribose: much better, somewhat better, no change, somewhat worse, or much worse.

RESULTS

Of the 41 patients enrolled in the study, five patients were considered noncompliant; therefore, they were excluded from the study and final analysis. Noncompliance was defined as having consumed half or less of the provided D-ribose during the study. Of the 36 remaining patients, the average age was 48 years, 78% were female. Patients had been ill with CFS/FMS for an average of 7.15 years. Further demographics are summarized in Table 1. The average length of time on D-ribose was 25 days (range, 17 to 35 days).

Subjectively, significant improvements were found in energy levels ($p < 0.0001$), sleep patterns ($p < 0.0001$), mental clarity ($p < 0.003$), pain threshold ($p < 0.026$), and the patient's state of well-being ($p < 0.0001$) when comparing questionnaires at enrollment and at the completion of the study in all of the patients (Table 2). Table 3 denotes the pre- and postribose assessments in patient categories for each separate syndrome.

At the completion of the study, patients also felt a positive subjective improvement while taking D-ribose (Table 4). Twenty-three (23) of the 35 patients (65.7%) completing the assessment experienced improvement during the course of the study (somewhat better to much better) while taking D-ribose. The responses were compared to the null

Table 1. Patient Demographics

Patient demographics	
Sex	Female: 28 (78%)
Average age	48 years (21–62)
Previous diagnosis: FMS	75%
Previous diagnosis: CFS	58%
Average duration CORvalen therapy[a]	28 days (17–35)

FMS, fibromyalgia; CFS, chronic fatigue syndrome.
[a]Valen Labs, Minneapolis, MN.

Table 2. Pre- and Postribose Assessments: All Patients

Category	N	*Pre mean (std)*	*Post mean (std)*	*Difference (95% CI)*	p-*Value*
Energy level	36	3.8 (1.1)	5.5 (1.5)	1.7 (1.1, 2.2)	<0.0001
Sleep	36	4.8 (1.6)	6.0 (1.9)	1.2 (0.6, 1.7)	0.0001
Mental clarity	36	4.9 (1.5)	5.7 (1.7)	0.8 (0.3, 1.3)	0.003
Pain	36	4.9 (2.3)	5.6 (2.2)	0.7 (0.1, 1.3)	0.026
Well-being	36	4.3 (1.3)	5.6 (1.5)	1.3 (0.8, 1.9)	<0.0001

CI, confidence interval.

response of "No Change" in a one-sample nonparametric sign test and signed rank test. Both tests resulted in statistical significance ($p < 0.0001$).

The following subgroup analyses were also performed: gender, age, CFS, and FMS. Gender was at least a marginally significant predictor of measured outcomes: energy levels ($p < 0.02$), sleep patterns ($p < 0.001$), mental clarity ($p < 0.002$), pain threshold ($p < 0.06$), state of well-being ($p < 0.03$), and total score ($p < 0.001$). Age was not associated with any of the outcome parameters: energy levels ($p < 0.80$), sleep patterns ($p < 0.32$), mental clarity ($p < 0.97$), pain threshold ($p < 0.50$), a state of well-being ($p < 0.45$), and total score ($p < 0.58$). A prior diagnosis of CFS was not associated with any of the outcomes: energy levels ($p < 0.59$), sleep patterns ($p < 0.28$), mental clarity ($p < 0.33$), pain threshold ($p < 0.39$), state of well-being ($p < 0.39$), and total score ($p < 0.27$). Likewise, a prior diagnosis of FMS was not associated with any of the measured outcomes: energy levels ($p < 0.58$), sleep patterns ($p < 0.29$), mental clarity ($p < 0.20$), pain threshold ($p < 0.43$), state of well-being ($p < 0.33$), and total score ($p < 0.24$).

Of the five patients that were found to be noncompliant, three stopped taking D-ribose because of a hyperanxious feeling (one patient), lightheadedness (one patient), and increased appetite (one patient). Two others changed their mind and simply did not begin the study. Of the remaining 36 patients who completed the study, one patient experienced transient nausea and another felt mild anxiety. Both of these reactions were reversed by simply lowering the dose of D-ribose.

DISCUSSION

Fibromyalgia and CFS are common, nonarticular, debilitating syndromes that affect approximately 2%–4% of the population worldwide. Patients with FMS and/or CFS generally demonstrate reduced sustained exercise capacity, with lack of muscular contractile force and endurance.[11,12] Similar conditions are frequently associated with abnormal metabolism. Therefore, many FMS and/or CFS studies have investigated potential alterations in muscle metabolism.[6,13,14–19]

Table 3. Pre- and Postribose Assessments per Diagnosis

	FMS (N = 15)			*CFS (N = 9)*			*Both FMS/CFS (N = 12)*		
Category	*Pre mean (std)*	*Post mean (std)*	*Improvement (%)*	*Pre mean (std)*	*Post mean (std)*	*Improvement (%)*	*Pre mean (std)*	*Post mean (std)*	*Improvement (%)*
Energy	3.7 (1.0)	5.5 (1.5)	1.8 (48%)	4.2 (1.4)	6.1 (1.5)	1.9 (45%)	3.7 (1.2)	4.9 (1.4)	1.2 (32%)
Sleep	4.4 (1.2)	5.9 (1.6)	1.5 (34%)	5.6 (1.7)	7.2 (1.7)	1.6 (29%)	4.8 (1.9)	5.2 (2.2)	0.4 (8%)
Mental clarity	4.7 (1.0)	5.7 (1.8)	1.0 (21%)	5.2 (2.0)	6.6 (1.7)	1.4 (27%)	5.1 (1.7)	5.1 (1.3)	0
Pain	4.5 (2.3)	5.5 (2.0)	1.0 (22%)	6.7 (2.3)	7.8 (1.6)	1.1 (16%)	4.1 (1.6)	4.1 (1.2)	0
Well-being	4.1 (1.0)	5.7 (1.5)	1.6 (39%)	4.6 (1.7)	6.3 (1.2)	1.7 (37%)	4.3 (1.3)	5.0 (1.5)	0.7 (16%)

FMS, fibromyalgia; CFS, chronic fatigue syndrome.

Table 4. Global Subjective Feeling Rating

Response	N *(%)*
Much better	5 (14.3%)
Somewhat better	17 (48.6%)
Somewhat better/no change	1 (2.9%)
No change	9 (25.7%)
No change/somewhat worse	1 (2.9%)
Somewhat worse	2 (5.7%)
Much worse	0 (0%)

Adenosine triphosphate (ATP) is the primary energy source of all living cells. In tissues subjected to metabolic stress, such as hypoxia, ischemia, or known conditions of mitochondrial dysfunction, ATP is catabolized with compromised metabolic recovery. With ATP catabolism, adenosine diphosphate (ADP) levels accumulate, forcing the cell to try to balance ATP/ADP ratios in order to maintain energy stasis. However, these reactions ultimately lead to an increased intracellular concentration of adenosine monophosphate (AMP). In an effort to try to control energy balance, the cell catabolizes AMP, ultimately forming inosine, hypoxanthine, and adenine. These catabolic end products are washed out of the cell, resulting in a net loss of purines and an ultimate reduction in the total pool of adenine nucleotides. Potentially, up to 90% of these produced catabolites can be biochemically salvaged and recycled.[9,20,21]

The rate of recovery of these energy substrates in metabolically stressed cells is important for functional recovery of the cell, including muscle.[20,21–23] Therapeutic solutions that could try to maintain a cell's energy stasis include either blocking the degradation of adenine nucleotides or providing metabolic supplementation to enhance nucleotide recovery via the salvage or *de novo* pathways of purine synthesis.

The availability of 5-phosphoribosyl-L-pyrophosphate (PRPP) is rate limiting in adenine nucleotide *de novo* synthesis and salvage pathways, which is necessary to preserve or rebuild cellular energy stores.[9,20,21] 5-Phosphoribosyl-L-pyrophasphate is formed through pyrophosphorylation of ribose-5-phosphate that is, itself, synthesized from glucose via the pentose phosphate pathway (PPP; or hexose monophosphate shunt). The rate-limiting enzymes in the PPP, glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase, are poorly expressed in heart and muscle cells. As such, in skeletal muscle the PPP is suppressed, limiting ribose availability as a substrate to drive the purine nucleotide pathway and retarding purine nucleotide synthesis during or following a metabolic insult.

The energy reserve, phosphorylation potential (PP), and the ability to use oxygen (total oxidative capacity or V_{max}) have been determined using P-31 MRS in both normal and fibromyalgic muscle.[16] Both mean PP and V_{max} values are found to be significantly reduced in FMS.[16] These findings are consistent with reduced oxidative phosphorylation and ATP synthesis, which translate clinically to muscle fatigue, soreness, and stiffness.[24] Impairment in mitochondrial oxidative phosphorylation and potentially diminished glucose metabolism impact ATP turnover, suggesting that the muscles of fibromyalgia patients are energy starved. Further, decreased ATP concentrations with accompanying changes in energy metabolism have been found in the red blood cells of fibromyalgia patients,[25] suggesting that this energy deficiency may be systemic.

Muscular metabolic abnormalities in fibromyalgia have been proposed.[6] Dysfunctional metabolism has been shown to lead to cellular abnormalities[6] that impact cellular function, producing clinical symptoms. Muscle biopsies have shown that levels of phosphocreatine (PCr) and ATP are significantly reduced (21% and 17%, respectively) in muscle tissues of fibromyalgia patients and the synthesis of PCr, an important store of cellular high-energy phosphates, is deficient. Magnetic imaging of skeletal muscle has shown that resting levels of ATP are 15% lower in fibromyalgia patients than in normal controls and during exercise PCr and ATP levels remain significantly low.[14,16,19] During exercise there is an increase in metabolic breakdown products of ATP (phosphodiesters) in fibromyalgic skeletal muscle groups, indicating abnormal adenine nucleotide metabolism and disruption of cell membranes, which are common in other muscular diseases. There has been speculation that these findings may be similar in patients afflicted with CFS.[16]

It also has been shown that there are a decreased numbers of capillaries within fibromyalgic muscle fibers, which can reduce the oxidative capacity, leading to limited energy turnover, purine pool depletion, and increased pain.[24,26] Thickening of the capillary endothelium also contributes to restricted oxygen transport or delivery, further lowering oxygen tension in the muscle, affecting energy metabolism and contributing to functional fatigue and weakness. In general, the fibromyalgic muscle has lower ATP concentrations than normal muscle. Further, these factors can alter calcium and cellular ion stasis, which, clinically can produce muscle soreness, stiffness, fatigue, and diminished exercise capacity.

Patients with FMS and/or CFS may therefore have an alteration in muscular energy use and metabolism. Fibromyalgic muscle reaches anaerobic threshold earlier in exercise, thereby potentially using less available energy-rich phosphate metabolites at maximal work capacity. Patients with FMS may have abnormal high-energy phosphate metabolism with significantly lower levels of ATP and ADP in affected muscles as compared to normal controls.[24]

The findings in this pilot study, using daily D-ribose, revealed an increased improvement in the quality of life in patients afflicted with FMS/CFS. However, there are several limitations noted in this study. A major limitation centers on a lack of a placebo group. This was, however, meant as an initial pilot study with each patient acting as their own control. A follow-up RCT is, of course, critical and currently

under way using information (and impetus) gained from this pilot study. In addition, as patients were not seen in a clinic, initial assessment of each patient relied on their own personal physician providing an accurate clinical diagnosis of FMS/CFS. This pilot assessment was designed as a clinically focused, community-based study, and this reflects what occurs in most patients' cases.

Subjective outcome measures were only assessed in this study. The diagnoses and effectiveness of therapies of FMS and CFS are largely based on subjective symptoms. As no accepted diagnostic laboratory tests are available to confirm the diagnoses of and monitor progress in these syndromes, it is reasonable to rely on subjective outcome measurements in this clinical setting. Also, patients did not eliminate other stable treatment modalities they had been on during the study. However, patients were instructed not to make any changes in their treatment regimen during the study. D-Ribose produced a subjective beneficial outcome in these patients; therefore, the addition of D-ribose may offer an added benefit to their concurrent therapies.

CONCLUSIONS

This pilot study suggests that D-ribose may provide subjective benefits in patients with FMS and/or CFS. Given the biochemical benefits of D-ribose on increasing muscular energy pools and reducing metabolic strain in affected muscles, the use of this supplement may offer a valuable option for improving quality of life in patients afflicted with FMS and/or CFS.

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REFERENCES

1. Goldenberg DL. Fibromyalgia syndrome—an emerging but controversial condition. JAMA 1987;257:2782–2787.
2. Wolfe F, Ross K, Anderson J, et al. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheumatol 1995;38:19–28.
3. Travell JG, Simons DG. Myofascial Pain and Dysfunction: The Trigger Point Manual, vol. 1. Baltimore: Williams & Wilkins, 1983.
4. Peckerman A, LaMancha JJ, Dahl KA, et al. Abnormal impedance cardiography predicts symptom severity in chronic fatigue syndrome. Am J Med Sci 2003;26:55–60.
5. Teitelbaum JE, Bird B, Greenfield RM, et al. Effective treatment of CFS and FMS: A randomized, double-blind placebo controlled study. J Chronic Fatigue Syndrome 2001;8:3–24.
6. Bengtson A, Heriksson KG, Larsson J. Reduced high-energy phosphate levels in the painful muscles of patients with primary fibromyalgia. Arthritis Rheumatol 1986;29:817–821.
7. Eisinger J, Plantamura A, Ayavou T. Glycolysis abnormalities in fibromyalgia. J Am Coll Nutr 1994;13:144–148.
8. Omran H, Illien S, MacCarter D, et al. D-Ribose improves diastolic function and quality of life in congestive heart failure patients: A prospective feasibility study. Eur J Heart Failure 2003;5:615–619.
9. Hellsten Y, Skadgauge L, Bangsbo J. Effect of ribose supplementation on resynthesis of adenine nucleotides after intense intermittent training in humans. Am J Physiol 2004;286: R182–R188.
10. Gebhart B, Jorgenson J. Benefit of ribose in a patient with fibromyalgia. Pharmacotherapy 2004;24:1646–1648.
11. Lund N, Bengtsson A, Thorborg P. Muscle tissue oxygen in primary fibromyalgia. Scan J Rheumatol 1986;15:165–173.
12. Schachter CL, Busch AL, Peloso PM, Shepard MS. Effects of short versus long bouts of aerobic exercise in sedentary women with fibromyalgia: A randomized controlled trial. Phys Ther 2003;83:340–358.
13. Lund E, Kendall SA, Janerot-Sjoberg B, Bengtsson A. Muscle metabolism in fibromyalgia studied by P-31 magnetic resonance spectroscopy during aerobic and anaerobic exercise. Scand J Rheumatol 2003;32:138–145.
14. Strobl ES, Krapf M, Suckfull M, et al. Tissue oxygen measurement and 31P magnetic resonance spectroscopy in patients with muscle tension and fibromyalgia. Rheumatol Int 1997;16:175–180.
15. Krapf MW, Muller S, Mennet P, et al. Recording muscle spasms in the erector spinae using in vivo 31P magnetic resonance spectroscopy in patients with chronic lumbalgia and generalized tendomyopathies. Z Rheumatol 1992;51:229–237.
16. Park JH, Phothimat P, Oates CT, et al. Use of P-31 magnetic resonance spectroscopy to detect metabolic abnormalities in muscles of patients with fibromyalgia. Arthritis Rheumatol 1998;41:406–413.
17. Jacobsen S, Jensen KE, Thomsen C, et al. Magnetic resonance spectroscopy in fibromyalgia. A study of phosphate-31 spectra from skeletal muscles during rest and after exercise. Ugeskr Laeger 1994;156:6841–6844.
18. Kushmerick MJ. Muscle energy metabolism, nuclear magnetic resonance spectroscopy and their potential in the study of fibromyalgia. J Rheumatol 1989;(Suppl 19):40–46.
19. Sprott H, Rzanny R, Reichenbach JR, et al. 31P magnetic resonance spectroscopy in fibromyalgic muscle. Rheumatology (Oxford) 2000;39:1121–1125.
20. Brault JJ, Terjung RL. Purine salvage to adenine nucleotides in different skeletal muscle fiber types. J Appl Physiol 2001;91:231–238.
21. Tullson PC, Terjung RL. Adenine nucleotide synthesis in exercising and endurance-trained skeletal muscle. Am J Physiol 1991;261:C342–C347.
22. Reibel D, Rovetto M. Myocardial ATP synthesis and mechanical function following oxygen deficiency. Am J Physiol. 1978;234:H620–H624.

23. Williamson DL, Gallagher PM, Goddard MP, Trappe SW. Effects of ribose supplementation on adenine nucleotide concentration in skeletal muscle following high-intensity exercise. Med Sci Sport Exc 2001;33(5 suppl):5166.
24. Olson NJ, Park JH. Skeletal muscle abnormalities in patients with fibromyalgia. Am J Med Sci 1998;315:351–358.
25. Eisinger J, Bagneres D, Arroyo P, et al. Effects of magnesium, high-energy phosphates, piracetam and thiamin on erythrocyte transketolase. Magnet Res 1994;7:59–61.
26. Bengtsson A, Henriksson KG. The muscle in fibromyalgia—a review of Swedish studies. J Rheumatol Suppl 1989;19:144–149.

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