

# Ribose

## Addressing compromised cellular energy metabolism.

By Philip Rouchotas, MSc, ND

**R**ibose, a pentose sugar, is a required substrate for the de novo synthesis of AMP, subsequently phosphorylated to ATP. In the absence of an exogenous source, ribose is synthesized from glucose, through the pentose phosphate pathway. A rapid rate of ATP utilization, compromised ability to rephosphorylate ADP and/ or a decrease in the total adenosine pool is a common finding in several pathological processes, notably coronary heart failure (CHF) as well as chronic muscle/neurological inflammatory disorders (myalgic encephalomyelitis [chronic fatigue syndrome], fibromyalgia). Repeated, intense muscle contraction is also accompanied by alterations in adenosine pools described above.

Oral administration of ribose possesses the ability to replete compromised adenosine metabolites, allowing for a more rapid recovery of skeletal or myocardial muscle following ischemia or high-intensity exercise (Baliga 20087, Dodd 2004, Hellsten 2004). In settings where compromised cellular energy metabolism characterizes a pathological process, ribose administration has been demonstrated to deliver therapeutic benefit in controlled clinical trials. The following review will summarize evidence from clinical trials in the realms of coronary heart failure, chronic fatigue syndrome/ fibromyalgia and athletic performance enhancement. Mechanistic basis for observed phenomena will also be presented.

### RIBOSE ADMINISTRATION IN CORONARY HEART FAILURE

Table 1 provides a summary of available human clinical intervention trials examining the impact of D-ribose administration among patients with coronary heart failure.

Energy depletion in the myocyte has been a recognized feature of heart failure for over three decades (Baliga 2008). Several experimental observations have led to the understanding that all three of the key processes of energetics within the



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myocardium are compromised among patients with heart failure or left ventricular hypertrophy. The first process, substrate utilization, describes the relative contributions of carbohydrate and fat as providers of inputs, ultimately, into the Krebs cycle. Among patients with heart failure, there is an observed shift towards increasing glucose utilization at the expense of compromised fatty acid oxidation. Oxidative phosphorylation, the process of generating ATP with CO<sup>2</sup> and water as waste products in the presence of oxygen, is also compromised in heart failure patients, and forms the basis for interest in CoEnzyme Q10 and thiamine as therapeutic options in settings of secondary coronary prevention. ATP transfer and utilization forms the third aspect of myocardial energetics of interest. In heart failure patients, free ATP, ADP and creatine phosphocreatine levels have all been shown to be depressed.

Direct quantification of high-energy phosphates in humans has confirmed compromised energetics within the myocardium of patients with heart disease. Modest exertion (hand-grip exercise) produces significant declines in the myocardial phosphocreatine: ATP ratio, a finding

not observed among healthy patients exposed to the same physical stressor (Weiss 1990). AMP and ADP levels rise. Lactate levels also increase, indicative of anaerobic glycolysis compensating for compromised oxidative phosphorylation. AMP and ADP are degraded to adenosine, due to a lack of rephosphorylation. Adenosine is subsequently lost from the myocardium, degraded to inosine and hypoxanthine. Exertion of as little as 12 minutes is sufficient to produce ischemia sufficient to significantly reduce myocardial levels of high-energy phosphates (Omran 2004, Pauly 2000).

Preclinical evidence has directly correlated compromised diastolic function to depleted myocardial levels of high-energy phosphates. A “dose-response” relationship has been observed between the magnitude of recovery of high-energy phosphates and improved diastolic function. In the absence of provision of an exogenous source of ribose, recovery of myocardial levels of high-energy phosphates takes several days (Omran 2004, Pauly 2000). Oral administration of ribose affords the opportunity to prevent compromised myocardial energetics.

**Table 1. D-Ribose Administration Among Patients with Heart Failure**

Reference	Description	Outcomes
MacCarter 2009	16 patients with NTHA class III-IV heart failure were administered 5000mg D-ribose TID. Eight-week intervention. VO <sup>2</sup> , tidal volume/VC0 <sup>2</sup> , and heart rate/ tidal volume (measured at anaerobic threshold) served as endpoint measures.	Overall the population experienced a 44% improvement in Weber class. Ventilation efficiency improved 16%, tidal volume/CO <sup>2</sup> improved 17% and heart rate/ tidal volume improved 21%. Vo2 improved 19%.
Sawada 2009	26 patients with ischemic cardiomyopathy assigned to single IV bolus of placebo or ribose, crossover design. Following the infusion dobutamine echocardiography was performed.	19 patients developed ischemia following placebo administration versus 13 patients following ribose administration.
Omran 2003	15 patients with coronary heart failure randomized to ribose (5000mg TID) or placebo. Three-week intervention period, followed by one-week washout and crossover. Echocardiography, functional capacity assessed through cycle ergometer, and quality of life assessed using SF-36 served as endpoint measures.	D-ribose administration resulted in significant improvement in atrial contribution to left ventricular filling, smaller left atrial dimension and shortened E- wave deceleration. Patients also scored significantly higher on quality-of-life assessment while taking ribose.
Pliml 1992	20 patients with documented severe coronary artery disease were randomized to placebo or ribose, 15000mg TID for three days. Following three days of supplementation, patients underwent exercise testing (walking) to determine the impact of ribose of induction of ischemia.	Relative to placebo, ribose significantly prolonged the time taken for walking to induce a 1mm ST-segment depression. Relative to baseline, ribose-treated patients also demonstrated a significant prolonging to time of angina, although this was not different relative to the placebo-treated patients.
Illien 2001	15 patients with NYHA class II or III heart failure assigned to ribose or placebo. 5000mg tid for three weeks, one-week washout, then crossover.	Ribose supplemented- patients demonstrated improved diastolic compliance, and improved quality of life scores/physical functioning scores.

**Table 2. D- Ribose Administration Among Patients with Chronic Fatigue Syndrome/Fibromyalgia**

Reference	Description	Outcomes
Teitelbaum 2006	41 patients with chronic fatigue syndrome or fibromyalgia received D-Ribose 5000mg TID for 19 days. Discrete Visual Analog Scale (dVAS) served as endpoint measures (energy, sleep disturbance, mental clarity, pain and overall wellbeing).	66% of patients experienced significant improvement during D-ribose administration. The energy subscale of the sVAS increased 45% and the assessment of overall wellbeing increased 30%.
Gebhart 2004	37 yo F, surgeon by profession, with Dx of fibromyalgia. Reported daily episodes of muscle pain and stiffness, mental cloudiness, bouts of diarrhea and sleep disturbance.	30 days of D- ribose at 5000mg BID lead to significant improvement in sleep, pain, mental clarity and a normalization of bowel function. The patient discontinued and reinitiated ribose additional three times. Symptoms returned and resolved with each cycle. The patient has continued to take ribose daily since.

**RIBOSE ADMINISTRATION IN CHRONIC FATIGUE SYNDROME/FIBROMYALGIA.**

Compromised cellular metabolism is a phenomena observed in many common pathological processes. Chronic fatigue syndrome and fibromyalgia are disorders in which high-energy phosphate levels are known to be compromised in muscle (Bengtsson 1986, Lindh 1995). Given direct demonstration of the ability of oral ribose administration to replete muscle stores of high-energy phosphates, intervention with ribose for symptomatic improvement of chronic fatigue syndrome and fibromyalgia has been attempted. Table 2 highlights available evidence of intervention with ribose for management of chronic fatigue syndrome/fibromyalgia.

**RIBOSE AS AN ERGOGENIC AID?**

Repeated bouts of intense exercise induce declines in nucleotide pools of skeletal muscle. It has been proposed that oral administration of ribose will enhance performance, by allowing for a rapid repletion of skeletal muscle nucleotides. For the most part, outcomes of intervention trials in this realm have failed to produce an ergogenic benefit from ribose administration. None-the-less, the ability to replete nucleotide pools has been reproducibly demonstrated in this study population.

It is the opinion of this reviewer that existing trials have not appropriately sought

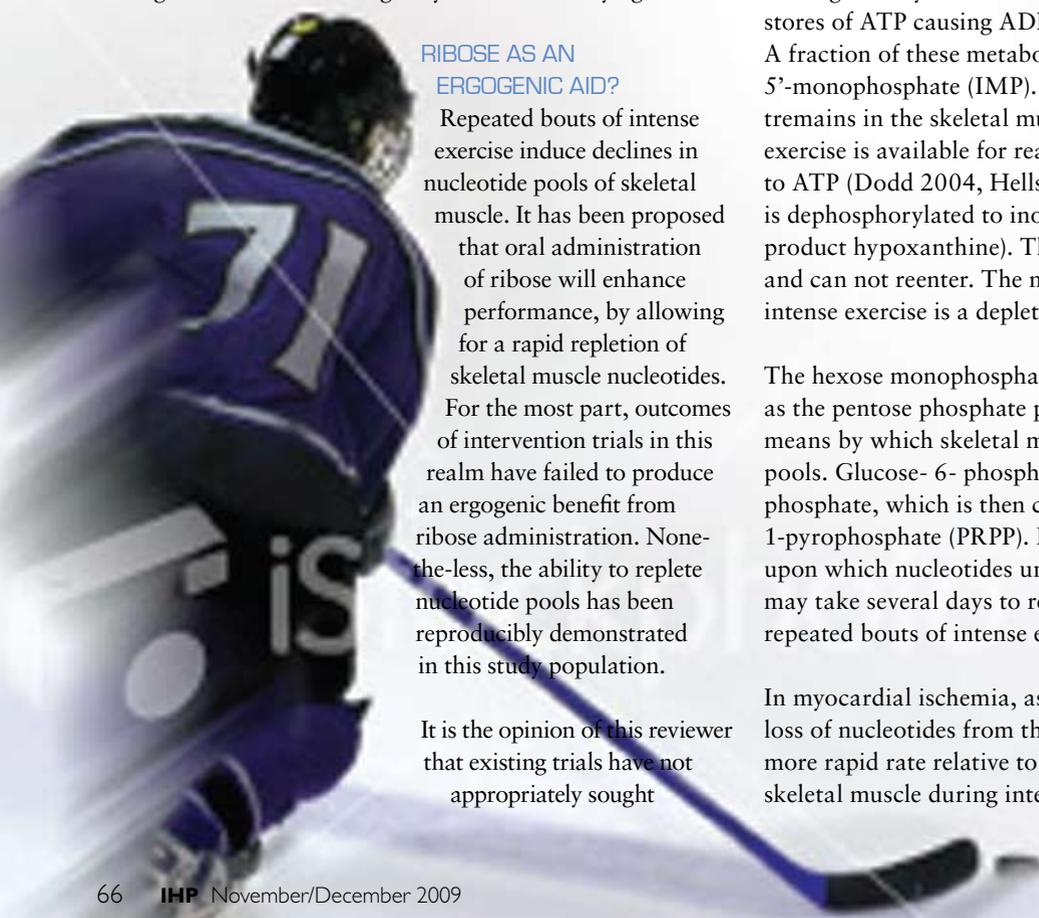
to determine the ergogenic impact of ribose; they have been of far too short duration. A more appropriate application is among athletes participating in 15+ hours per week of training/competition. Prolonged, intense training of this nature causes athletes performance to stabilize/ slightly improve during the course of a “season”. The hypothesis is that ribose administration, through prevention of nucleotide depletion from muscle, will allow the athlete to experience modest gains in performance throughout the training/competition season.

**MOMECHANISMS OF ACTION**

Among healthy individuals, exercise depletes intramuscular stores of ATP causing ADP and AMP levels to increase. A fraction of these metabolites are degraded to inosine 5'-monophosphate (IMP). The majority of IMP formed remains in the skeletal muscle, and upon termination of exercise is available for reamination and rephosphorylation to ATP (Dodd 2004, Hellsten 2004). A fraction of IMP is dephosphorylated to inosine (and inosine's degradation product hypoxanthine). These products leave muscle and can not reenter. The net result of repeated bouts of intense exercise is a depletion of nucleotides from muscle.

The hexose monophosphate shunt, otherwise known as the pentose phosphate pathway (PPP) is the principle means by which skeletal muscle replenishes nucleotide pools. Glucose- 6- phosphate is converted to ribose- 5- phosphate, which is then converted to 5-phospho-D-ribose 1-pyrophosphate (PRPP). PRPP is the parent molecule upon which nucleotides undergo de novo synthesis. It may take several days to replete adenine pools following repeated bouts of intense exercise (Pauly 2000).

In myocardial ischemia, as seen in coronary heart failure, loss of nucleotides from the myocardium occurs at a more rapid rate relative to healthy tissues, also relative to skeletal muscle during intense exercise. Greater proportions



**Table 3. D-Ribose Administration and Athletic Performance**

Reference	Description	Outcomes
Hellsten 2004	Eight subjects participated in a randomized, blinded trial with crossover. Subjects performed 15, 10s maximal exertion cycling sprints twice per day for seven days. Subjects were then administered 200mg/kg body weight ribose TID for three days. After the three-day intervention, the exercise test was repeated.	The training session induced reductions in muscle ATP levels of 25%. Muscle [ATP] remained depressed for 24 hours in both the placebo and ribose groups. After 72 hours, muscle [ATP] had returned to pre-training levels in the ribose group but remained depressed in the placebo group. Mean and peak power output did not differ between groups.
Op 't Eijnde 2001	Twenty male athletes, RCT design. Participants underwent six days of training on maximal exertion sprints using cycle ergometer. Ribose was supplemented at 4000mg 4X per day during the training period. Assessments were made at baseline and on day.	There was no difference in power output, post-exertion plasma lactate or plasma ammonia levels between ribose and placebo groups.
Dunne 2006	31 women collegiate rowers, RCT design, eight-week intervention. 10,000mg ribose per day versus dextrose placebo. Pre and post 2,000m time trial served as main endpoint measure.	Both groups performed superior at week eight versus baseline. The group assigned to dextrose performed significantly better than the group assigned to ribose.
Seifert 2009	Seven healthy subjects cycled at lactate threshold for 25 minutes, crossover design. 7,000mg ribose (or placebo) was consumed before and after the exercise session. Markers of oxidative stress served as the main endpoint measure.	Urinary malondialdehyde levels increased during the training session in the placebo group, but remained equivocal to baseline in the ribose group. Likewise, glutathione levels were reduced 14% during the placebo phase but were maintained at baseline levels during the ribose phase.
Peveler 2006	11 subjects performed two, 30 second windgate tests, each separated by one minute. The test was repeated one week later. Each subject performed one test having taken placebo, and the second test having taken 625mg ribose.	There was no difference in peak power, mean power and percent decrease in power between ribose and placebo phases.
Kerksick 2005	12 cyclists completed two exercise trials separated by one week. Subjects consumed placebo or 3,000mg ribose immediately prior to exercise trial, crossover design. Exercise test consisted of five, 30 second maximal exertion cycling sprints, separated by three minutes of rest between each sprint.	No impact on any marker of performance or metabolism, ribose versus placebo.
Kreider 2003	19 trained male subjects, two, 30-second windgate cycle sprints (separated by three minutes rest) as exercise test, separated by five days. Subjects consumed placebo or 10g ribose per day for the five-day period between tests.	No impact on peak power, average power, torque, fatigue index, lactate, ammonia, glucose or uric acid levels, ribose versus dextrose placebo. Total work output was superior during ribose versus placebo phase.
Berardi 2003	Crossover design. Six, 10-second cycle sprints with 60 seconds rest between each sprint. Subjects then consumed placebo or ribose for 36 hours (four doses, 8,000mg per dose). After 36 hours, subjects repeated a single bout of cycle sprint (10 seconds). After a five-day washout, subjects repeated the protocol.	During ribose treatment, subjects experienced improved mean power and peak power during the second of six sprints. No impact was observed during any other sprint or with any other measured variable.

of IMP are degraded to inosine and hypoxanthine, due to the fact that adenosine kinase (responsible for regeneration of AMP from IMP) is inhibited by hypoxia. The result is a more rapid, and more prolonged, decline in myocyte nucleotide pools (Pauly 2000). Preclinical models and human trials have demonstrated that oral administration of ribose significantly reduces the time required to replete skeletal muscle and myocyte nucleotide pools (Hellsten 2004). Cardiovascular function has been assessed through different stages of nucleotide pool recovery in stressed myocardium, and has been shown to correlate directly with magnitude of recovery of the nucleotide pool (Hellsten 2004, Pauly 2000).

## CONCLUSIONS

Compromised cellular metabolism represents a novel therapeutic target for a growing list of commonly presenting pathologies. As the field of mitochondrial dysfunction continues to be categorized, the list of indications for strategies demonstrated to improve cellular metabolism will grow. Presently, established cardiovascular disease, specifically coronary heart failure, as well as chronic neuromuscular disorders characterized by compromised cellular metabolism (chronic fatigue syndrome and fibromyalgia) appear to be the most appropriate therapeutic application of oral ribose administration. Areas for which clinical trials do not yet exist, but for which application of ribose appears appropriate given its mechanism of action include genetic muscular degenerative disorders (Duchenne's muscular dystrophy, gyrate atrophy

of the eye, other Muscular Dystrophies) as well as diseases in which mitochondrial dysfunction has been characterized (Huntington's, MS, certain cancers).

The failure of existing trials to demonstrate an ergogenic benefit of ribose in athletes likely stems from too short duration of administration. Administered over several months, during an athletes peak training/ competition "season", ribose is likely to prevent declines in performance, and achieve modest performance enhancement.

Baseline status of a study population is a powerful determinant of the ability to produce an "effect" from an agent in a setting of a controlled clinical trial. As such, the grossly compromised health status of patients with advanced cardiovascular disease remains the perfect stage to further the concept of compromised cellular metabolism as an important therapeutic target. A number of essential nutrients/ nutraceutical agents directly impact cellular energy metabolism, and each independently has support from clinical intervention trials as agents of therapeutic utility among individuals with heart disease. A brief list of such agents includes ribose, CoEnzyme Q10, L- carnitine, and thiamine. Each agent independently demonstrates an impressive magnitude of efficacy, and across all trials safety has never come into question. Perhaps the time has come to initiate studies which aggressively address the concept of cellular energy metabolism among patients in settings of secondary coronary prevention. The combined impact of these four agents will invariably prove superior to any one of the agents in isolation. ■

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