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Why does High-Dose Thiamine Relieve Fatigue in Individuals with Diverse Conditions? — Hypotheses Grounded in Thiamine's Role as a Carbonic Anhydrase Inhibitor

by Jeffrey Lubell[1]

In a series of case studies, Italian researchers reported that high-dose thiamine led to marked reductions in fatigue among patients with a wide range of conditions. While these case studies were all non-experimental, a randomized controlled trial published in November 2020 by researchers in Denmark found similar benefits for patients with quiescent inflammatory bowel disease (IBD) and extreme fatigue, strengthening the case for thiamine's effectiveness.

This exploratory working paper reviews the literature on high-dose thiamine and fatigue and considers the hypothesis that the results can be explained, in whole or in part, by thiamine's inhibition of carbonic anhydrase isoenzymes (Özdemir et al. 2013). I hypothesize that the benefits accrue through one or more of four potential pathways: (a) by reducing intracranial hypertension and/or ventral brainstem compression; (b) by increasing blood flow to the brain; (c) by facilitating aerobic cellular respiration and lactate clearance through the Bohr effect; or by (d) damping down the pro-inflammatory Th-

17 pathway, again through the Bohr effect, possibly mediated by reductions in hypoxia-inducible factor 1.

Another possibility is that the diuretic effect of carbonic anhydrase inhibition leads to temporary improvements by reducing lymphatic fluid that is not moving well through the lymphatic system, reducing pain and nerve compression. Such benefits are unlikely to be sustained, however, as the diuresis could lead to the concentration of protein in the lymphatic system that would block the movement of lymphatic fluid and potentially exacerbate underlying lipedema or lymphedema.

I would welcome constructive feedback on the ideas discussed in this working paper.

Research on High-Dose Thiamine and Fatigue

Costantini Case Studies on 600–1,800 mg daily of thiamine

Costantini and his collaborators have published a series of non-experimental case studies on the use of high-dose thiamine to treat a range of conditions. In a pilot study of eight individuals with ulcerative colitis and four individuals affected by Crohn's disease, Costantini and Pala (2013) found that 600 mg to 1,500 mg of thiamine daily led to the complete regression of fatigue in ten patients and near-complete regression in the remaining two. Costantini et al. also found improvements from similar levels of thiamine in 14 of 15 patients with Multiple Sclerosis (2013a) and through daily doses of 600 to 1,800 mg of thiamine in three patients with Fibromyalgia (2013b). Costantini et al. (2018) found dramatic improvements in the cluster headaches of a 40-year old man from a daily dose of 750 mg of thiamine.

The benefits were not limited to individuals with serum thiamine deficiency before treatment.

Costantini Parkinson's Series

Costantini and his colleagues have also conducted studies on the use of high-dose thiamine to treat Parkinson's disease and appear to have made that a major focus of their current practice. Costantini and Fancellu (2016) found substantial improvements in patients with Parkinson's disease who were treated with 100 mg of intramuscular thiamine twice a week. In a long-term study, Costantini et al. (2015) reported substantial improvements in a population of 100 patients who were followed for 95 to 831 (mean 291) days. In this study, the patients improved over the course of about three months and then sustained that level of improvement for the balance of the study. See also Costantini et al. 2013(c).

According to a website Costantini and his colleagues have set up focused on the use of high-dose thiamine in patients with Parkinson's Disease, starting doses can be 2 to 3 grams of oral thiamine hydrochloride (HCL) per day, with doses customized to the patient's symptoms and weight, often ending up at 4 grams per day orally in 2 divided doses or 2 injections of 100 mg of intramuscular thiamine per week, which they assert are equivalent in impact.

Randomized Trial of High-Dose Thiamine for Fatigue in IBD Patients

In November 2020, researchers in Denmark reported the results of a randomized double-blinded placebo-controlled crossover trial of high-dose thiamine on 40 patients with quiescent IBD and severe fatigue (Bager et al. 2021). Building on the results of the Italian pilot study, the researchers

studied the effects of 600 to 1800 mg of thiamine, assigned based on gender and weight, and found a substantial reduction in fatigue resulting from the high-dose thiamine as measured using the IBD-F, Section 1 scale.

The daily dose used in this study was as follows, using 300 mg tablets:

"The daily dose depended on gender and body weight (BW) according to the following scheme: 1) Females: BW < 60 kg: 600 mg (2 tablets), BW 60–70 kg: 900 mg (3 tablets), BW 71–80 kg: 1200 mg (4 tablets), and BW > 80 kg: 1500 mg (5 tablets); 2) Males: BW < 60 kg: 900 mg (3 tablets), BW 60–70 kg: 1200 mg (4 tablets), BW 71–80 kg: 1500 mg (5 tablets), and BW > 80 kg: 1800 mg (6 tablets)."

To examine whether the results were dependent on baseline thiamine levels, "Plasma thiamine levels were monitored before and during the study and were analysed after study completion by Bevital AS, Norway (http://bevital.no). Bevital AS use (2–50 nmol/L) as the normal range for thiamine. At baseline, 12 patients had p-thiamine levels below 2 nmol/L. [However, c]hanges in fatigue scores did not differ between patients who had thiamine levels below 2 nmol/L and those with thiamine within the reference range."

Other Research

Thiamine has been found to be beneficial for individuals with Alzheimer's disease, Wernicke's encephalopathy, and Korsakoff's psychosis (Pavlović 2019). Several studies have also found benefits of high-dose thiamine for neuropathy and other complications of diabetes (Thornalley 2005 and Winkler et al. 1999).

Side Effects

In their study of the use of high-dose thiamine to treat patients with ulcerative colitis and Crohn's disease, Costantini and Pala (2013) noted that one patient experienced mild tachycardia; this was resolved by reducing the dosage. To address concerns about insomnia — an issue that apparently arose in earlier tests — the authors administered the last dose by 5 p.m. No other side effects were reported in this study. No side effects were reported in the case studies on Fibromyalgia (Costantini et al. 2013a) or Multiple Sclerosis (Costantini et al. 2013b).

In their study of the use of high-dose thiamine on patients with Parkinson's disease, Costantini et al. (2015) report: "No patients experienced adverse events or discontinued treatment; the only clinical issue to monitor in patients with diabetes treated with insulin was the slightly increase of glycemia levels and subsequent increased insulin dosage." (Ibid.) A website Costantini and his colleagues have set up focused on the use of high-dose thiamine in patients with Parkinson's disease notes that among 2,500 or more patients treated, they have had four allergic reactions to thiamine when administered intramuscularly.[2]

In their randomized controlled trial of thiamine in patients with IBD fatigue, Bager et al. (2021) found only mild side effects. As they note, "Because thiamine is a water-soluble vitamin with renal clearance, the risk of thiamine accumulation is limited for patients with normal kidney function."

In my experience, high-dose thiamine can lead individuals to become thirsty. If the hypothesis I articulate in this paper about high-dose thiamine being a carbonic anhydrase inhibitor is correct, additional side effects to monitor for include the possibility of hypokalemia (especially if combined with a diuretic), kidney stones, and mild acidosis. The diuretic effects could also aggravate or cause lipedema or lymphedema.

Potential Mechanisms of Action

The exact mechanism through which high-dose thiamine reduces fatigue is unclear. In this section, I briefly summarize the mechanisms suggested by the authors of the studies discussed above.

After noting that the symptoms resolved by the thiamine were similar to those of thiamine deficiency, Costantini and Pala (2013) propose that high-dose thiamine works by correcting a mild thiamine deficiency through the following mechanism:

> *The presence of the symptoms of mild thiamine deficiency in patients with normal concentrations of thiamine and TPP [thiamine pyrophosphate] in the blood could be explained by a form of thiamine deficiency that's due to dysfunction of the vitamin B1 [i.e., thiamine] active transport mechanism from the blood to the mitochondria, or to structural enzymatic abnormalities.*
>
> *The administration of large quantities of vitamin B1 oral increases the concentration in the blood to levels in which the passive transport restores the normal glucose metabolism. The glucose metabolism of all organs goes back to normal values and fatigue disappears.*

In the same article, one of the authors proposes a different mechanism:

> *This author states that in the presence of a genetic dysfunction of the SLC19A3 [gene], high doses of thiamine may induce the expression of the SLC19A2 that encodes for the transporter 1 (hTHTR1), thereby increasing intracellular thiamine transport in enterocytes and neuronal cells, which were the object of the cited study.*

Other articles in the Costantini series on the use of 600–1800 mg of thiamine daily propose similar mechanisms.

A third mechanism is proposed in one of the Costantini articles on Parkinson's disease (Costantini and Fancellu (2016):

> *We suppose that the improvement of the energetic metabolism of the survivors neurons in the* substantia nigra*, due to the high doses of thiamine, could lead to an increase of synthesis and release of the endogenous dopamine, to an increase of activity of the thiamine-dependent enzymes, or to a better utilization of the exogenous levodopa (Jiménez-Jiménez et al., 1999; Lu'o'ng and Nguyên, 2012; Costantini et al. 2015). We suggest that the abnormalities in the thiamine-dependent processes could be overcome by a diffusion-mediated transport at supranormal thiamine concentrations.*

After noting that they observed no significant difference in outcomes based on baseline thiamine deficiency Bager et al. (2020) write:

> *The theory of a dysfunction in thiamine transport from blood to mitochondria remains a plausible explanation. The participants in our study were exposed to high doses of thiamine which induces passive diffusion that will add thiamine to the cells and the mitochondria. Consequently, the carbohydrate metabolism can normalise, and a reduction of fatigue is likely to follow. This theory is supported by literature describing how low intracellular thiamine levels can lead to acute energy failure, a propensity to oxidative stress and mitochondrial abnormalities. Furthermore, an animal study revealed high absorbability, high transformability and significant effect of oral thiamine on fatigue in rats.*

One final hypothesis is suggested by thiamine expert Derrick Lonsdale in an online comment:

> *There is a strong physician bias against the idea of vitamin deficiency in the United States, because there is a rooted idea that "vitamin deficiency disease is conquered. What they do not understand is that thiamine, and particularly its derivatives, are being used as 'drugs'. It is nothing to do with simple vitamin replacement. The enzymes that require thiamine have been deprived of it for so long that it can be expected that they have deteriorated 'physically' in their metabolic responsibility. The cofactor has to be used in megadoses in order to stimulate the enzymes back into their normal function. Of course, this is a hypothesis formulated to explain the 'miraculous' effect that results clinically. But until a researcher becomes interested in the clinical results and begins to research it, it will remain as the 'concept of misguided physicians and health workers'. I have the rooted idea that a biochemically- minded clinician in an academic position will eventually pick up the idea and perform further research.*

For an overview of the therapeutic uses of thiamine and the theoretical basis for them, including thiamine's role in energy production, see Lonsdale (2018) and Lonsdale and Marrs (2017).

Thiamine as a Carbonic Anhydrase Inhibitor

More research is needed to evaluate the hypotheses offered by the authors of the pioneering research on high-dose thiamine. In addition to investigating these ideas further, I would encourage exploration of the alternative hypothesis that high-dose thiamine's effects derive from the inhibition of carbonic anhydrase isoenzymes, which leads to symptomatic improvement through one or more of four potential pathways: (a) by reducing intracranial

hypertension and/or ventral brainstem compression; (b) by increasing blood flow to the brain; (c)by facilitating aerobic cellular respiration and lactate clearance through the Bohr effect; or by (d) damping down the pro-inflammatory Th-17 pathway, again through the Bohr effect. This hypothesis is supported by an in-vitro study (Özdemir et al. 2013) showing that thiamine operates as a carbonic anhydrase inhibitor with a potency similar to acetazolamide.

Ozdemir and his co-authors evaluated the relative efficacy of thiamine and several other compounds, including acetazolamide, in inhibiting three of the 16 (or more) carbonic anhydrase isoenzymes. They found that thiamine had effects similar to (though not quite as strong as) acetazolamide against all three of the isoenzymes studied. The level of thiamine needed to inhibit each isoenzyme varied, however, which may help explain why different patients in the Costantini case studies a different dose in order to fully relieve their symptoms, as some patients may require more inhibition of cerebral spinal fluid (CSF) than others. Commenting on the results of Ozdemir et al. (2013) and an analysis of the pharmacokinetics of oral thiamine HCL by Smithline et al. (2012), one Internet forum commentator noted the following:

> *The highest concentration of thiamine is required to inhibit hCA I and it is 380nM/L. This . . . is achievable using a 1,500mg dose. The concentration[s] required to inhibit the other isoenzymes of hCA were 85nM and 62nM, which are easily achieved with a thiamine dosage of 300mg — 500mg.*

Assuming this reading of Ozdemir et al. (2013) and Smithline et al. (2012) is correct, it appears that the levels of high-dose thiamine used by Costantini et al. in their non-Parkinson's studies and Bager et al. (2021) are in the same general ballpark as those needed to inhibit at least some carbonic anhydrase

isoenzymes. The higher doses of thiamine used by Costantini and his colleagues to treat Parkinson's disease could potentially inhibit additional isoenzymes.

I describe below four mechansims through which carbonic anhydrase inhibition could potentially lead to reductions in fatigue, along with a fifth mechanism whose benefits are likely to be more transitory and could potentially cause complications.

Effects of Carbonic Anhydrase Inhibitors on Cerebral Brain Flow

Acetazolamide increases cerebral brain flow and velocity, (Hojer-Pedersen 1987 and Eicke et al. 1999). The mechanism is not entirely clear, though it could potentially be related to the production of CO2 by acetazolamide, as the ingestion of CO2 has a similar effect (Hojer-Pedersen 1987). With acetazolamide, CO2 is eventually reduced in the blood, as bicarbonate is excreted, resulting in lower levels of CO2 and higher levels of oxygen. The effects of acetazolamide in increasing cerebral brain flow are transient (*ibid.)*, which could potentially correspond to this shift in CO2 levels.

To the extent that thiamine functions as a carbonic anhydrase inhibitor similar to acetazolamide, it could increase cerebral brain flow, leading to a reduction in patients' fatigue.

Effects of CSF Inhibition on Intracranial Hypertension and (Potentially) Brainstem Compression

A second potential mechanism of action is the reduction of intracranial hypertension produced by a reduction in CSF production. The Idiopathic Intracranial Hypertension Treatment trial found that high doses of

acetazolamide (averaging 2.5 grams daily) were effective in relieving the symptoms of intracranial hypertension (Wall 2017). The effects appear to be related to acetazolamide's effects in inhibiting the production of CSF (Millichap and Millichap 2015). (Smaller doses are generally used when acetazolamide is prescribed for the treatment of glaucoma, though the mechanism of action is presumably the same.) Patients in the Intracranial Hypertension Treatment trial ended up feeling most comfortable at different doses, similar to what Costantini and his colleagues have found (though Costantini posits consideration of weight in addition to severity of symptoms in calculating dosage).[3]

In Driscoll et al. (2015), the authors share patient and provider reports that acetazolamide reduces fatigue among people with Ehlers-Danlos syndrome and Craniocervical instability, which they attribute to reductions in intracranial hypertension.

A related possibility is that reduced CSF flow reduces the pressure on the brainstem at the Craniocervical junction, which may lead to improvements in individuals with Craniocervical instability, Chiari malformation and other neurological issues that can cause brainstem compression. Henderson et al. (2019) describe how a combination of Craniocervical instability and Chiari malformation, also known as complex Chiari, causes a range of problematic symptoms. They call the overall cluster of problems the Cervical Medullary Syndrome (Henderson et al. 2018). As Henderson (2016) explains, an acute clivo-axial angle can lead to brainstem deformity and stress of the neuraxis:

> *The Clivo-Axial Angle (CXA) is that angle formed between a line drawn along the posterior aspect of the lower clivus and the posterior axial line. The angle of less than 135 degrees is pathological. Increasing acuteness of clivo-axial angle creates a fulcrum by which the odontoid deforms the brainstem. The*

> *medulla becomes more kinked as the angle becomes more acute, and this results in deformative stress of the neuraxis.*

In complex Chiari, an acute CXA is exacerbated by the presence of a Chiari malformation that together operate to increase the risk of ventral brainstem compression. (Henderson et al. 2019).

High-dose thiamine could be facilitating aerobic respiration and lactate clearance

A third potential pathway through which carbonic anhydrase inhibition may be operating to reduce fatigue (and in particular, post-exertional malaise) is by facilitating aerobic respiration, rather than anaerobic respiration, and increasing lactate clearance. An over-reliance on anaerobic respiration has been observed in individuals with some chronic conditions. For example, elevated ventricular lactate levels have been observed in individuals with both ME-CFS and Fibromyalgia, which may be caused by an excessive reliance on anaerobic respiration (Natelson, Vu and Coplan, 2017).

To the extent the over-reliance on anaerobic respiration is due to mitochondrial deficiencies that are impairing aerobic respiration, it is not clear to me that carbonic anhydrase inhibition could help, though the passive thiamine transport hypothesis offered by Costantini and Pala (2013) and Bager et al. (2021) could be a potential explanation. To the extent the problem is due to hypoxia or hypoxemia, however, the production of carbon dioxide produced by high-dose thiamine when it inhibits carbonic anhydrase isoenzymes could be helpful in two related ways. As Vesela and Wilhelm (2002) explain, increases in the concentration of carbon dioxide in the blood could help to increase the amount of oxygen available for aerobic respiration at the tissue level and inhibit the production of lactate in cases of systemic hypoxia:

> *An increase in blood pCO2 shifts the oxygen hemoglobin dissociation curve to the right (Bohr effect), the result of which is a decrease in the affinity of hemoglobin for oxygen. Therefore, at the capillary level, CO2 would tend to raise pO2, increase the gradient for any given oxyhemoglobin saturation, and facilitate transfer of O2 to the tissue for oxidative processes. CO2 might also preserve cardiac function during systemic hypoxia. The inhibition of systemic lactate production by CO2 inhalation during hypoxia would serve to maintain optimal cardiovascular function.*

Similarly, Weyne et. al. (1970) note that lactate levels increase when Co2 levels decrease. The production of CO2 through carbonic anhydrase inhibition could thus also facilitate lactate clearance. (While not a conventional medical citation, Peat (2006) includes a helpful discussion of these biochemical processes.)

An alternative explanation could be that thiamine is playing its traditional role of facilitating the aerobic metabolism of pyruvate through the citric acid cycle (rather than the fermentation of pyruvate into lactate). If this is the case, it is not clear why such a large amount of thiamine would be needed to achieve the effect, as the body requires a much smaller amount to avoid a deficiency. This is where the passive transport hypothesis advanced by Costantini and Pala (2013) and Bager et al. (2021) comes in, as they posit that a high blood volume of thiamine is needed to generate the passive transport of thiamine from the blood to the mitochondria in cases where the active transport mechanism is dysfunctional.

Damping down of the Th-17 Pro-Inflammatory pathway

A fourth potential pathway through which carbonic anhydrase inhibition by high-dose thiamine may reduce fatigue is by damping down the Th-17 pro-inflammatory pathway. Th-17 activation has been linked with a number of autoimmune diseases, including Rheumatoid Arthritis, Inflammatory Bowel Disease, Psoriasis and Type 1 Diabetes (Waite and Skokos 2012). The Th-17 pathway also appears to be a significant factor contributing to the cytokine storm in COVID-19 (Hotez et al. 2020).

Researchers searching for ways to prevent the cytokine storm associated with COVID-19 found that high-dose thiamine tamped down the Th-17 pathway, leading to a reduction in pro-inflammatory IL-17 cytokines and an increase in anti-inflammatory IL-22 cytokines (Vatsalya et al. 2020). The authors recommend studying thiamine more closely to see if it could reduce the chances that individuals with COVID-19 experience a worsening of their condition due to COVID-19.

Researchers have found that reductions in IL-17 cytokines are important for allowing muscles to properly regenerate after exertion. In a study of mice, researchers found that a class of regulatory T-Cells known as Tregs “helped the muscle-healing process by suppressing an inflammatory signal called IL-17. Lowering levels of this signal during a precise time window moderated the inflammatory response and helped stop inflammation when it was no longer needed for the healing process.” (Loomis 2023). The Tregs are produced by bacteria in the gut, implying that gut dybiosis could lead to problems with muscle repair and recovery after exercise. (Hanna et al. 2023). By lowering IL-17 levels, high-dose thiamine may produce a similar effect in people who are unable to produce sufficient Tregs on their own.

It is unclear why thiamine might tamp down the Th-17 pro-inflammatory pathway. One possibility is that the activation of Th-17 may be due to tissue-

level hypoxia that is remedied by the increased oxygenation that follows through the Bohr effect from the increase in carbon dioxide produced during the inhibition of carbonic anhydrase isoenzymes. Nutsch and Hsieh (2017) and Fearon et al. (2016) discuss the process through which hypoxia may lead to activation of the Th-17 pathway, which involves the hypoxia-inducible factor 1 (HIF-1). As Deng et al. (2016) explain, HIF-1 plays an important role in a number of autoimmune diseases, including rheumatoid arthritis, inflammatory bowel disease, psoriasis, systemic sclerosis and multiple sclerosis.

Diurectic effects

A final possibility is that some of the effects of high-dose thiamine are related to the diuresis caused by carbonic anhydrase inhibition. In addition to potentially helping to reduce intracranial hypertension, the diuresis could temporarily reduce lymphatic fluid that has accumulated in individuals that have lipedema, lymphedema or another condition in which the lymphatic flow is impaired. While this could lead patients to experience short-term benefits, in the long run, it could lead to worsening lipedema or lymphedema by concentrating protein in the lympathic system that further obstructs the lymphatic flow and leads to fibrosclerosis (Herbst 2012).

This issue merits further follow up to determine what level of high-dose thiamine, if any, is safe for individuals susceptible to these conditions.

Conclusion

High-dose thiamine has shown promise in treating fatigue across a range of conditions. Additional randomized trials are needed to confirm high-dose thiamine's promise. This paper explores a number of hypotheses for why

thiamine might help reduce fatigue and also flags a caution that merits further study. Further research is needed to explore the validity of these and alternative explanations.

An accompanying working paper explores whether high-dose thiamine could be helpful for individuals with ME/CFS and the neurological complications of Ehlers-Danlos Syndrome.

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Endnotes

[1] I am the parent of a child with Ehlers-Danlos Syndrome and a series of related conditions. I offer this analysis to encourage and facilitate future research. I am not a doctor and have no medical training. I would welcome constructive feedback on the hypotheses explored in this paper.

[2] See https://highdosethiamine.org/hdt-therapy/ and https://highdosethiamine.org/frequently-asked-questions-about-hdt/#Q-1 (accessed March 29, 2020).

[3] An alternative pathway to investigate would be the diuretic effect of acetazolamide and other carbonic anhydrase inhibitors, which could alleviate pressure simply by reducing the volume of one of more bodily fluids.

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As the parent of an individual with Ehlers-Danlos and Chronic Fatigue Syndromes, I am hoping to stimulate further research on how to treat her illness.

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