Mitochondrial Enhancers for Chronic Fatigue Syndrome (ME/CFS) and Fibromyalgia Pt. I: D-Ribose, CoQ10 and PQQ

by **Cort Johnson** | Dec 18, 2020 | **CoQ10**, **Homepage**, **Supplements** | **44 comments**

This is the first part in a series on mitochondrial enhancers for chronic fatigue syndrome (ME/CFS), fibromyalgia (FM), and long COVID series. The series uses the book "**Mitochondria and the Future of Medicine**", by **Lee Know**, a former naturopathic doctor in Canada, as a starting point, and includes insights from ME/CFS/FM practitioners.

- **Pt I: D-Ribose, CoQ10 and PQQ**
- **Pt II: L-carnitine and Acetylcarnitine**
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Mitochondrial Enhancement

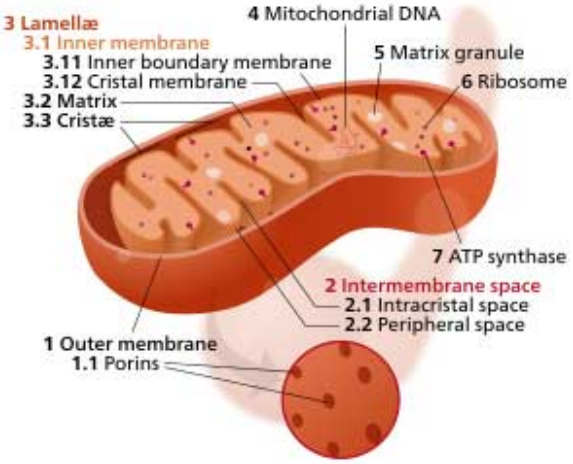
Is more energy the cure-all for chronic fatigue syndrome (ME/CFS) and fibromyalgia? Dr. Lerner observed years ago that symptoms in ME/CFS/FM tend to go up when energy levels go down and decline when energy levels go up. Even at rest, our muscles are affected by low energy levels. Because it takes more energy to relax a muscle than contract it, the muscle tension and pain many of us feel could be due to low energy levels in the muscles.

The low energy situation in ME/CFS/FM makes one think immediately of the main energy producers in the body – the mitochondria. Of course, it's not as easy as that: it never is.

Two recent reviews of the mitochondrial findings in ME/CFS noted that significant problems with the mitochondria have been found, but the results have been inconsistent. A recent review of **mitochondrial studies** found that alterations of mitochondrial structure, DNA/RNA, respiratory function, metabolites, and coenzymes have been reported, but it highlighted the inconsistent results. Three New Zealand researchers proposed that doctors and researchers should focus on the **mitochondria** when treating and studying the COVID-19 long haulers, but they too pointed out the numerous inconsistencies found.

Some studies have found decreased proton leaks, while others have found the opposite. Three studies found reduced ATP production, while two found normal ATP production. Glycolysis has been impaired in some studies and not others. Two studies found no issues with the levels of the five complexes that make up the electron transport, but one recently found reductions in Complex V and an upregulation in Complex 1.

One consistent outcome has been the lack of mitochondrial DNA changes; i.e. it's pretty clear that ME/CFS is not a **primary** mitochondrial disorder. Decreased CoQ10 levels have also been found in three studies (but not in another), and two studies have found a lower reserve capacity for energy production.



Problems with the mitochondria have been found, but the results overall have been inconsistent.

The takeaway: it's not at all clear what's going with the mitochondria in ME/CFS. The same is true with energy production overall. While the exercise studies have produced consistent evidence that energy production is impaired – and have provided plenty of ideas why – no cause has been agreed upon. We simply don't have enough precise information to target what's going on.

Plus, if there's a problem in **one part** of the mitochondria, something that enhances **another** part of the mitochondria probably won't help. If the mitochondria aren't receiving enough oxygen, then mitochondrial enhancers might not make a difference. If a hydrogen sulfide imbalance is the issue, then that will have to be dealt with. If free radicals are a problem, then enhancing the mitochondria – the source of many free radicals in the body – could make things worse! (On the other hand, Know (see below) points out that because mitochondrially produced free radicals play an important signaling role in the cell, having too many antioxidants present could conceivably be a problem.)

Helping the mitochondria to do better, then, falls into the same category that virtually every other treatment for ME/CFS/FM does: it's kind of a crapshoot. Certainly, some studies and much anecdotal evidence suggest that it can be helpful for some patients. Several ME/CFS/FM doctors have prescribed mitochondrial enhancers. On the other hand, there's not much hard evidence in the form of large, well-designed placebo-controlled studies.

Still, we are talking about energy production and while the results are mixed, enough have been found to suggest that something may be going on with the mitochondria.

The Mitochondrial Enhancers Pt. I

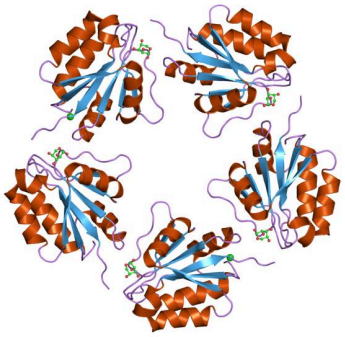
In "Mitochondria and the Future of Medicine", **Lee Know**, a licensed naturopathic doctor in Canada, has written an engagingly written overview of the field. It will provide the basis for this overview. Know, though, warns that he's by no means providing an exhaustive list of mitochondrial enhancers. This, then, is a basic overview of the major ones.

D-Ribose

Know starts out with a supplement that made quite a splash in ME/CFS over a decade ago with Dr.

Teitelbaum – D-Ribose.

D-Ribose plays a major role in the pentose-phosphate pathway – a **metabolic pathway** that runs parallel to **glycolysis** which generates **NADPH**, **pentoses** (5-**carbon sugars**) and **ribose 5-phosphate**. Every time D-Ribose is produced, NADPH and these other substances are as well.



A D-Ribose transport protein.

D-Ribose is also a component of many compounds (ATP, RNA, NADH, coenzyme-A), needed for **proper mitochondrial functioning**. It binds together purines/pyrimidines to form a kind of a backbone for these substances.

If low oxygen levels make it difficult for the mitochondria to produce ATP, our cells take an alternative approach: they combine the ADP molecules that have been building up in the cell to create it. As with all compensatory approaches, though, this comes with a cost.

That process leaves AMP as a by-product, which is then broken down and washed out of our system. The loss of AMP, though, reduces the pool of purines available – creating a real problem – as purines are key building blocks for ATP, RNA and DNA.

Know believes that the high lactic levels and early entry into anaerobic metabolism found in ME/CFS means little glucose is left to build D-Ribose.

The Gist

- Studies suggest problems with energy production exist, but we still don't know why.
- The mitochondria – the main energy producers of the cell – are a possibility. A variety of mitochondrial problems have been found, but the study results have been inconsistent.
- Since we don't know which parts, if any, of the mitochondria have problems in ME/CFS/FM, it's impossible to precisely target the mitochondria.
- Plus, if problems outside of the mitochondria exist – such as reduced oxygen delivery to the tissues or hydrogen

sulfide issues – then enhancing mitochondrial production may not help.

- Still, quite a few ME/CFS doctors do recommend mitochondrial enhancers, and some study results suggest they may be helpful.
- **D-Ribose** – By bringing purines and pyridimines together, D-Ribose provides the underpinnings for important substances such as DNA, RNA and ATP.
- D-Ribose levels decline during the low oxygen states which may be present in ME/CFS and FM. When those conditions are present, cells turn to bringing two ADP molecules together to form ATP. The AMP left over is washed out – leaving the cell depleted in purines. Bob Naviaux found reduced purines in ME/CFS.
- D-Ribose is able to enhance purine levels. Two non-placebo blinded studies from Dr. Teitelbaum suggest the D-Ribose may be helpful in a number of ways.
- Several ME/CFS doctors recommend using 3 scoops of D-Ribose a day for several weeks and then dropping down.
- **PQQ** – is a mitochondrial generator, nerve cell protector, an anti-inflammatory, and is able to protect the mitochondria from oxidative stress.
- PQQ may be able to improve short-term memory, attention and information processing.

- PQQ may work better when taken with CoQ10. Doses appear to be around 10-20 mgs/day
- **CoQ10** – arguably the most important mitochondrial enhancer, CoQ10 carries electrons from one part of the electron transport chain to the other, and it reduces oxidative stress. It's used in a number of diseases.
- Several studies have found low CoQ10 levels in ME/CFS and FM, and several trials suggest it could help.
- CoQ10 comes in two forms: ubiquinone and ubiquinol. Ubiquinol is best absorbed and is recommended particularly as we age. It's more expensive, but less is needed.
- It may take up to a month for CoQ10 levels to plateau while taking ubiquinol 2-300 mg/day. It should be taken with fats. Be wary of taking it before bedtime.
- NADPH – does not appear to be used as a mitochondrial enhancer, but it's mentioned here because Bob Naviaux focused on it with regards to the metabolism in ME/CFS.
- He believes that all the metabolic abnormalities found in ME/CFS may be a consequence of redox issues or reduced levels of NADPH.
- Naviaux calls NADPH the cellular barometer of metabolic stress, but does

not recommend NADPH supplementation.

- Instead, he reports that theoretically, incremental improvements in NADPH could be produced with folate, B12, glycine, serine pools, and B6 metabolism.
- Mitochondrial enhancers probably work best when used together and in conjunction with a program to treat ME/CFS/FM.

Health Rising's End of the Year Fundraising Drive

If getting the latest news on cutting-edge research and treatments in ME/CFS, fibromyalgia, long COVID, and related diseases supports you, please support Health Rising in it's end of the year fundraising drive. We are entirely community supported.

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D-Ribose can help cells rebuild their purine reserves. Because it takes a long time for cells to make their own D-Ribose, Know asserts that in diseased states, D-ribose supplementation is necessary to do that.

Given the potential problems with the microcirculation, the early introduction of anaerobic energy production during exercise, the lactate buildup, and reduced glutathione levels, it certainly seems likely that low purines might be a problem in ME/CFS – and there's some evidence that they are. In "**Metabolic features of chronic fatigue syndrome**", Bob Naviaux reported finding just that. Naviaux found decreased purine levels that were "consistent with decreased synthesis and/or turnover (flux) of ATP and GTP and decreased reserve capacity".

Studies suggest that D-Ribose is able to restore energy to depleted muscles that have been subjected to low oxygen levels or ischemia. Know reports that studies in athletes indicates that D-Ribose can result in lower heart rates needed to do work, **increased exercise tolerance**, and more rapid recovery of stressed muscles. One interesting study found that **D-Ribose reduced free radical levels** in healthy people who exercised for 25 minutes at their anaerobic threshold. A 2020 study found that **D-Ribose did** reduce muscle soreness, increase muscle recovery and inhibit the

production of free radicals called lipid peroxides in healthy people. Other studies, however, have **not found benefits**.

If Naviaux has found evidence of depleted purines and NADPH in ME/CFS, and D-Ribose is, according to Know **and others**, the chief replenisher of purines in the cell, does that mean we in the clear? Do we just need to supplement D-Ribose in order to rebuild those cellular stores?

Unfortunately, D-Ribose is not well studied in ME/CFS and FM. Two studies from Dr. Teitelbaum, though, suggest that D-Ribose might help. Neither, unfortunately, were **placebo-controlled**. One simply had 41 ME/CFS and/or FM patients take one scoop of D-Ribose (Corvalen) three times a day until the bucket of D-Ribose was finished. Teitelbaum reported that 2/3rds received significant improvements in energy, sleep, mental clarity, pain intensity, and well-being. The average improvement in overall well-being was 30%.

Teitelbaum followed that up with a 203-person open label, **unblinded** 3-week study which again found significant improvements in energy (61%), overall well-being (37%), sleep (29%), mental clarity (30%) and pain (15.6%).

Rituximab taught us to be careful of the outcomes of studies like these. Rituximab, after all, fared very well in a **29-person open-label** study and a **30-person double-blinded, placebo-controlled** study before it utterly failed in a 151-person **double-blinded, placebo-controlled** study.

Other doctors have recommended it as well. **Dr. Tori Hudson** believes that many ME/CFS patients start out with FM and devolve into ME/CFS/FM patients as their energy levels decline. She believes that:

> "As cellular energy is depleted, fatigue and muscle pain become more and more severe, and the muscles require additional energy in their recovery efforts. Energy is used faster than fuel is made available to renew it, and the fatigue, soreness, pain and stiffness continue to progress. Energy depletion reaches a critical point, and CFS/FMS becomes a state in which the mechanisms for recovery are overwhelmed."

She reported that she's found "D-Ribose to be the single most important nutrient in the search for alleviation of symptoms and a path towards health" in her ME/CFS and FM patients.

Using D-Ribose

It should be noted that while D-Ribose is a sugar which does not affect glucose or insulin levels, it is very sweet.

Teitelbaum recommends using using pure D-Ribose or D-Ribose with malic acid/magnesium. (See **his formulation here**.) He recommends using 15 grams (5 grams or 1 scoop 3x's/day) for two weeks and then 2 scoops once a day afterwards. He reported it took about two weeks to see the results in one study. Both **Dr. Lapp** and **Dr. Myhill** also recommend using 5 grams (1 scoop) three times a day. After a couple of weeks, Lapp recommends the dose be dropped to 1 scoop a day. Myhill has her patients stay on the original dose until the effects plateau, and then has them then experiment with lower doses.

Although Know reports that 3-5 grams a day are the normal dose, he states that larger doses are safe and clinical trials usually use 10-15 grams (2-3 scoops) and have even gone **much** higher. For people with chronic health conditions, he recommends upping the dose until an effect is found.

Myhill recommends that some people who have gut issues with it (it is a sugar but does not affect glucose or insulin levels) should absorb it in their mouth and reduce the daily dose to 1 scoop. If you're

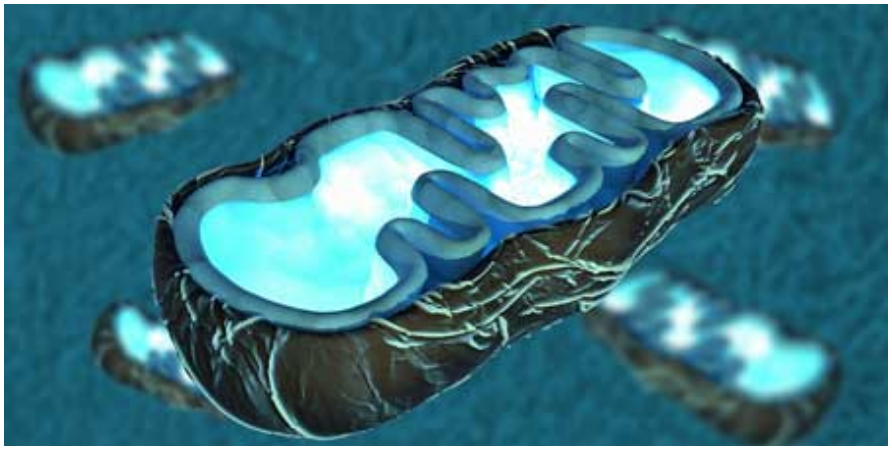
sensitive to corn, a **corn-free product** is available.

Dr. Myhill reported that D-Ribose will work best when the "other aspects of mitochondrial metabolism are addressed, such as Co-enzyme Q10, L-carnitine, magnesium, niacinamide, detoxification and antioxidant regimes where appropriate." When ME/CFS patients are following her program, she says that she expects "D-ribose to improve the symptom of delayed fatigue in sufferers as well as improve stamina".

Pyrroloquinoline Quinone (PQQ)

PQQ (thank god for acronyms) is mainly known as a **mitochondrial generator**. That aspect of PQQ may not help in ME/CFS, as mitochondrial levels seem, thus far, to be normal. PQQ also, though, appears to be able to protect nerve cells, support nerve growth and protect the mitochondria from oxidative stress.

Most PQQ studies are lab or animal studies, but one human study found that it reduced oxidative stress, decreased inflammation and immune activation (C-reactive protein, IL-6) and appeared to enhance **mitochondrial functioning**. Another human study suggested PQQ may be able to improve short-term memory, attention and information processing – all of which could be helpful in ME/CFS/FM.



PQQ appears to be able to increase mitochondrial generation, improve mitochondrial functioning and, when taken with CoQ10, enhance cognition.

Its effects may be significantly enhanced when it's taken with CoQ10. It's found in a variety of foods but is off-the-charts high in dark chocolate.

One patient reports that Dr. Klimas recommends taking PQQ with ubiquinol, but getting CoQ10 levels up to snuff first by taking it for a couple of weeks. Another patient reports that taking 20 mg PQQ before bed was helpful for having deeper and more restful sleep. Others, though, haven't noticed much effect.

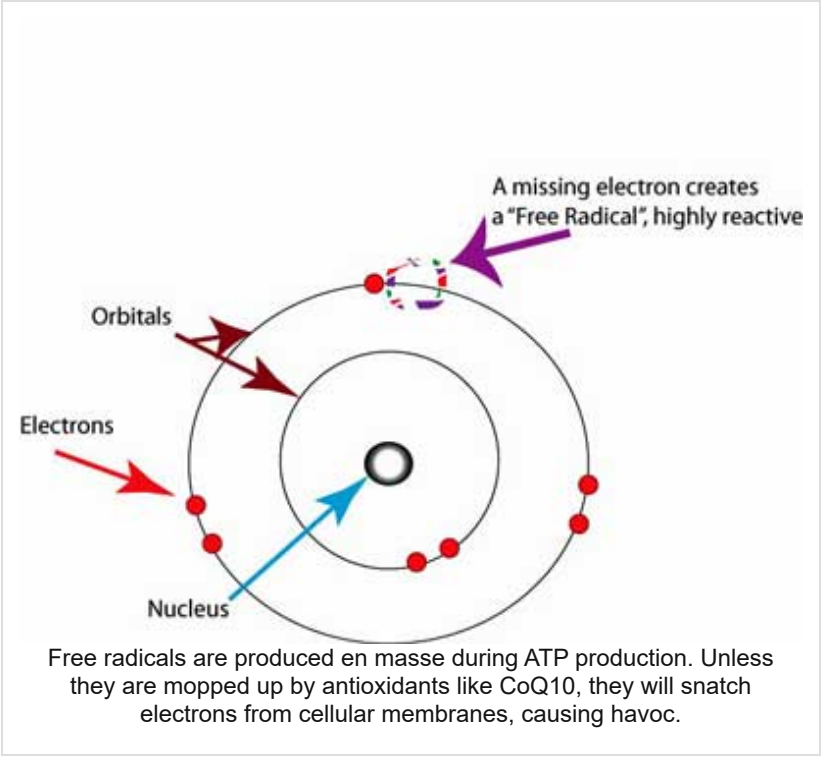
Doses appear to range from 10-20 mg daily.

Neither Courtney Craig nor Sarah Myhill have reported on PQQ.

CoQ10 (Ubiquinone/ubiquinol)

If any mitochondrial enhancer is going to help in ME/CFS and FM, it may be CoQ10. Know calls it "arguably the single most mitochondrial nutrient for mitochondrial health" and states that "CoQ10 supplementation has been shown to dramatically improve the status of patients with all sorts of health conditions." Eighty percent of it is found in the mitochondria.

Coenzyme Q10 (CoQ10) is a potent free radical scavenger, ATP production enhancer, anti-inflammatory, and has neuroprotective effects. It plays a particularly important role in complexes 1 and 2 of the electron transport chain (ETC) where it acts as an electron carrier. If not enough CoQ10 is present, not only will the ETC (and ATP production) shut down, but reactive oxygen species (ROS) or free radicals will be formed.



Free radicals are produced en masse during ATP production. Unless they are mopped up by antioxidants like CoQ10, they will snatch electrons from cellular membranes, causing havoc.

Fisher's finding that complex 1 was compensating for problems in complex 5 in ME/CFS suggests CoQ10 might help. (Know writes that CoQ10 has been able to return low levels of complex 1 activity in Parkinson's to normal).

Dr. Myhill reports it's "very common" to find low levels of CoQ10 in her patients. Plus, several studies suggest CoQ10 levels are low and supplementation may be helpful in fibromyalgia and ME/CFS.

Because as we age we produce less and less CoQ10, it might be a good idea for anyone as they get older to supplement with CoQ10.

Find out more about why CoQ10 may be helpful and how future formulations may improve it in this recent blog post.

Using CoQ10

- **Conventional CoQ10 or Ubiquinone** – is the oxidized form of CoQ10. This form is more stable, but has to be transformed into ubiquinol first. As we age, we become less able to convert ubiquinone into its usable form. Some people, particularly of Hispanic or Chinese descent, may also lack the enzyme to **transform ubiquinone**.
- **Ubiquinol** – is absorbed better, increases energy output, and scavenges free radicals in the mitochondria and cellular membranes. It's particularly the preferred form for older people. Ubiquinol is more expensive than CoQ10, but you need to take less of it.

Life Extension reported that one study showed that it took just 150 mg of ubiquinol to produce the same CoQ10 blood levels (3.96 mcg/ml) as 1,200 mg of CoQ10 (ubiquinone) over four weeks.

Life Extensions recommends 100-150 mg of ubiquinol daily for adults over the age of 30 and 200-300 mg a day for those attempting to receive its "anti-aging" benefits. Large doses (150-300 mg) may result in an "exponential increase in blood CoQ10 levels", which is sustained longer.

Dr. Mercola recommends starting with 200 to 300 mg per day, and then ramping down to 100 mg/day after three weeks when your CoQ10 plasma levels plateau. If you experience a lot of stress, though,

200-300 mg/day Is recommended. Other reports, though, suggest that it may take up to four weeks for the CoQ10 levels in your blood to reach their maximum levels.

Co-Q10 should be taken with a fatty or oily meal. Dr. Klimas warns against using it before going to bed. It will take about 4 weeks for levels to plateau. At that poin, a lower does can be used.

Myhill asserts that **Co-Q10 works best** when used with magnesium, D-Ribose, acetyl L-carnitine and NAD.

NADPH

Know does not mention NADPH, and it does not appear to be used to boost mitochondria, but it's mentioned here because after noting that purine levels were lower in ME/CFS, Naviaux focused more on NADPH, which is produced alongside D-Ribose in the pentose pathway. (From what I can tel,l supplementing with D-Ribose does not increase NADPH levels.)

If anyone knows the mitochondria, **Dr. Naviaux does**. The co-founder and a former president of the Mitochondrial Medicine Society (MMS), Naviaux was a founding associate editor of the journal Mitochondrion. He also discovered the cause of the oldest Mendelian form of mitochondrial disease – Alper's disease.

Naviaux reported that "all of the metabolic abnormalities" found in ME/CFS were either regulated via redox or oxidative stress or "the availability of NADPH". NADPH plays such a central role that Naviaux called it a "global barometer of cellular fuel status".

The consequences of low (reduced and total) NADPH levels, Naviaux reported, are profound and include problems producing key cellular factors such as sterol, fatty acid, protein, and nucleotide synthesis falls to baseline survival levels. When NADPH levels are higher, on the other hand, cells grow, biomass is created and cellular repair factors are produced and stored.

Naviaux described NADPH as a global barometer of cellular fuel status but does not recommend NADPH as a supplement.

Naviaux believes, though, that while NADPH levels appear to be low in ME/CFS, "NADPH is neither the problem nor the solution by itself". If I'm reading him correctly, the problem is the dauer or hibernation-like state that NADPH is responding to.
Naviaux's *Dauer* hypothesis suggests that the mitochondria have been turned down for a reason, and that turning them back on will take more than shoving more nutrients down their throats, so to speak.

> "NADPH cannot be simply added as a nutritional supplement to produce the tidal change in metabolism needed to shift the dauer state of CFS to normal health". Instead, Naviaux states that "**incremental** improvements in NADPH production could **theoretically** be supported by interventions directed at folate, B12, glycine, and serine pools, and B6 metabolism."

Like Myhill, **Naviaux believes** it will take treating all of ME/CFS/FM. For him, effective treatments “are likely to be achieved by careful attention to nutrition, metabolism, triggers, stressors, and physical activity as an integrated system, combined with a systems biological understanding of the triggers of the CDR (7) and dauer entry and exit”.

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