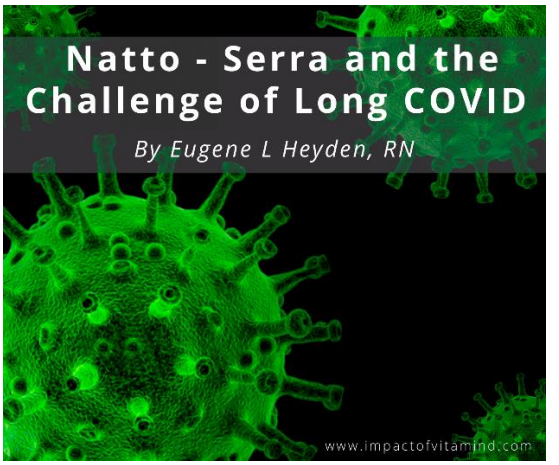

Natto - Serra and the Challenge of Long COVID

By Eugene L. Heyden, RN

Introduction

The symptoms of long COVID are multifarious and include breathlessness, fatigue, chest pain, myalgia, cognitive dysfunction, innate immune responses coupled to inflammatory cytokine production, ***and a pro-coagulant state****.* **∼Kell et al., 2022, emphasis added)**

Ongoing vascular endothelial damage promotes platelet adhesion and coagulation, resulting in the impairment of various organ functions. Meanwhile, thrombosis will further aggravate vasculitis contributing to further deterioration. Thus, ***long COVID is <u>essentially</u> a thrombotic sequela****.* **∼Wang et al., 2022, emphasis added**

Simply put, and in view of the above, the challenge of Long COVID is the challenge of dealing with all the clotting that is occurring, silently, underappreciated—negatively impacting a life, perhaps your life.

And what is driving it all? All the clotting? All the harm? I believe we have found the answer. In long COVID there is a persistence of spike protein, the protruding portion of the virus that serves to attach to and infect the target cell. They are just not going away! And there must be a ton of them hanging around, post-infection, just waiting to stir up trouble.

> *When comparing patients with post-COVID symptoms and patients without,* ***we found that Spike protein and viral RNA were more likely to be present in patients with PASC [Long COVID] and <u>in some cases at higher levels compared to acute COVID-19 patients</u>.*** *We also observed that the percent positivity of circulating viral RNA increased in the PASC positive individuals compared to acute COVID-19 group while Spike protein positivity remained the same.* (Craddock et al., 2022, emphasis added)

Oh, but there is more!

> *We report that both viral RNA and/or Spike protein remain in circulation long after acute infection (****more than one-year*** *post-infection in some cases) and this* ***persistent circulation of viral components*** *is associated with PASC [AKA Long COVID].* (Craddock et al., 2022, emphasis added)

We will assume it is you who is the victim here. During your COVID infection, you were exposed to a lot of viruses and a lot of spike protein. Not particularly pleasant, but thankfully you survived. And now you have lingering symptoms, likely most distressing, and are left wondering what is going on. It looks you are in it for the long haul.

Or perhaps your brush with death was barely noticeable, as some cases of Long COVID arise out of the mildest of cases (Crook et al., 2021). Whatever the case may be, in Long COVID there is continued exposed to spike protein, all hidden from view. And although the virus has been vanquished, parts of it remain, namely the spike protein (Craddock et al., 2022; Patterson et al., 2022; Kell et al., 2022). Spike protein exposure, as we are now learning, stimulates clot formation which, in turn, creates blockages within the microcirculation (i.e., capillaries) (Kell and Pretorius, 2022). And because of this, you get to remain ill—experiencing an array of symptoms that can easily be attributed to impaired

oxygenation at the tissue and cell level (Kell et al., 2022). Certainly, there is something that can be done to address all of this. We'll explore the possibilities here. But first, a little review is in order.

COVID-19 in brief

> *Immunothrombosis is supported by immune cells and by specific thrombosis related molecules and generates an intravascular scaffold that facilitates the recognition, containment and destruction of pathogens, thereby protecting host integrity without inducing major collateral damage to the host.* **~Engelmann et al., 2013**

In COVID-19, clot formation (AKA thrombosis) plays a major role in the disease process. Surprisingly, the clotting that is occurring within the capillary bed, particularly in the alveoli of the lungs, is a **defensive action**–an effort put forth by the body to isolate and prevent the spread of the virus into the systemic circulation, in a strategy called **immunothrombosis.** You can read all about immunothrombosis in my article entitled ***Taken by Storm: The Legacy of COVID-19 and the Future of Heparin*.** Hold everything! Read the article. I'll wait.

According to the scheme of things, the clotting occurring in COVID-19 is evoked by the presence of the coronavirus spike protein (Zhang et al., 2020, Kell and Pretorius, 2022). The body recognizes it as foreign by, of all things, the coagulation system, including the circulating platelet (Zhang et al., 2020). Decisive action follows. The clotting within the capillary bed serves to isolate and restrict the movement of the virus, pinning it down so it cannot spread. And there is a bonus! The platelets involved, all bound up within the microclot, can act to disable or destroy the virus by secreting virucidal (virus killing) proteins (Kell et al., 2022). This is a brilliant mechanism used to defend against viral attack, right at the point of entry. But it's not without cost. Symptoms can follow, some most distressing.

But that's COVID (minus all the confusing immune system activity). How about Long COVID?

Long COVID in essence

> *[The] aetiology of long COVID can be attributed to the formation of aberrant amyloid fibrin microclots, triggered in particular by the SARS-Cov-2 spike protein, and that by inhibiting the transport of erythrocytes [red blood cells] to capillaries, and hence O2 transfer, it is these amyloid microclots that are mainly responsible for the various long COVID symptoms observed.*
> **~Kell et al., 2022**

Long COVID, driven by spike protein persistence and mobility (Craddock et al., 2022), creates a state of ongoing microclotting and the accumulation of microclots within the capillary bed (Kell et al., 2022). And, it would appear, that the body is performing a defensive action once again.

Likely, the body can't help itself. It is somehow programed to respond to presence of spike protein in a particular manner, by clot formation. That's what it does. Oh, but there is more! (There always is.)

In Long COVID, the plot takes a little twist. The clots that form are assembled in a manner that resists normal dissolution, being amyloid in nature (Kell et al., 2022). You can see it for yourself (if you skip over to the next page).

The amyloid clot of which I speak is abnormally constructed—its fibrin has adopted the amyloid state (Kell et al., 2022). This makes the clot all the more menacing and allows the clot to persist and persist and persist (and persist). And invites all sorts of trouble.

> *A few years ago, we discovered that fibrinogen in blood can clot into an anomalous 'amyloid' form of fibrin that (like other β-rich amyloids and prions) is relatively resistant to proteolysis (fibrinolysis). The result, as is strongly manifested in platelet-poor plasma (PPP) of individuals with Long COVID, is extensive fibrin amyloid microclots that can persist, can entrap other proteins, and that may lead to the production of various autoantibodies.* (Kell et al., 2022)

> *The microclots may also present novel antigens that lead to the production of autoantibodies, that can exacerbate symptoms further.* (Kell et al., 2022)

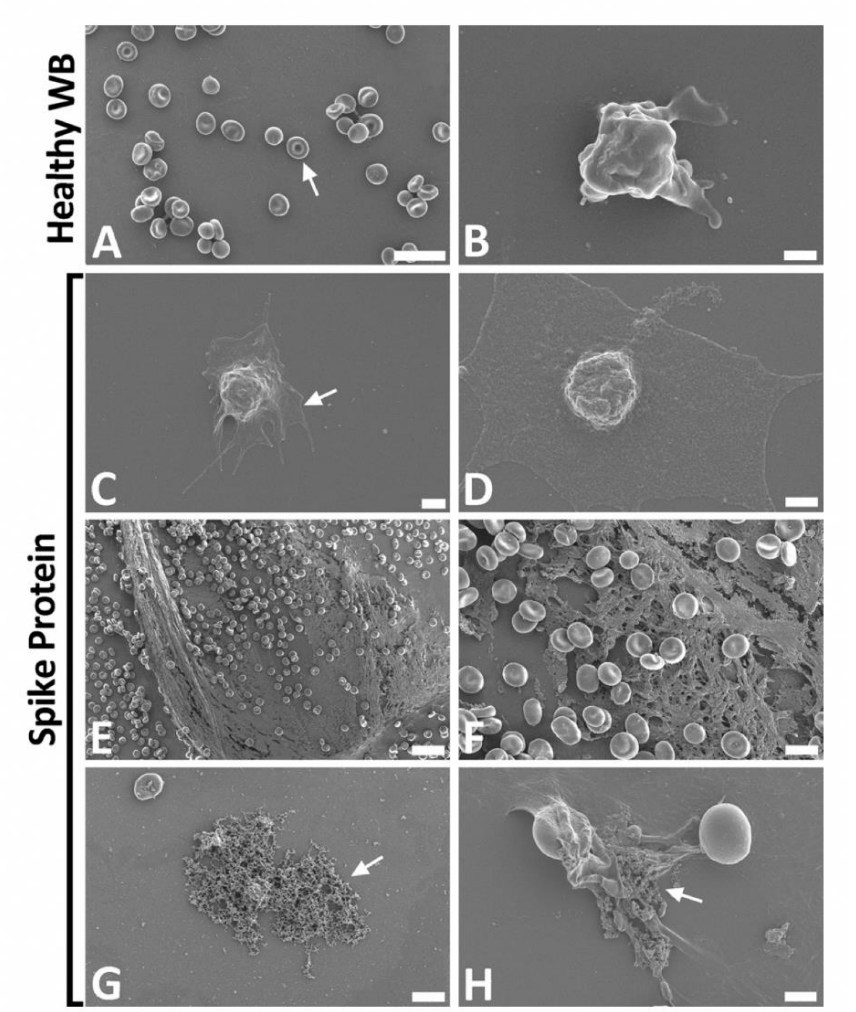

Figure 6. Whole blood sample of healthy volunteers, before and after exposure to spike protein

(**A–H**) Representative scanning electron micrographs of healthy control WB, with and without spike protein. (A,B) Healthy WB smears, with arrow indicating normal erythrocyte ultrastructure. (C–H) Healthy WB exposed to spike protein (1 ng.ml^{-1} final concentration), with (C,D) indicating the activated platelets (arrow), (E,F) showing the spontaneously formed fibrin network and (G,H) the anomalous deposits that is amyloid in nature (arrows) (scale bars: (E) 20 μm; (A) 10 μm; (F,G) 5 μm; (H) 2 μm; (C) 1 μm; (B,D) 500 nm).

Note: WB is an abbreviation for whole blood. An erythrocyte is a red blood cell. Images and description are from Grobbelaar et al., 2021. Use by author is permitted by the re-use policy of Portland Press.

So, there you have it! What you see above is a big problem. In the exhibit, you see the amyloid clotting in the context of Long COVID—clotting capable of creating blockages within the capillary bed, leading to impaired oxygen exchange and lasting symptoms. It's enough to make you sick.

> *Although the symptoms of Long COVID are multifarious, we here argue that the ability of these fibrin amyloid microclots (fibrinaloids) to block up capillaries, and thus to limit the passage of red blood cells and hence O2 exchange, can actually underpin the majority of these symptoms.* (Kell et al., 2022)

Notably, the clots that form in Long COVID resist enzymatic breakdown and, thus, are referred to as "fibrin amyloid microclots" (Pretorius et al., 2021; Kell et al., 2022). Let's dig a little deeper.

One crucial protein involved in clot formation, but abnormally formed in Long COVID, is fibrin. Normally, fibrin can be readily disassembled when the time is right, and the associated clot has served its usefulness. But in Long Covid, the fibrin formed resembles other abnormally-formed proteins, collectively referred to as amyloids—a category of proteins that are structurally unique and notoriously resistant to enzymatic breakdown (Kell et al., 2022). So, you, the Long COVID sufferer, are stuck with blood clots that will need to be addressed in a unique manner. I've made it my mission to sort it all out. (You can thank me later.)

There are a couple of procedures, performed by trained personnel in a clinical setting, that address the clotting that is occurring in Long COVID. One procedure is **H.E.L.P. apheresis**. Another procedure is called **Therapeutic Plasma Exchange**. Both remove circulating viruses, spike protein, and various clotting factors. Unfortunately, there is considerable expense involved. I discuss both methods in an article entitled *What is Taking so Long: Understanding Long COVID (And what can be done)* (https://rb.gy/avvc23). In the article, I also discuss a blood filter called **Seraph-100**, which uses stationary, heparin-coated beads to bind and remove from the circulation viruses and viral components, as well as bind and remove abnormal cytokines involved in aberrant clotting. The device must work wonders, as it has received Emergency Use Authorization in the USA for the treatment of COVID-19 (https://extheramedical.com/results-published-for-seraph-100-treatment-of-covid-19-confirm-survival-benefit-signal/), and there are reports of success.

As an alternative to the methods mentioned above, there are other ways to "dissolve" the fibrin amyloid clot and deal with the problem of Long COVID. I

write about such one method in an article entitled, *Lumbrokinase for Long COVID: Considering the possibilities* (https://rb.gy/aovqxl).

Regarding lumbrokinase, this enzyme is an earthworm enzyme (actually, a family of earthworm enzymes), capable digesting fibrin, perhaps even amyloid fibrin.

But there may be an alternative to lumbrokinase. Which begs the question,

Why send in a worm when you can send in a germ?

> *Nattokinase (NK), an alkaline serine protease extracted from the traditional Japanese food "natto" (fermented soybean) is now widely used as a health-promoting over-the-counter medicine for reducing the risk of thrombosis due to its fibrinolytic activity.* **~Ahmed et al., 2013**

> *Serrapeptase (SP) is one of the world's most exciting enzymes being studied in regard to its wide variety of clinical applications.* **~Ahmed et al., 2013**

There are two enzymes known to attack amyloid clot formations, namely nattokinase and serrapeptase—which is why we are having this discussion. Both enzymes are derived from bacteria, and both are available as a dietary supplement. Nattokinase is involved in the fermentation of soybean to produce a traditional Japanese food called natto (Ahmed et al., 2013). Serrapeptase is an enzyme produced by bacteria residing within the gut of the silkworm, and used to digest the fibers of the silkworm cocoon, allowing its release from confinement (Fadl et al., 2013; Kell and Pretorius, 2022).

In the context of dealing with the fibrin amyloid microclot, here are the properties of each enzyme that have attracted our attention, starting first with nattokinase:

- Nattokinase promotes fibrinolysis (enzymatic breakdown of fibrin) (Ahmed et al., 2013; Kell and Pretorius, 2022)
- Nattokinase dissolves and prevents the formation of amyloid fibrils, such as found in Alzheimer's disease (Ahmed et al., 2013)
- Nattokinase has antiplatelet activities, downregulating the hyperactivity of a cell intimately involved in clot formation (Kell and Pretorius, 2022)

- Nattokinase stimulates the release of tPA, a clot dissolving protein that also regulates fibrinolytic activity in the fibrinolytic cascade (Chen et al., 2018; Kurosawa et al., 2015)
- Nattokinase inactivates PAI-1, a protein that *"is the primary inhibitor of tPA and regulates fibrinolytic activity in the fibrinolytic cascade."* (Kurosawa et al., 2015)
- Nattokinase has a broad range of anticoagulant properties, activating *"multiple fibrinolytic and anti-thrombotic pathways simultaneously, either directly or indirectly."* (Kurosawa et al., 2015)
- Serrapeptase *"has considerable amyloid denaturing capacity"* (Metkar et al., 2017)
- Serrapeptase dissolves amyloid fibrils, such as found in Alzheimer's disease (Fadl et al., 2013)
- Serrapeptase can be combined with nattokinase to impede coagulation (Ghosh et al., 2019)

Once it is understood that **COVID-19 is, fundamentally, a clotting disorder which interferes with the oxygenation of tissues**, Long COVID all makes sense and potential treatments can be more easily identified. Sure, we can wait it out, hoping it will all go away, but we should probably be doing something a little more decisive that that. And didn't I hear you say, "Boy, this is getting old."

> *Given that there is a definite background removal rate of fibrinaloid microclots, albeit slower than that of normal non-amyloid clots, it is then mostly necessary to ensure that they do not form further.* (Kell et al., 2022)

Perhaps, then, we should address the clotting that is occurring in Long COVID. Perhaps we should reach for agents known to degrade the fibrin amyloid clot.

So, what to make of it all?

Both nattokinase and serrapeptase appear to be ideal agents in the treatment of Long COVID, addressing the fundamental problem of amyloid clot formation and the negative effect this has on the microcirculation and tissue oxygenation. On the other hand, "we" have basically nothing of real value to offer the patient who just can't get enough oxygen at the tissue and cell level to feel well. H.E.L.P. Apheresis and Therapeutic Plasma Exchanges can take care of the problem rather quickly, but are expensive and not general available for the treatment of Long

COVID. Therefore, I guess we're left with nattokinase and serrapeptase to offer us a little hope.

So, the question arises, should we give nattokinase and/or serrapeptase a try for Long COVID? Based on their anticoagulant and fibrin degrading properties, I say we should. But I also say the use of nattokinase, serrapeptase, even lumbrokinae, should only be done under the guidance and watchful care of a physician. Then let's see what happens.

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Acknowledgement: The author appreciates the thoughtful input of Toni M. Heyden, RN.

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