Enhancing Mitochondrial Function With D-Ribose

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Financial Disclosure: *The author has been involved in the development of nutritional supplements (all of his royalties for the products go to charity) and he sells supplements, including D-ribose, on his website.*

Each cell in the body contains mitochondria that produce energy by burning calories. Many illnesses and diseases, including genetic defects, nutritional deficiencies, and Epstein Barr viral infections, can suppress mitochondrial function.[1] Common syndromes associated with decreased mitochondrial function and associated drops in tissue levels of adenosine triphosphate (ATP) include chronic fatigue syndrome (CFS) and fibromyalgia (FMS).[2]

Having had both CFS and FMS in 1975, which knocked me out of medical school for a year and left me homeless during much of that time, I have devoted the last 30 years to researching these syndromes. In that time, I have treated more than 3000 CFS/FMS patients and authored a number of books, studies, and articles on the topic.

In my early-published research, I performed a double-blind, randomized, controlled trial to assess energy production. We obtained highly positive results from use of what we termed the "SHINE Protocol" (treatment for sleep disorders, hormonal deficiencies, infections, nutritional support, and exercise —though exercise was not controlled for in the study). In the study, published in 2001, patients reported an average 90% improvement in quality of life—as verified by using a visual analog scale (VAS) measuring fatigue, pain, sleep, cognitive dysfunction, and overall well-being. Highly significant improvement was also seen in the Tender Point Index, Fibromyalgia Impact Questionnaire, and patient self-rating ($P<.0001$ vs placebo for all 4 outcome measures).[3]

It recently became clear, however, that both CFS and FMS represent mitochondrial dysfunction, which, in turn, reduces energy production to inefficient levels. This led me to research ribose, which has turned out to be a very powerful tool for treating both CFS/FMS as well as many common cardiac problems.

In this article, I will discuss the use of D-ribose (often shortened to ribose) to help mitochondria work properly and explain how practitioners can use this information to dramatically help their fatigue, pain, and cardiac patients feel better.

The Role of Energy Production

Medical research shows there are many conditions that drain energy from the body, leaving a person fatigued and with such frequent complications as muscle pain, heart problems, and depression.

Of course, athletes who participate in high-intensity, endurance-type exercise often face fatigue and muscle pain associated with energy depletion. Typically, however, a few days of rest will allow an athlete's muscles to recharge. For the rest of our patient base, physiological factors that drain hearts and muscles of energy are not as easily overcome. In particular, aging has a decided effect on energy production. As the body ages, it goes through many changes that affect its ability to efficiently metabolize energy. For some, these changes occur more rapidly and are more pronounced, while for others the impact is seemingly absent.

As previously mentioned, illness and disease also have an effect. People with CFS/FMS, for example, have almost 20% less energy in their muscles than normal, and this lack of energy causes poor exercise tolerance and lack of endurance—making it hard to perform even the most basic of life's daily activities.[4,5]

The metabolic changes that occur in either an aging body or one with the onset of CFS/FMS are varied. Many people are found to have thickening of the capillary walls, making it harder for oxygen to move from blood to muscle tissue, reducing the oxygen tension of the muscle, and slowing the rate of energy synthesis.[6,7] In others, the mitochondria are found to be defective or inefficient, making them unable to keep up with the energy demand of cells and tissues as they work through daily activities.[8-10] For still others, cells and tissues are deficient in certain nutrients that are needed to process food into energy, leaving the tissues energy starved.[11-13] And in the most difficult conditions, the muscle itself is affected, leaking vital cellular

Patient Handout
Heart and Energy "Cocktail"

Following is recipe for dramatically improving cardiac function and energy production. Try this for 6 to 12 weeks to see the optimal effects, then use as needed.

Ribose: Take 5 g 3x/day for 6 weeks, then 5 g 2x/day for 6 more weeks. This nutrient is outstanding for heart disease.

Coenzyme Q10: Take 400 mg/day for 6 weeks, then 200 mg/day for 6 more weeks. This nutrient is especially critical for anyone on cholesterol-lowering medications, even if there are no heart problems, as these medications cause Co-Q10 deficiency (a nutrient critical for energy production).

Magnesium: Take 200 mg/day for 12 weeks.

Vitamin B complex: Take 50+ mg/day for 12 weeks.

Acetyl-L-carnitine: Take 500 mg 2x day for 6 weeks, then 500 mg/day for 6 weeks (and it can often simply be stopped after the first 6 weeks).

constituents that include energy compounds and fuels needed to restore energy levels in affected tissues.[14]

No matter the cause, the impact of energy depletion is to propel a downward spiral of fatigue, muscle pain, soreness, and stiffness that becomes self-sustaining until reversed. As energy is used faster than it can be renewed, muscles become more painful, stiff, and fatigued because it takes energy for tight muscles to release and relax. This causes even more energy to be used as the muscle struggles to recover, causing even more fatigue, soreness, and stiffness,[15-17] and the cycle is perpetuated. If conditions leading to energy depletion are not arrested in time, fatigue and myalgias can become overwhelming and debilitating—as occurs in CFS and FMS.

Consequences of Mitochondrial Dysfunction

Mitochondrial malfunction can create numerous problems, including particularly severe changes in the hypothalamus that result in hypothalamic suppression.[18] The hypothalamus controls sleep and pituitary and autonomic functions. Along with this, diseases of the mitochondria appear to cause the most dysfunction in organs and systems that require a great deal of energy: the brain, heart, skeletal muscles, liver, and endocrine systems.[19] The following outlines how all of these can contribute to the myriad symptoms that occur in CFS/FMS.

Hypothalamic suppression:

- **Sleep.** The hypothalamus is becoming recognized as a key center for regulating sleep.[20] Insomnia is severe in CFS/FMS, and sleep deprivation has been shown to be a potent trigger for immune suppression.[21]
- **Autonomic function.** The autonomic nervous system controls blood pressure, pulse, sweating, and peristalsis. Dysfunction can lead to neurally mediated hypotension, bowel dysfunction with irritable bowel syndrome, and small intestinal bacterial overgrowth (SIBO), as well as the unusual sweating patterns commonly seen in CFS/FMS.[22]
- **Pituitary/endocrine function.** Disruptions result in widespread hormonal dysfunction, including deficiencies of growth hormone as well as hypothalamic-pituitary-adrenal and thyroid axis dysfunction.[23-26]

Dysfunction in the brain, heart, skeletal muscles, liver, and endocrine systems:

- **Brain fog.**
- **Heart dysfunction.** In a 2007 personal communication with noted CFS researcher Paul Cheney, MD, he related that mitochondrial dysfunction associated with inadequate antioxidant production/function may contribute to the severe cardiac dysfunction that he sees in CFS patients undergoing echocardiography.
- **Post-exertion fatigue.** Low energy production can cause an accumulation of excessive amounts of lactic acid in muscles, thus inhibiting recovery after exercise.
- **Volume and osmotic regulation.** Secondary to hypothalamic

Ribose Studies

For those who would like more information about ribose, please see the following studies:

- Berthold HK, Naini A, Di Mauro S, et al. Effect of ezetimibe and/or simvastatin on coenzyme Q10 levels in plasma: a randomised trial. *Drug Saf.* 2006;29(8):703-712.
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- Palan PR, Connell K, Ramirez E, et al. Effects of menopause and hormone replacement therapy on serum levels of coenzyme Q10 and other lipid-soluble antioxidants. *Biofactors.* 2005;25(1-4):61-66.
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- Pauly D, Johnson C, St Cyr JA. The benefits of ribose in cardiovascular disease. *Med Hypotheses.* 2003;60(2):149-151.

dysfunction, low anti-diuretic hormone also contributes to the increased thirst and urination seen in CFS/FMS.[27]

- **Sensitivities and allergies**. So called "leaky gut" combined with a decreased ability of the liver to eliminate toxins and medications can contribute to both medication and environmental sensitivities.

Thus, mitochondrial dysfunction might well be the root cause of—or at least a contributing factor to—hypothalamic, nutritional, immune, cardiac, detoxification, and sleep disorders.

What can be done to make the cellular mitochondrial energy furnaces work better? Though a number of natural treatments are available, I see D-ribose as the key to energy production.

D-Ribose—The Natural Body Energizer

When considering energy production, it helps to look at the "energy molecules" such as ATP, nicotinamide adenine dinucleotide, and the reduced form of flavin adenine dinucleotide. These represent the energy currency of the body and are like the paper that money is printed on. A person can ingest all the fuel he wants, but if it cannot be converted to these molecules, it is useless. In particular, ATP is important because the amount of ATP people have in their tissues determines whether they will be fatigued or have the energy needed to live vital, active lives.

For years I talked about the importance of B vitamins, which are a key component of these energy molecules. The Bs helped to a degree, but it was clear that some key component was still missing. Then, in looking at the biochemistry of these energy molecules, I saw they are made of 2 other critical components: adenine and ribose. Adenine is plentiful in the body and supplementing with adenine does not help CFS. So my coworkers and I then turned our attention to ribose.

D-ribose is a simple, 5-carbon sugar that is found naturally in our bodies. But ribose is not like any other sugar. The familiar sugars, such as table sugar (sucrose), corn sugar (glucose), milk sugar (lactose), honey (predominantly fructose), and others are used by the body as fuel. These sugars are consumed and, with the help of oxygen, "burned" by the body to recycle energy. Ribose, on the other hand, is different. When consumed as a supplement (ribose is not found in food), the body recognizes that ribose is different from other sugars and preserves it for the vital work of actually creating the energy molecules that power the brain, heart, muscles, and every other tissue in the body.

As it turns out, ribose provides the key building block of ATP, and the presence of ribose in the cell stimulates the metabolic pathway our bodies use to actually produce the ATP we require. If the cell does not have enough ribose, it cannot make ATP. So, when cells and tissues become energy starved, the availability of ribose is critical to energy recovery—and is often the rate-limiting nutrient for ATP production.

Normal, healthy muscle and heart tissue has the capacity to make all of the ribose it needs. When normal tissue is stressed by overexertion, several days of rest will usually allow it to fully recover. The muscle may be sore during recovery, but

Ribose Studies (continued)

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eventually energy levels will be restored and the soreness will disappear. But when the muscle is chronically stressed in heart disease, fibromyalgia, or other conditions that affect tissue energy metabolism, the cells and tissues simply cannot make enough ribose quickly enough to recover. The result is chronic, persistent pain, stiffness, soreness, and overwhelming fatigue that may never go away unless energy production is restored.

Ribose Research

As mentioned above, ribose does not come from food; it is made in the body by a slow, laborious process (the "pentose phosphate shunt"). From published research, we knew that CFS/FMS causes the body to dump certain key energy molecules like carnitine. Looking further, we then found that the body did the same with ribose, dumping it as well, and making it hard to get the mitochondrial "furnaces" working again even after other problems had been treated.

This was one of those exhilarating "Eureka!" moments where things came together. Not having ribose would be like trying to build a fire without kindling—nothing would happen. We wondered if giving ribose to people with CFS would jumpstart their energy furnaces. The answer was a resounding *yes*.

This discovery led me and 2 research collaborators to design an open-label, uncontrolled pilot study on 41 patients with either CFS or FMS.[28] Our study, published in 2006, was intended to determine whether or not ribose would be effective in relieving the overwhelming fatigue, pain, soreness, and stiffness suffered by patients with these debilitating symptoms. For an average of 3 weeks, patients were given ribose at a dose of 5 g 3 times per day.

We found that ribose treatment led to significant improvement in energy levels, sleep patterns, mental clarity, pain intensity, and well-being. Of the patients participating in the study, 65.7% experienced significant improvement while on ribose (rating themselves as "better or much better"). On average, improvement began at 12 days. The study's primary outcome measure was the patients' individual rating of fatigue, pain, sleep, cognitive function, and overall well being on a VAS. Patients rated themselves as having an average increase in energy of 44.7% and in overall well being of 30% on their VAS—remarkable results from a single nutrient (normally a 10% improvement for a single nutrient is considered excellent).[28] A 44.7% increase left us amazed, and I am now recommending ribose for all of my CFS/FMS patients, for athletes, and for anyone with pain, fatigue, or heart problems. The only significant side effects were that 2 people felt too energized and hyper/anxious on the ribose. That was dealt with simply by lowering the dose and/or having the patients take the ribose with food.

On a personal note, several of the patients participating in the study have contacted me regarding the relief they found with ribose therapy. Most importantly, they speak to the profound joy they feel when they are able to begin living normal, active lives after sometimes years of fatigue, pain, and suffering. Here is a sample of what one patient, an elementary teacher, wrote: "I had so much pain and fatigue I thought I was going to have to quit teaching. When I take [ribose], I feel like a huge weight is being lifted from my chest, and I'm ready to take on those kids again!" The relief patients feel with ribose therapy is heartwarming, and goes directly to the dramatic impact ribose has on increasing energy, overcoming fatigue, enhancing exercise tolerance, and raising the patient's quality of life.

The Link Between Ribose, Energy, and Fatigue

Clinical and scientific research has repeatedly shown that giving ribose to energy-deficient hearts and muscles stimulates energy recovery. One important study involved healthy athletes participating in high-intensity, endurance exercise over the course of 1 week. After exercise, the energy level in the athlete's muscle was reduced by almost 30%. Giving 10 g of ribose per day for 3 days following exercise restored muscle energy levels to normal, while treatment with placebo provided virtually no effect.[29] This study clearly showed that ribose stimulated the energy recovery pathways in the body, helping the muscle rebuild its energy supply quickly and completely. Even after 3 days of rest, muscle that was not treated with ribose remained energy starved and fatigued.

Two very interesting animal studies showed how dramatically ribose could affect energy recovery in fatigued muscle. Researchers found that ribose administration in fatigued muscle shortened the duration of recovery by 340% to 430%, depending on the type of muscle.[30] They also found that even very small amounts of ribose had the effect of helping the muscle cell preserve energy, a process known as energy salvage, and that the higher the ribose dose, the more dramatic its effect on energy preservation.[31] Although this groundbreaking research was done in animals, it was instrumental in defining the biochemistry and physiology associated with use of ribose in overcoming heart and muscle fatigue.

Research on ribose and CFS/FMS began with a case study that was published in the journal *Pharmacotherapy* in 2004.[32] This case study told the story of a veterinary surgeon diagnosed with fibromyalgia. For months, this dedicated doctor found herself becoming more and more fatigued, with pain becoming so profound she was finally unable to stand during surgery. As a result, she was forced to all but give up the practice she loved.

Upon hearing that a clinical study on ribose in congestive heart failure was underway in the university where she worked, she asked if she could try the ribose to see if it might help her overcome the mind-numbing fatigue she experienced from her disease. After 3 weeks of ribose therapy she was back in the operating room, practicing normally with no muscle pain or stiffness, and without the fatigue that had kept her bedridden for many months.

Being a doctor, she was skeptical, not believing that a simple sugar could have such a dramatic effect on her condition. Within 2 weeks of stopping the ribose therapy, however, she was out of the operating room and back in bed. So, again to test the theory, she began ribose therapy a second time. The result was similar to her first experience and she was back doing surgery in days. After yet a third round of ribose stopping (with

return of symptoms) and starting (with reduction of symptoms), she was finally convinced, and has since remained on ribose therapy.

To further validate such research on ribose and to continue with our own published research began earlier, we are currently conducting a placebo-controlled study using ribose in fibromyalgia; we hope to have the results published in the coming year. Interestingly, one of our earlier ribose pilot study patients had atrial fibrillation. Ribose is also outstanding in treatment of heart disease because it restores energy production in the heart muscle. Because of this, it was not surprising that this man's atrial fibrillation went away within a few weeks on the ribose and he was able to stop his heart medications as well. I use ribose in all of my cardiac patients, as improving muscle efficiency can decrease tissue oxygen needs, and, therefore, congestive heart failure, in addition to arrhythmias and angina. Because of its importance and the research showing marked heart muscle dysfunction (because of low energy) in CFS, let us take a closer look at ribose and the heart.

Ribose and Heart Disease

Decades of research have shown that ribose has a profound effect on heart function in patients with congestive heart failure, coronary artery disease, and cardiomyopathy (a weakened heart muscle). Like the muscles in patients with fibromyalgia, sick hearts are energy starved.[33] This energy deprivation keeps the heart from relaxing between heartbeats, making it impossible for the heart to completely fill with blood (it takes more energy for the heart muscle to relax than contract).[34] Because the heart does not fill completely, less blood is pumped to the body with each heartbeat. The heart then gets stiff as it strains to contract. Ultimately, the heart becomes hypertrophic (enlarged) and is unable to pump normally.

You can compare this to the effect of weight training on the biceps of the upper arm. Over time, weight training against more and more weight makes the muscle larger and harder. Similarly, when the heart becomes stiff, it is forced to contract against more and more pressure, making the heart muscle grow. While in the case of the biceps this may be a desirable outcome, in the heart it can be deadly. In contrast to the biceps muscle, hearts must remain supple so they can fill properly and empty fully with each contraction. If a heart cannot pump normal volumes of blood, muscles of the arms and legs as well as brain tissue become oxygen starved. The result is fatigue, shortness of breath and/or pain on standing or walking, loss of interest in or the inability to perform any physical activity, brain fog, and depression. In the end, the heart cannot pump enough blood to supply even itself with life-giving oxygen. The result can be a heart attack.

Using ribose to optimize the energy level in the heart allows it to fully relax and fill and completely empty so as to more efficiently circulate blood to the outer reaches of the body.[35] Circulating more blood means muscles in the arms and legs, and in the tissues of the brain, get the oxygen they need to function normally. This result was made evident in several important studies in patients with congestive heart failure and angina, described below.

In one study conducted at the University of Bonn in Germany, patients with congestive heart failure were treated every day for 3 weeks with either 10 g of ribose or a sugar placebo. [36] They were then tested for heart function, exercise tolerance (a measure of fatigue), and quality of life using a questionnaire designed for this purpose. In this study, ribose therapy had a significant effect on all measures of diastolic heart function, showing that increased energy in the heart allowed the heart to relax, fill, and pump more normally. When they were on ribose, patients in the study were also much more tolerant to exercise and, through their responses to the questionnaire, showed they had a resultant higher quality of life.

Two additional studies went on to help explain how ribose therapy in congestive heart failure may positively affect fatigue and exercise tolerance.[37,38] These studies showed that ribose treatment increased ventilatory and oxygen utilization efficiency, meaning that the patients were able to breathe better and use the oxygen they inhaled more efficiently. Improving the patient's ability to use oxygen means more oxygen is available to be carried by the blood out to the tissues. Having more oxygen available allows the muscle to burn fuel more efficiently, helping it keep pace with its energy demand. The result is less fatigue, a greater ability to tolerate exercise, and a higher quality of life. An added benefit to improving ventilatory efficiency is that ventilatory efficiency is a dominant predictor of mortality in congestive heart failure. Increasing ventilatory efficiency with ribose therapy is, therefore, a direct correlate to prolonging life in this patient population.

Side Effects

The main side effect seen with ribose is that some 4% to 5% of patients feel "hyper" or over energized on it. If this occurs, simply have them take the supplement with food and lower the dose. This side effect occurs because ribose has a negative glycemic index, lowering blood sugar. Diabetics using it mostly need to watch for a drop in blood sugar, although rarely a rise in blood sugar can occur.

Additionally, I would use it very carefully in bipolar patients to avoid activation (we have not seen this, but it is possible). When used in conjunction with prescription medications, caution is required. If ribose is used with Coumadin (warfarin), for example, it is important to check initial bleeding times.

Conclusion

Very few nutritional therapies can legitimately boast of having such a profound effect on the tissues they target, especially such an effect in cell or tissue energy metabolism. Ribose is a unique and powerful addition to our complement of metabolic therapies in that it is completely natural, safe—proven by strong, well-designed clinical and scientific evidence—and fundamental to vital metabolic processes in the body.[39-43]

Ribose regulates how much energy we have in our bodies, and for those suffering from fatigue, muscle soreness, stiffness, heart disease, and a host of related medical complications, the

relief found in energy restoration can be life changing. This is why I recommend that all CFS/FMS and cardiac patients begin with D-ribose. Ribose recently became available (over the counter) to physicians, and is one of the few natural products actually starting with physicians and then moving out into health food stores.

I take my ribose every day because, even though I feel great, it makes me feel even better!

Jacob Teitelbaum, MD, is medical director of the Fibromyalgia and Fatigue Centers, a nationwide group of clinics. He is senior author of "Effective Treatment of CFS and FMS: A Randomized, Double-Blind Placebo Controlled Study," *Journal of Chronic Fatigue Syndrome* 2001;8(2):3-24), and "The Use of D-ribose in Chronic Fatigue Syndrome and Fibromyalgia: A Pilot Study, *Journal of Alternative and Complementary Medicine* 2006;12(9):857-862. Dr Teitelbaum is also author of *From Fatigued to Fantastic!* (3rd ed, Penguin/Avery, 2007), *Three Steps to Happiness! Healing through Joy* (Deva Press), and *Pain Free 1-2-3 A Proven Program to Get YOU Pain Free!* (McGraw Hill, 2006). Dr Teitelbaum lives in Kona, Hawaii.

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