

D-Ribose in Fibromyalgia and Neuromuscular Disease

Introduction

Fibromyalgia is a common, nonarticular, rheumatic syndrome that affects the upper and lower body, right and left sides. Concrete diagnosis of fibromyalgia is difficult since many other diseases and conditions present with similar symptoms and there are no laboratory tests that can be used as a primary diagnosis. As a result, accurate diagnosis must be made by excluding these other diseases or conditions. The American College of Rheumatology has defined the clinical diagnosis of fibromyalgia following two criteria: 1) widespread musculoskeletal pain in all four quadrants of the body for at least three months, and 2) tenderness at 11 or more of 18 specific tender points (or trigger points) located on the upper back and chest, insides of the elbows, lower back, upper thighs and front of knees.

Pathophysiology of Fibromyalgia

Patients suffering with fibromyalgia suffer from constant pain, sleep disturbances, overwhelming fatigue, weakness, muscle stiffness and soreness, headaches, irritable bowel, anxiety and depression. The condition is most commonly diagnosed in females, aged 20 to 50 years, and is generally treated by analgesic drugs and antidepressants.¹⁻⁴

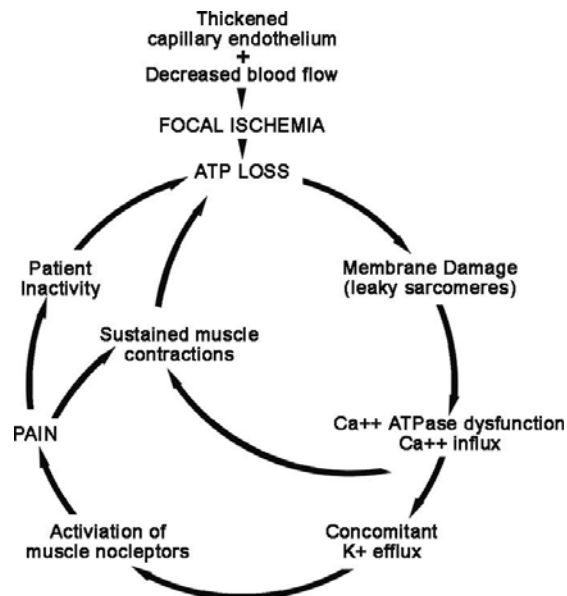
The cause of fibromyalgia is unknown, but it has been associated with stress, tension, trauma, overexertion, hormone deficiency diseases (particularly thyroid disease), alterations in brain chemistry, anemia, parasites, and viral infections. Conditions that may be associated with, or mimic, fibromyalgia include chronic fatigue syndrome, myofascial pain syndrome, carpal tunnel syndrome, mitral valve prolapse, Raynaud's syndrome and rheumatic disease.⁵⁻⁷

While a great deal of popular press can be found discussing the disease, scientific research is, in large part, lacking. However, many conclusions can be drawn from the scientific press.

Controlled examination of the vastus lateralis muscle of the quadriceps group, trapezius and brachioradial muscle has shown that the blood flow to the tissue is lower in fibromyalgia patients than normal controls leading to low tissue oxygenation levels.^{2,4,8-10} Electron microscopic evaluation of the capillaries supplying the trapezius showed thickening and derangement of the capillary wall.² Further, examination of small muscle fibers revealed mitochondrial derangement in fibromyalgia patients.^{2,4} These small muscle fibers were not found in normal subjects. Reduced blood flow, changes in capillary wall thickness and structural changes to the mitochondria contribute to hypoxia, decreased oxidative phosphorylation, lower ATP synthesis and reduced levels of adenine nucleotides in fibromyalgic muscle. Since it is postulated that the pain associated with fibromyalgia is of nociceptor origin⁴, the primary hypothesis is that any condition that could lead to constant

muscle hypoxia, and prolonged energy deficiency, might be a cause of fibromyalgic pain (Figure 1).

Figure 1: Diagram of proposed interactions of various muscle abnormalities to pain and muscle dysfunction



From: Olson NJ, JH Park.²

Energy Status of Fibromyalgic Muscle

Patients with fibromyalgia generally demonstrate reduced exercise capacity, with muscles that lack contractile force and endurance.^{10,11,13} Since these conditions are frequently associated with abnormal metabolism, many studies have investigated muscle metabolism in fibromyalgia using both traditional biopsy techniques¹² and nuclear magnetic resonance spectroscopy (P-31 MRS).^{10,13-18} Biopsy studies investigating the metabolism of ATP, creatine phosphate (PCr), ADP, AMP, pyruvate and glycogen have shown that levels of PCr and ATP are significantly lower (21% and 17%, respectively) in fibromyalgic muscle and the synthesis of PCr, the most important store of high energy phosphate in the cell, is defective. Biochemical studies have confirmed that energy metabolism is abnormal in fibromyalgia, requiring appropriate metabolic therapy.

P-31 MRS studies are even more revealing. P-31 MRS looks directly into the muscle to determine the absolute values of energy compounds, muscle pH and changes in metabolism as they occur at rest and during exercise. Magnetic resonance spectra of the quadriceps muscle have shown that resting levels of ATP are 15% lower in fibromyalgia patients than in normal controls and during exercise PCr and ATP levels are also significantly lower (each 15%). In addition, during exercise there is an increase in metabolic breakdown products of ATP (phosphodiesteres) that indicate abnormal ATP metabolism and disruption of cell membranes, both associated with muscle disease.

The energy reserve, or phosphorylation potential (PP), and the ability to utilize oxygen (total oxidative capacity or V_{max}) have been determined using P-31 MRS. The mean PP is significantly lower in fibromyalgia patients and V_{max} is also significantly reduced.¹⁵ These findings are consistent with reduced oxidative phosphorylation and ATP synthesis in the muscles of fibromyalgia patients and may translate into the clinical symptom of fatigue.

The poor bioenergetic status of muscles in fibromyalgia may be due to reduced blood flow to affected tissue and thickening of capillary walls, leading directly to reduced levels of ATP, lower energy reserves and oxidative capacity (V_{max}) and abnormal levels of phosphodiesteres in the muscle. The additional complication of impaired oxidative phosphorylation in the mitochondria and diminished glucose metabolism, both lowering ATP turnover, suggests that fibromyalgic muscle is energy starved. Decreased levels of ATP and changes in energy metabolism have also been found in the red blood cells of fibromyalgia patients¹⁹, suggesting that fibromyalgia may be a more general and systemic problem than originally thought, possibly impinging on other organ systems.

The metabolic abnormalities in fibromyalgic muscle have been well established and show multiple interactions that may impact on the clinical symptoms. Decreased numbers of capillaries that reduce oxidative capacity may increase pain, while thickened capillary walls lowering oxygen delivery and abnormal mitochondria lead to fatigue and weakness. All are associated with reduced levels of ATP and energy metabolism that, in turn, leads to disruptions in calcium stasis, muscle soreness and stiffness. At the same time, these metabolic changes force morphological changes in the muscle that continue to exacerbate the problem with metabolism.

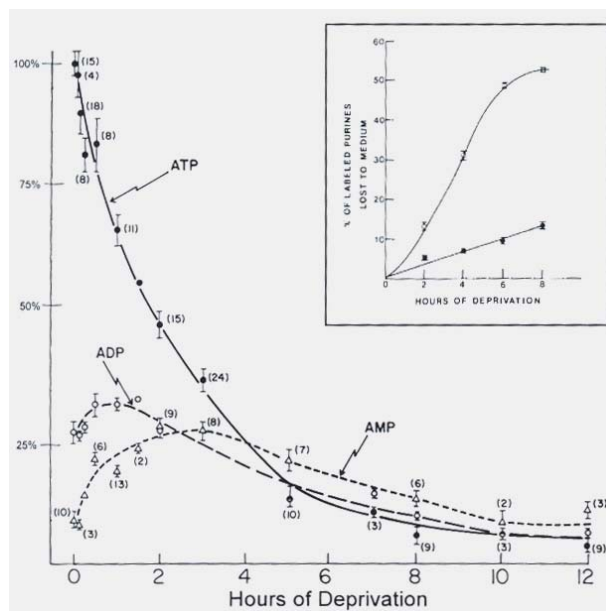
Ribose in Maintaining Tissue Energy Stasis

Tissue hypoxia leads to a progressive depression of the cellular purine nucleotide pool creating an energy deficit (Figure 2). The adenine nucleotide ATP is the primary energy source of all living cells. In tissues suffering the metabolic stress of hypoxia or ischemia, ATP is broken down and the metabolic machinery to recycle expended energy is disrupted. As such, adenosine diphosphate (ADP) levels accumulate leading to a series of reactions undertaken by the cell to balance ATP/ADP ratios and maintain energy stasis. These reactions ultimately lead to increased concentrations of adenosine monophosphate (AMP) in the cell. In a further effort to control energy balance, heart cells catabolize AMP, in reactions catalyzed by 5'-nucleotidase and AMP deaminase, to form inosine, hypoxanthine

and adenine. These catabolic end products are washed out of the cell netting a reduction in the total pool of adenine nucleotides available to the tissue and lowering its phosphorylation potential (Figure 2). Up to 90% of these catabolites can be biochemically salvaged and recycled.²⁰⁻²²

The availability of phosphoribosyl-5-pyrophosphate (PRPP) is rate limiting in adenine nucleotide synthesis and salvage pathways required to restore nucleotide pools and rebuild cellular energy stores.²⁰⁻²³ PRPP is formed through a pyrophosphorylation reaction from ribose-5-phosphate that is, in turn, synthesized from glucose via the Pentose Phosphate Pathway (PPP; or Hexose Monophosphate Shunt). The activity of the PPP varies between organs, with those synthesizing fatty acids and sterols being most active. The rate limiting enzymes in the PPP, glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase, have limited expression in muscle. As such, energy production in muscle via this mechanism is delayed and cannot be relied upon to replenish depressed adenine nucleotide pools during or following a metabolic insult, such as prolonged periods of hypoxia.

Figure 2: Effect of Oxygen Deprivation on Cardiac Purine Nucleotide Content (Relative ATP, ADP and AMP Contents Measured by HPLC)



ATP, ADP and AMP contents with time (hours) of deprivation of O₂ and oxidizable substrates (ATP set to 100% at time = 0 minutes). Insert shows % radiolabeled purines lost from control (filled) and injured (open) hearts. The numbers in parenthesis represent the number of experiments performed. (From: Ingwall JS²⁶)

The rate of recovery of depressed energy levels following ischemia and/or hypoxia is important for functional recovery of muscle^{20,21,23,24}, providing adequate levels of AMP and

ADP necessary for complete repletion of ATP. Blocking the degradation of adenine nucleotides, or by providing metabolic supplementation to enhance nucleotide recovery via the salvage or *de novo* pathways are potential solutions to maintaining energy stasis. Exogenous ribose administration provides the metabolic support required to bypass the rate limiting enzymes of the PPP, form PRPP and restore energy stasis in metabolically stressed muscle.²⁰⁻²⁵

Ribose has been extensively studied in both hearts and muscles. Safety data is well accepted, with no noted significant adverse reactions. Experiments on the use of ribose to enhance myocardial and skeletal muscle adenine nucleotide synthesis and salvage have involved both animal and human investigations and the effects of ribose in hearts are not species specific.²⁶ The low activity of glucose-6-phosphate dehydrogenase is in the same order of magnitude in human, rat, guinea pig and dog hearts.

The effect of ribose treatment in myoadenylate deaminase deficiency (AMP deaminase deficiency)²⁷⁻³¹ and adenylosuccinase deficiency^{32,33} has been well documented. Like fibromyalgia, these conditions lead to progressive depletion of cellular energy pools, leading to muscle pain, soreness and stiffness. The beneficial role in energy recovery in these disease conditions with ribose treatment is suggestive of its potential role in energy recovery in fibromyalgia. As in the case of myoadenylate deaminase deficiency, anecdotal reports from fibromyalgia patients indicate a reduction in fatigue, muscle soreness and stiffness associated with the condition. While further research continues, it is apparent that ribose can play a beneficial role as an adjunctive, metabolic treatment for fibromyalgia.

References:

1. Eisinger J, A Plantamura, T Ayavou. Glycolysis abnormalities in fibromyalgia. *J Am Coll Nutr* 1994;13(2):144-148.
2. Olson NJ, JH Park. Skeletal muscle abnormalities in patients with fibromyalgia. *Am J Med Sci* 1998;315(6):351-358.
3. Guymer EK, KJ Clauw. Treatment of fatigue in fibromyalgia. *Rheum Dis Clin North Am* 2002;28(2):67-78.
4. Bengtsson A, KG Henriksson. The muscle in fibromyalgia – a review of Swedish studies. *J Rheumatol Suppl* 1989;19:144-149.
5. Rooks DS, CB Silverman, FG Kantrowitz. The effects of progressive strength training and aerobic exercise on muscle strength and cardiovascular fitness in women with fibromyalgia: a pilot study. *Arthritis Rheum* 2002;47(1):22-28.
6. Douche-Aourik F, W Berlier, L Feasson, T Bourlet, R Harrath, S Omar, F Grattard, C Denis, B Pozzetto. Detection of enterovirus in human muscle from patients with chronic inflammatory muscle disease or fibromyalgia and healthy subjects. *J Med Virol* 2003;71(4):540-547.
7. Geenen R, JW Jacobs, JW Bijlsma. Evaluation and management of endocrine dysfunction in fibromyalgia. *Rheum Dis Clin North Am* 2002;28(2):389-404.
8. Henriksson KG. Muscle pain in neuromuscular disorders and primary fibromyalgia. *Neurologija* 1989;38(3):213-221.
9. Lund N, A Bengtsson, P Thorborg. Muscle tissue oxygen in primary fibromyalgia. *Scan J Rheumatol* 1986;15(2):165-173.
10. Strobl ES, M Krapf, M Suckfull, W Bruckle, W Fleckenstein, W Muller. Tissue oxygen measurement and ³¹P magnetic resonance spectroscopy in patients with muscle tension and fibromyalgia. *Rheumatol Int* 1997;16(5):175-180.
11. Schachter CL, AJ Busch, PM Peloso, MS Shepard. Effects of short versus long bouts of aerobic exercise in sedentary women with fibromyalgia: a randomized controlled trial. *Phys Ther* 2003;83(4):340-358.
12. Bengtson A, KG Heriksson, J Larsson. Reduced high-energy phosphate levels in the painful muscles of patients with primary fibromyalgia. *Arth Rheum* 1986;29(7):817-821.
13. Lund E, SA Kendall, B Janerot-Sjoberg, A Bengtsson. Muscle metabolism in fibromyalgia studied by P-31 magnetic resonance spectroscopy during aerobic and anaerobic exercise. *Scan J Rheumatol* 2003;32(3):138-145.
14. Krapf MW, S Muller, P Mennet, T Stratz, W Samborski, W Muller. 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(5):229-237.
15. Park JH, P Phothimat, CT Oates, M Hernanz-Schulman, NJ Olson. Use of P-31 magnetic resonance spectroscopy to detect metabolic abnormalities in muscles of patients with fibromyalgia. *Arth Rheumatol* 1998;41(3):406-413.
16. Jacobsen S, KE Jensen, C Thomsen, B Danneskiold-Samsoe, O Henriksen. Magnetic resonance spectroscopy in fibromyalgia. A study of phosphate-31 spectra from skeletal muscles during rest and after exercise. *Ugeskr Laeger* 1994;156(46):6841-6844.

17. Kushmerick MJ. Muscle energy metabolism, nuclear magnetic resonance spectroscopy and their potential in the study of fibromyalgia. *J Rheumatol Supp* 1989;19:40-46.
18. Sprott H, R Rzanny, JR Reichenbach, WA Kaiser, G Hein, G Stein. ³¹P magnetic resonance spectroscopy in fibromyalgic muscle. *Rheumatol (Oxford)* 2000;39(10):1121-1125.
19. Eisinger J, D Bagneres, P Arroyo, A Plantamura, T Ayavou. Effects of magnesium, high-energy phosphates, piracetam and thiamin on erythrocyte transketolase. *Magnet Res* 1994;7(1):59-61.
20. Tullson PC, Terjung RL. Adenine nucleotide synthesis in exercising and endurance-trained skeletal muscle. *Am J Physiol.* 1991; 261: C342-C347.
21. Brault JJ, Terjung RL. Purine salvage to adenine nucleotides in different skeletal muscle fiber types. *J Appl Physiol.* 2001; 91: 231-238.
22. 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(1): R182-R188.
23. Williamson DL, PM Gallagher, MP Goddard, SW Trappe. Effects of ribose supplementation on adenine nucleotide concentration in skeletal muscle following high-intensity exercise. *Med Sci Sport Exc.* 2001; 33(5 suppl).
24. Reibel D, Rovetto M. Myocardial ATP Synthesis and Mechanical Function Following Oxygen Deficiency. *Am J Physiol.* 1978; 234(5): H620-H624.
25. Ingwall JS. *ATP and the Heart*. Kluwer Academic Publishers, Boston, Massachusetts. 2002.
26. Zimmer HG, Ibel H, Suchner U. Ribose Intervention in the Cardiac Pentose Phosphate Pathway is Not Species-Specific. *Science.* 1984; 223: 712-714.
27. Gross M, Dormann B, Zollner N. Ribose administration during exercise: effects on substrates and products of energy metabolism in healthy subjects and a patient with myoadenylate deaminase deficiency. *Klin Wochenschr.* 1991; 69: 151-155.
28. Wagner DR, Gresser U, Zollner N. Effects of oral ribose on muscle metabolism during bicycle ergometer in AMPD-deficient patients. *Ann Nutr Metab.* 1991; 35: 297-302.
29. Gross M, S Reiter, N Zollner. Metabolism of D-ribose administered to healthy persons and to patients with myoadenylate deaminase deficiency. *Klin Wochenschr.* 1989; 67: 1205-1213.
30. Zollner N, Reiter S, Gross M, Pongratz D, Reimers CD, Gerbitz K, Paetzke I, Deufel T, Hubner G. Myoadenylate deaminase deficiency: successful symptomatic therapy by high dose oral administration of ribose. *Klin Wochenschr.* 1986; 64: 1281-1290.
31. Patton BM. Beneficial effect of D-ribose in patients with myoadenylate deaminase deficiency. *Lancet.* May 1982; 1701.
32. Salerno C, D'Eufemia P, Finocchiaro R, Celli M, Spalice A, Crifo C, Giardini O. Effect of D-ribose on purine synthesis and neurological symptoms in a patient with adenylosuccinase deficiency. *Biochim Biophys Acta.* 1999; 1453: 135-140.
33. Salerno C, M Celli, R Finocchiaro, P D'Eufemia, P Iannetti, C Crifo, O Giardini. Effect of D-ribose administration to a patient with inherited defect of adenylosuccinase. *Purine Metabolism in Man IX*. Plenum Press, New York, 1998.