NEW - BIOTIN 5000

INTRODUCTION

As you will see from one of the research papers I am about to review shortly, it has been generally assumed, given that true deficiency is quite rare due to improvements in diet, food availability, and increased use of supplementation, plus the fact that it is produced by gut microflora, and is recycled by the body, that there is no great need to emphasize biotin supplementation. Have I been swayed by publications such as this? Up until now I must admit that the answer is yes, which certainly explains why Moss Nutrition has not produced a biotin supplement until now. Because of this, I must also admit that I was taken a bit by surprise by how many of you have been requesting that we produce a biotin product. I kept on wondering whether these requests were based on good science and genuine physiological need by many patients or was it based on susceptibility to marketing “hype?”

Even though my initial sense was to dismiss increased demand to marketing hype, an examination of the published literature, a review of which you will see shortly, convinced me very quickly and dramatically that my initial sense was wrong. After I started to gain a better understanding of the biochemical and physiological role of biotin in human health, I realized that another allostatic load scenario was playing out in terms of biotin where, even though many chronically ill patients have adequate levels of biotin from a strict, “textbook” standpoint, chronic illness, in many cases, can greatly increase demand, particularly with aspects of human function that are very demanding from an energy production and glucose utilization standpoint.

The main reason this is true is that biotin plays an indispensable role in the production of glucose during times when no food is being ingested, which generally occurs using a process with which I am sure most of you are familiar, **gluconeogenesis**.

Of course, we often think of gluconeogenesis in negative terms due to the fact that excessive gluconeogenesis and the resultant excessive production of glucose can occur as the result of virtually any environmental stressor, including but not limited to poor diet. However, given the following, as noted by Jitrapakdee and Wallace in their paper “Structure, function and regulation of pyruvate carboxylase” (Jitrapakee S & Wallace JC, Biochem J, Vol. 340, pp. 1-16, 1990), for many patients, we need to consider the idea that increased gluconeogenic activity may not be a bad thing per se, but a necessary and vital response to an adverse set of environmental stressors:

“In fasting conditions, gluconeogenesis accounts for up to 96% of total glucose production.”

As you will see, biotin is a major rate-limiting factor in gluconeogenic activity. Therefore, for those patients whose environmental stressors increase demand for glucose, it stands to reason that the usual, “textbook” amount of biotin will not be enough. How might this relative deficiency based on increased demand play out? From a clinical standpoint it could be suggested that some of the most energy demanding functions of the body, such as fetal growth and nail growth, will be the first to be compromised.
With that introduction, I would now like to review some published papers on biotin and its involvement in enzyme activity that make it clear that the assumption held by many, including, up until recently, me, that there is little need to pay much attention to biotin in today’s world of clinical nutrition, is certainly in error.

**BIOTIN FROM AN HISTORICAL PERSPECTIVE – WHERE DID THE IDEAS ABOUT IRRELEVANCE COME FROM?**

The first line of the paper “Biotin: From nutrition to therapeutics” by Mock (Mock DM. *J Nutr*, Vol. 147, pp. 1487-92, 2017) states:

“Hamid Said, an eminent investigator in biotin nutrition and physiology, asked the following in the *American Journal of Clinical Nutrition* more than a decade ago: ‘Biotin bioavailability and adequate intake: why bother?’”

Why would Said say this? Mock goes on to point out that, indeed, true biotin deficiency is quite rare:

“Frank symptomatic biotin deficiency is a rare occurrence. The only well-documented cases have occurred in association with total or near-total intravenous feeding without biotin supplementation during the chronic consumption of undenatured egg white and with inborn errors of metabolism that lead to biotin wasting.”

However, in line with my hypothesis stated above, Mock goes on to suggest:

“…some studies have suggested that the absence of overt biotin deficiency does not imply optimal biotin status.”

**AN IN DEPTH DISCUSSION OF BIOTIN PHYSIOLOGY AND METABOLISM**

With the above suggestion in mind, I would now like to give a better understanding of why Mock would make such a statement by examining biotin in depth. The following quote from “Biotin in metabolism and its relationship to human disease” by Pacheco-Alvarez (Pacheco-Alvarez D et al. *Archives of Med Res*, Vol. 33, pp. 439-447, 2002) gives a good, basic but direct explanation of what biotin is and what it does:

“Biotin is a water-soluble vitamin found in all organisms that functions as a cofactor of enzymes known as biotin-dependent carboxylases. The role of biotin in carboxylases is to act as a vector for carboxyl-group transfer between donor and acceptor molecules during the carboxylation reaction.”

In simple terms, biotin does just one thing but this one thing is absolutely crucial to virtually all life forms, it catalyzes the addition of a carboxyl group to various molecules. As you might expect, the addition of carboxyl groups also involves enzymes that are specific to the various molecules to which the carboxyl group is added. Gravel and Narang in their paper “Molecular genetics of biotin metabolism: old vitamin, new science” (Gravel & Narang. *J Nutr Biochem*, Vol. 16, pp. 428-431, 2005) point out:

“Biotin acts as a carboxyl carrier in carboxylation reactions. There are four biotin-dependent carboxylases in mammals: those of propionyl-CoA (PCC), β-methylcrotonyl-CoA (MCC), pyruvate (PC) and acetyl-CoA carboxylases (isoforms ACC-1 and ACC-2). All but ACC-2 are mitochondrial enzymes.”

In terms of gluconeogenesis, one enzyme of the four mentioned above is crucial, pyruvate carboxylase. What does pyruvate carboxylase (PC) do? Jitrapakdee and Wallace state:

“Pyruvate carboxylase, a member of the biotin-dependent enzyme family, catalyses the ATP-dependent carboxylation of pyruvate to oxaloacetate.”

Furthermore, PC plays many other important roles in energy production and metabolism besides enabling gluconeogenesis:

“In mammals, PC plays a crucial role in gluconeogenesis and lipogenesis, in the biosynthesis of neurotransmitter substances, and in glucose-induced insulin secretion by pancreatic islets.”
More on this discussion on biotin and PC later.

Now, I would like to present some quotes on biotin basics. First, where does our biotin come from? Gravel and Narang note:

“We now appreciate that our biotin requirement is fulfilled in part through diet, through endogenous reutilization of biotin and perhaps though capture of biotin generated in the intestinal microflora. The utilization of biotin for covalent attachment to carboxylases and it reutilization through the release of carboxylase biotin after proteolytic degradation constitutes the ‘biotin cycle.’”

I would surmise that one reason dietary intake of biotin has been downgraded in terms of importance is the fact that biotin can not only be recycled but be produced by gut microflora. Of course, as I have suggested, this may be enough for “healthy” individuals. However, is it enough for the chronically ill patients we see? As you will see from the discussion that follows on pyruvate carboxylase (PC) from the paper by Jitrapakdee and Wallace, the answer may very well be no.

The next quote I would like to feature from the Jitrapakdee and Wallace paper points out that, with certain environmental stressors, PC expression, which requires biotin to optimally function, is elevated:

“During fasting or starvation when endogenous glucose is required for certain tissues (brain, white blood cells and kidney medulla), expression of PC and other gluconeogenic enzymes has been shown to be elevated.”

The next set of quotes from this paper point out the various ways the body’s response to various stressors increases demand for PC. First consider glutamine production:

“The anaplerotic role of PC has been proposed to be necessary for the production of glutamine, the precursor of excitatory amino acid neurotransmitters, via the operation of the glutamate/glutamine cycle.”

The next quote discusses the fact that PC is part of the allostatic response mechanism to environmental stressors:

“PC is one of a number of important metabolic enzymes whose expression is regulated in a differential manner between particular tissues in order to achieve an appropriate response to various physiological and pathological stimuli.”

In addition:

“Different physiological conditions have been shown to alter the level of PC expression: these include nutritional alterations, diabetes, hormonal changes, neonatal development, adipogenesis and lactation.”

What specific stressors and conditions might increase PC activity? Jitrapakdee and Wallace point out the following:

**Toxic exposure** – Concerning cadmium the authors state the following:

“Cadmium has long been known to increase the activities of gluconeogenic enzymes, including hepatic and renal PC in rats…”

**Diabetes** – “The rate of hepatic gluconeogenesis is increased dramatically in the diabetic state, concomitant with increases in the activities of all gluconeogenic enzymes…”

The authors go on to note that PC plays another important role in glucose metabolism beyond gluconeogenesis and lipogenesis:

“Apart from being both a gluconeogenic and a lipogenic enzyme, PC also plays an important role in glucose-induced insulin secretion in pancreatic islets…”

I will have more to say about the relationship between diabetes and biotin later in this monograph.

**Hormone metabolism – thyroid hormone**

“It has long been known that thyroid hormone affects the hepatic gluconeogenic rate in rats by increasing the activity of gluconeogenic enzymes, including PC.”

**Hormone metabolism – cortisol**
Given that many of our patients demonstrate increased cortisol production, the impact of cortisol on PC activity is particularly significant in terms of determining the need for biotin supplementation:

“Glucocorticoids have been shown to acutely stimulate gluconeogenesis and to result in an increased glucose output in rat hepatocytes. It was suggested that glucocorticoids induce…PC…”

**Hormone metabolism – Epinephrine**

“Adrenaline is also known to stimulate pyruvate carboxylation by isolated liver mitochondria.”

Thus, as the above quotes demonstrate, even though absolute biotin deficiency may be quite rare, particularly now with ready availability of B vitamin supplements and food that is fortified with B vitamins, it is very possible and even probable that, due to chronic illness and allostatic responses such as elevations in cortisol that occur during chronic illness, a relative deficiency exists of biotin due to increased, PC-driven demand.

**SIGNS AND SYMPTOMS OF BIOTIN DEFICIENCY**

With the idea that biotin deficiency may be somewhat common due to increased demand, signs and symptoms of biotin deficiency take on more significance than what was initially suggested in the quote that began this monograph. According to Gravel and Narang, these signs and symptoms include the following:

“Biotin deficiency is associated with neurological manifestations, skin rash, hair loss and metabolic disturbances that are thought to relate to the various carboxylase deficiencies (metabolic ketoacidosis with lactic acidosis). It has also been suggested that biotin deficiency is associated with protein malnutrition, and that marginal biotin deficiency in pregnant woman may be teratogenic.”

**Biotin and pregnancy**

As suggested in the above quote, biotin deficiency can be a concern during pregnancy. Because of this, routine supplementation may be advised in this instance, as noted by Mock:

“…marginal biotin deficiency occurs spontaneously in a substantial proportion of women during normal human pregnancy and it is suggested that a biotin intake ≥2-3 times the adequate intake is likely needed to meet the requirement of pregnancy.”

**Biotin and lactation**

Similar to pregnancy, increased need for biotin during lactation can also be an issue. Again, Mock points out:

“Lactating women excreted substantially more of the inactive metabolite bisnorbiotin, which is created by the oxidation of the valeric acid side chain, than did control women. This observation suggests that lactation accelerates biotin turnover and loss. Indeed, the accelerated biotransformation of biotin to bisnorbiotin has been reported in early pregnancy; however, in that study, bisnorbiotin excretion returned to normal by late pregnancy.”

**CLINICAL USE OF BIOTIN SUPPLEMENTATION**

With the above in mind, it would make sense that research exists that suggests biotin supplementation would be beneficial under certain circumstances. What follows is a summary of research on clinical uses of biotin supplementation.

**Biotin and nail health**

It has been suggested for years that biotin supplementation can enhance nail health. The paper “Nutrition and nail disease” by Cashman and Sloan (Cashman MW & Sloan SB. *Clinics in Dermatology*, Vol. 28, pp. 420-425, 2010) points out that good research supports this contention:

“One nutritional supplement that has been seriously investigated and has recently shown promise is biotin, or vitamin H. Biotin use to abate pathologic horse hoofs in veterinary medicine suggested it could be used to treat human nail disease. A role for biotin in nail disorders is also indicated by its favorable effect on other skin disorders, such as
Seborrheic dermatitis, Leiner disease, and disorders of hair growth. Biotin deficiency may be caused by insufficient intake, ingestion of raw eggs, absorption disorders, production antagonists by intestinal bacteria, or disturbance in the intestinal flora by oral therapy with sulfonamides, antibiotics, or anticonvulsant drugs.

One study demonstrated a 25% increase in the thickness of the nail plate in patients diagnosed with brittle nails of unknown cause and treated with biotin (2.5 mg daily) for 6 to 15 months. Another study showed that biotin was not equally effective in all patients, but a definite trend toward benefit was noted in most of those who took between 1.0 and 3.0 mg daily, with 2 months being the average time before clinically notable results. This same study also showed that approximately 10 weeks after biotin was discontinued, nail ridging gradually returned and nail brittleness recurred. Both studies provide clinical evidence that biotin is possibly effective in treating patients with nail brittleness.

More on diabetes and biotin

In the study “Therapeutic evaluation of the effect of biotin on hyperglycemia in patients with non-insulin dependent diabetes mellitus” by Maebashi et al (Maebashi M et al. J Clin Biochem Nutr, Vol. 14, pp. 211-218, 1993) 43 patients with non-insulin dependent diabetes mellitus (NIDDM) aged 35 to 56 years were evaluated. The duration of NIDDM ranged from 2 to 6 years.

At baseline, the NIDDM patients had lower levels of serum biotin compared with 63 controls and serum biotin levels in the patients were inversely correlated with fasting glucose levels. In addition serum pyruvate and lactate levels were elevated. After one month of receiving 9 mg daily of supplemental biotin, the serum levels of fasting glucose, pyruvate, and lactate all decreased significantly. Interestingly, serum testing performed one month after cessation of biotin supplementation demonstrated that fasting glucose, pyruvate, and lactate all returned to baseline values. With the above in mind, five patients were administered long-term biotin supplementation (More than four years). What were the results of the long-term supplementation?

“The fasting blood glucose level decreased to normal level within 2 months and remained within the normal range thereafter.”

Of course, the results of this study lead to two important questions. First why were the diabetic patients deficient in biotin compared to controls? The authors suggest:

“The reason for the low serum biotin in the patients in this study is not clear. Since biotin is mainly produced by intestinal microflora, absorbed from the intestine into the circulation and utilized, its depletion may be attributed to the insufficient synthesis of the vitamin, increased digestion or degradation of the vitamin by an abnormal level of microflora impaired absorption of the vitamin from the intestine, increased renal loss of the vitamin, or any combination of these possibilities.”

Second, why did supplemental biotin demonstrate an impact on serum fasting glucose, pyruvate, and lactate in the diabetic patients? As you will see from the quote below, it may all come back to what I discussed at length above, the enzyme pyruvate carboxylase. Maebashi et al hypothesize:

“These observations suggest that the biotin administration ameliorates abnormal glucose metabolism in diabetic patients, presumably by enhancing the activity of the biotin-dependent enzyme pyruvate carboxylase, with the subsequent promotion of glucose utilization for the entry into the tricarboxylic acid cycle.”

**Biotin Supplementation – Is There a Downside?**

With the above in mind, I would suggest that there are a great many patients who might benefit from biotin supplementation. However, there is one significant downside that, while it does not present a contraindication, it does suggest judicious use.

As noted by Mock, a common technology used today for hormone testing is streptavidin-biotin-based immunoassay. Since biotin is involved in
the testing process, could biotin supplementation adversely affect results, skewing findings either too high or too low? The author states:

“For those receiving biotin therapy, the interference may induce either falsely increased or falsely decreased results, depending on the assay design.”

Furthermore:

“…excess plasma biotin in competition assays characteristically lead to an overestimation of the analyte…”

Finally:

“…the artifacts acting on 2 hormone assays in the same profile can simulate a seemingly coherent hormonal profile; e.g., falsely increased free thyroxin and falsely decreased thyroid-stimulating hormone in the same plasma sample suggests hyperthyroidism.”

Specifically, which hormones can be affected by biotin supplementation and how will the hormones be affected? Consider the following list as described in “False biochemical diagnosis of hyperthyroidism in streptavidin-biotin-based immunoassays: the problem of biotin intake and related interferences” by Piketty et al (Piketty ML et al. Clin Chem Lab Med, Vol. 55, No. 6, pp. 780-788, 2017)

- TSH (Low)
- Free T3, Free T4 (High)
- Thyroid antibodies (High)
- 25 hydroxyvitamin D (High)
- Parathyroid hormone (Low)
- Cortisol (High)
- ACTH (Low)
- Testosterone (High)
- Estradiol (High)
- FSH (Low)
- LH (Low)
- IGF-1 (Low)
- Growth hormone (Low)
- Human chorionic gonadotrophin (Low)
- Insulin (Low)
- C-peptide (Low)
- Prolactin (Low)

**SOME FINAL THOUGHTS ON SUPPLEMENTAL BIOTIN**

As I have demonstrated, there is good research on biotin chemistry and physiology plus its use as a supplement. Unfortunately, this research has been published in somewhat obscure journals, creating a situation where, in my opinion, biotin need has not received the attention it deserves. However, clinical feedback from many of you have made it clear that, even without extensive research documentation, biotin supplementation has proven itself clinically. Hopefully, this monograph will convince even more of you to consider the need for biotin supplementation.

Nevertheless, enthusiasm for biotin supplementation needs to be tempered with the reality that it must be used judiciously in relation to any hormone testing your patient may be undergoing. This would include, most especially, vitamin D testing in the form of the most common vitamin D test, 25 hydroxyvitamin D.

**Biotin 5000 – 90 Vegetarian Capsules**

![Image of Biotin 5000 supplement]

**New Look for our Labels!**

We are excited to announce a new label design for our supplement bottles! The updated look and feel of our label features an extended color scheme and premium, satin finish.