Management of Fibromyalgia: Rationale for the use of Magnesium and Malic Acid

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FROM ABSTRACT:

Primary Fibromyalgia (FM) is a common condition affecting mainly middle-aged women.

Of the etiologies previously proposed, chronic hypoxia seems the one best supported by recent biochemical and histological findings.

We postulate that FM symptoms are predominantly caused by enhanced gluconeogenesis with breakdown of muscle proteins, resulting from a deficiency of oxygen and other substances needed for ATP synthesis.

We present data supporting a critical role for magnesium and malate in ATP production under aerobic and hypoxic conditions; and indirect evidence for magnesium and malate deficiency in FM.

After treating 15 FM patients for 8 weeks with an oral dose between 1200-2400 mg of malate and 300-600 mg of magnesium, fibromyalgia tender point scores were reduced by about 60% at 4 weeks and 66% at 8 weeks.

Subjective improvement of myalgia occurred within 48h of supplementation.

THESE AUTHORS ALSO NOTE:

"Fibromyalgia (FM) is a common clinical syndrome of generalized musculoskeletal pain, stiffness and chronic aching, characterized by reproducible tenderness on palpation of specific anatomical sites, called tender points."

Fibromyalgia is *primary* when not associated with systemic causes, trauma, cancer, thyroid diseases and pathologies of rheumatic or connective tissues.

"FM is nine times more common in middle-aged women (between the ages of 30 and 50 years) than in men."

FM is one of the most common rheumatic complaints with clinical prevalence of 6%-20%.

Fibromyalgia is associated with irritable bowel syndrome, tension headache, primary dysmenorrhea, mitral valve prolapse and chronic fatigue syndrome.

Various treatment modalities have been tested in FM patients with poor results, including tryptophan, ibuprofen, and tricyclic drugs.

"Elevated catecholamines are observed in urine of FM patients." **[Important]**

Hypoxia is postulated to play an etiologic role in the development and the symptoms of FM.

There is evidence that fibromyalgia is a result of deficiencies of substances needed for ATP synthesis.

The synthesis of proteins, fats and carbohydrates is dependent on ATP availability, which supplies the energy for their synthesis and actions.

The synthesis of ATP by the mitochondria requires the presence of oxygen, magnesium, substrate [food], ADP, and inorganic phosphate (phosphate).

When all substances are present in optimal concentrations, the integrity of the mitochondrial membrane and the capacity of the enzymatic system in the respiratory chain become the rate-limiting factor in the synthesis of ATP.

The five ingredients required for the synthesis of ATP are:
1) Oxygen
2) Magnesium
3) Substrate [food]
4) ADP
5) Inorganic phosphate

Therefore, the synthesis of ATP is reduced by reduction of any of the 5 ingredients, as follows:
1) Oxygen is reduced by hypoxia, magnesium deficiency, malate deficiency.
2) Magnesium is reduced by excess aluminum and/or excess calcium.
3) Substrate is reduced by malnutrition.
4) ADP is reduced by phosphate deficiency and/or magnesium deficiency.
5) Inorganic phosphate is reduced by magnesium and/or malate deficiency or from excess calcium and/or aluminum.

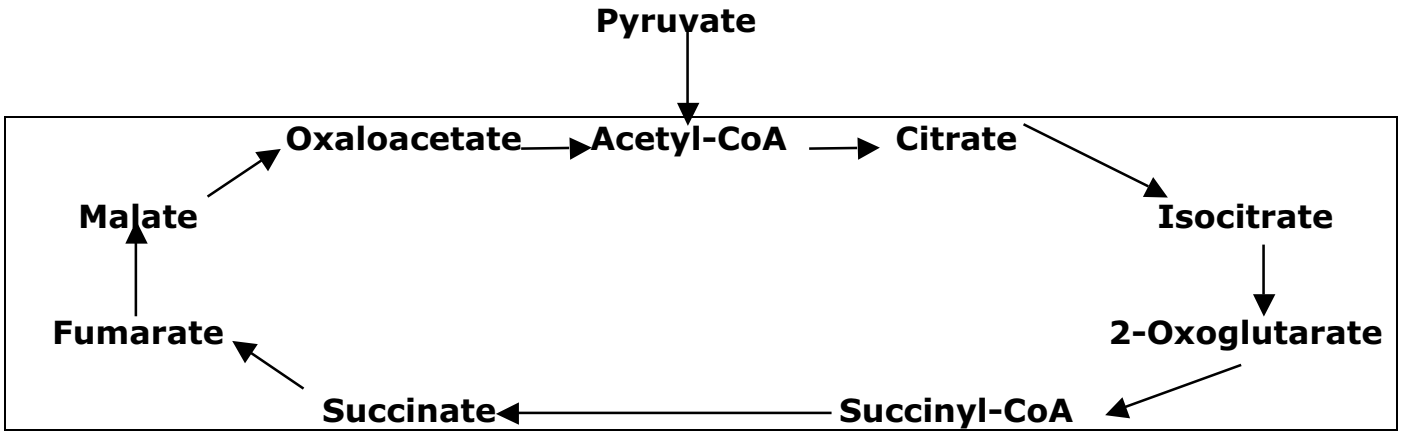
Additionally, the capacity of the respiratory chain to produce ATP is controlled by the vitamins thiamine (B1), riboflavin (B2), and pyridoxine (B6) because they are essential for the electron transport system. "All three vitamins require a magnesium dependent phosphate transfer reaction to become biologically active."

Lastly, the production of ATP is dependent upon mitochondrial membrane integrity. "Magnesium deficiency causes mitochondrial swelling, increased membrane permeability and uncoupling of oxidative phosphorylation."

Therefore, magnesium and malate play a pivotal role in mitochondrial membrane integrity, mitochondrial respiration and oxidative phosphorylation in the production of ATP.

During anaerobic glycolysis, from glucose to acetyl-Co A, there are 11 distinct steps; 9 of 11 [82%] steps require magnesium.

The Krebs Cycle (Citric Acid Cycle) has 9 steps, and 3 of them require magnesium:



Anaerobic glycolysis delivers 2 moles of ATP per mole of glucose whereas aerobic glycolysis to carbon dioxide and water through the citric acid cycle delivers 36-38 moles of ATP per mole of glucose. "Therefore, adequate oxygen supply enhances ATP yield by 18-19 fold."

"Relative hypoxia has been demonstrated in FM patients; and FM symptoms improved following aerobic conditioning."

"Magnesium plays a critical role in key enzymatic reactions for both aerobic and anaerobic glycolysis."

"The uptake and accumulation of magnesium by mitochondria is associated with enhanced uptake of phosphate and proton extrusion. The uptake of phosphate is required for phosphorylation of ADP, and the proton extrusion is the driving force in the oxidative phosphorylation of ADP."

"Aluminum inhibits glycolysis and oxidative phosphorylation with decreased intramitochondrial ATP levels."

Aluminum has a high affinity for phosphate groups and therefore blocks the absorption and utilization of phosphate for ATP synthesis, causing an intramitochondrial phosphate deficiency.

Adequate levels of magnesium prevent this toxic effect of aluminum.

Additionally, malic acid is one of the most potent chelators of aluminum.

Malic acid is most effective in decreasing brain aluminum levels.

Both magnesium and malate improve the efficiency of oxygen utilization in producing ATP. Magnesium and malate deficiency induce a relative hypoxia.

There is evidence of magnesium deficiency in FM patients. "Magnesium deficiency causes swelling and disruption of cristae in mitochondria, with a decreased number of mitochondria per cell." These mitochondrial abnormalities have been reported in muscle biopsies of tender points obtained from FM patients.

"The most common symptoms associated with FM—myalgia, chronic fatigue syndrome, irritable bowel syndrome, mitral valve prolapse, tension headache and dysmenorrhea —have been reported in patients with magnesium deficiency, and magnesium supplementation improves these symptoms."

Malate plays an important role in generating mitochondrial ATP.

Three moles of ATP are formed for each mole of malate oxidized to oxaloacetate. [see picture]

"Only tissue malate is depleted following exhaustive physical activity, in spite of the fact that the other key metabolites from the citric acid cycle necessary for ATP production remain unchanged." The malate deficiency is the cause of the physical exhaustion.

"Malate acts as an electron donor and generates a large proton motive force, believed to be the driving force for the mitochondrial synthesis of ATP."

"Relatively small amounts of exogenous malate are required to increase mitochondrial oxidative phosphorylation and ATP production."

"Under hypoxic conditions, there is an increased demand for malate because malate is not only oxidized to oxaloacetate but also reduced to succinate. [see picture]

"Malate is the only metabolite of the citric acid cycle which correlates positively with physical activity."

"In humans as well as in other animals tested, when there is increased demand for ATP, there is also an increased demand and utilization of malate."

Vitamin B6 and magnesium are required for normal activity of malate dehydrogenases, [the Kreb's Cycle enzyme that catalyzes the conversion of malate into oxaloacetate (see picture)]. A deficiency of malate dehydrogenases creates a relative malate deficiency in fibromyalgia patients. Thyroid hormones stimulate malate dehydrogenases, and therefore help fibromyalgia patients.

Respiratory chain ATP synthesis requires adequate amounts of the vitamins thiamine and riboflavin, which are the precursors of NAD and FAD [required for electron transport] respectively.

Vitamins thiamine (B1), riboflavin (B2), and pyridoxine (B6), require a magnesium-dependent phosphate transfer reaction to become biologically active. "Magnesium deficiency would therefore create a sluggish respiratory chain and a decreased efficiency in the transfer of reducing equivalents from the cytosol to the mitochondria."

Malate demands are greater in hypothyroid fibromyalgia patients.

"ADP deficiency has been reported in muscle biopsies of tender points obtained from FM patients." The following are known to cause mitochondrial ADP deficiencies:

1) Mitochondrial ADP deficiency occurs if magnesium concentrations are below optimal levels.
2) Mitochondrial ADP deficiency occurs if phosphate concentrations are below optimal levels.
3) The mitochondrial uptake of phosphate depends on malate levels, which are required for exchange with phosphate.
4) The uptake of phosphate is also enhanced by the uptake and accumulation of magnesium by mitochondria.
5) Therefore, intramitochondrial phosphate deficiency occurs in the presence of low levels of magnesium and malate.
6) Excess calcium and aluminum also predispose to intramitochondrial phosphate deficiency.

"Magnesium plays an important role in the integrity of the mitochondrial membrane. Magnesium deficiency is associated with swelling of the mitochondria; increased permeability and decreased selectivity of mitochondrial inner membrane and uncoupling of oxidative phosphorylation." "Abnormalities of mitochondrial membranes have been reported in FM patients."

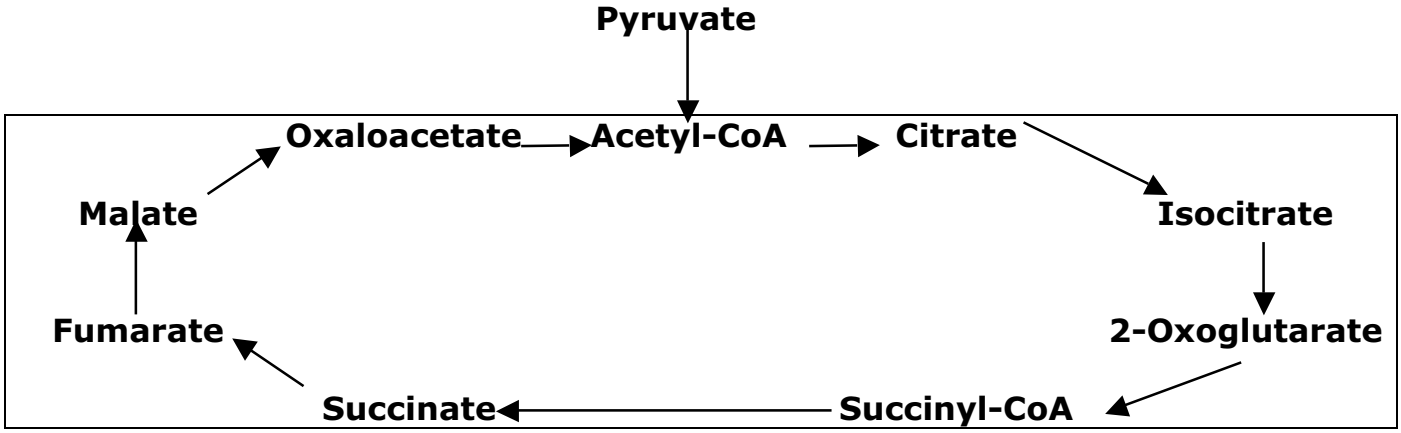
In this study, 15 patients (age 32-60) with a diagnosis of fibromyalgia based on the American College of Rheumatology criteria were supplemented with a total daily dosage of 300-600mg of elemental magnesium and 1200-2400 mg of malic acid. "All patients reported significant subjective improvement of pain within 48 h of starting."

DISCUSSION FROM DAN MURPHY

Oxygen is required to make ATP. Chronic hypoxia results in reduction of ATP. The body will respond by increasing anaerobic glycolysis, resulting in increased pyruvate production and increased lactic acid, both of which increase pain perception. The

pain of fibromyalgia is caused in part by hypoxia (which is in itself painful) and the increase of lactic acid from increased anaerobic glycolysis.

Glucose is also required to make ATP. Therefore, the body will also respond by attempting to increase the genesis of glucose. The body can make glucose for the purpose of producing ATP by assembling it from smaller molecules, especially from amino acids. The process of assembling glucose from smaller molecules is termed *gluconeogenesis*. To make glucose from amino acids, the body has to breakdown proteins, a process termed *proteolysis*, and the best source of protein for this purpose is from the muscles. The pain of fibromyalgia is also caused by the *proteolysis* of muscle tissue that occurs in order for the required *gluconeogenesis* to increase ATP synthesis in these patients.



KEY POINTS FROM DAN MURPHY:

1) "Fibromyalgia (FM) is a common clinical syndrome of generalized musculoskeletal pain, stiffness and chronic aching, characterized by reproducible tenderness on palpation of specific anatomical sites, called tender points."

2) Fibromyalgia is *primary* when not associated with systemic causes, trauma, cancer, thyroid diseases and pathologies of rheumatic or connective tissues.

3) "FM is nine times more common in middle-aged women (between the ages of 30 and 50 years) than in men."

4) The best proposed etiology for fibromyalgia is chronic hypoxia.

5) These authors propose that fibromyalgia symptoms are predominantly caused by enhanced gluconeogenesis with breakdown of muscle proteins, resulting from a deficiency of oxygen and other substances needed for ATP synthesis.

6) Magnesium and malate have a critical role in ATP production and therefore fibromyalgia symptoms may be caused by magnesium and malate deficiency.

7) Fibromyalgia is associated with irritable bowel syndrome, tension headache, primary dysmenorrhea, mitral valve prolapse and chronic fatigue syndrome.

8) Various treatment modalities have been tested in FM patients with poor results, including tryptophan, ibuprofen, and tricyclic drugs.

9) "Elevated catecholamines are observed in urine of FM patients." **[Important: elevate catecholamines (norepinephrine and epinephrine) are the result of increased sustained sympathetic tone. Increased sustained sympathetic tone can be the consequence or reduced mechanical integrity, such as a vertebral subluxation].]**

10) Reduced oxygen reduces ATP synthesis. Oxygen is reduced by hypoxia, magnesium deficiency, malate deficiency.

11) Magnesium is reduced by excess aluminum and/or excess calcium.

12) ATP production is controlled by the vitamins thiamine (B1), riboflavin (B2), and pyridoxine (B6) because they are essential for the electron transport system, and all three vitamins require magnesium to become biologically active.

13) During anaerobic glycolysis, from glucose to acetyl-Co A, there are 11 distinct steps; 9 of 11 [82%] steps require magnesium.

14) The Krebs Cycle (Citric Acid Cycle) has 9 steps, and 3 of them require magnesium:

15) An "adequate oxygen supply enhances ATP yield by 18-19 fold."

16) Fibromyalgia symptoms improve following aerobic conditioning.

17) Aluminum has a high affinity for phosphate and blocks the absorption and utilization of phosphate for ATP synthesis, causing decreased mitochondrial ATP levels. Adequate levels of magnesium prevent this toxic effect of aluminum.

18) Malic acid is one of the most potent chelators of aluminum and is most effective in decreasing brain aluminum levels.

19) "The most common symptoms associated with FM—myalgia, chronic fatigue syndrome, irritable bowel syndrome, mitral valve prolapse, tension headache and dysmenorrheal —have been reported in patients with magnesium deficiency, and magnesium supplementation improves these symptoms."

20) Malate deficiency is the cause of the ATP deficiency seen with exhaustive physical activity.

21) "In humans as well as in other animals tested, when there is increased demand for ATP, there is also an increased demand and utilization of malate."

22) Malate demands are greater in hypothyroid fibromyalgia patients.

23) Fibromyalgia patients supplemented with a daily dose of 300-600 mg magnesium plus 1200-2400 mg of malic acid "all patients reported significant subjective improvement of pain within 48 h of starting." Additionally, the fibromyalgia tender point scores were reduced by about 60% at 4 weeks and 66% at 8 weeks.

COMMENTS FROM DAN MURPHY

The malic acid plus magnesium supplement I use in the management of fibromyalgia patients is:

Complete FM from Nutri-West: 800-443-3333

Each capsule contains 294 mg of malic acid and 59 mg of magnesium.

Each capsule also contains a balance of compounds that have also been shown to benefit patients with fibromyalgia:
grapeseed extract, betatine HCL, silymarin extract, bromelain, papain, trypsin, lipase, amylase, pancreatin, lecithin (phosphytidal choline), l-leucine, l-valine, glucosamine sulfate, N-acetyl glucosamine, and ornithine alpha keto-glutarate.

Another article [Article 17-07: **Treatment of fibromyalgia syndrome with Malic Acid: Journal of Rheumatology, May 1995;22(5):953-8**] suggests that the minimum dosage should be 6 tablets per day (2 with each meal), which would supply:

1,764 mg of malic acid and 354 mg of magnesium

For some patients, the optimal dosage should be 9 tablets per day (3 with each meal), supplying:

2,646 mg of malic acid and 531 mg of magnesium