

70. Nattokinase

Last Updated: 3/18/2007

Q1: "The subject of Nattokinase seems to have grown over the past year. Seems that a lot of folks are jumping off the coumadin band wagon to take Nattokinase (or Natto) as an anticoagulant. Do you have any knowledge of Nattokinase being a valid anticoagulant?"

A1: Nattokinase may have activity in preventing blood clots, but due to the lack of clinical studies (except for one of limited quality) it can not be concluded that it is a valid anticoagulant.

Q2: "Several people on the list at the factor V web site are using Nattokinase as a clot dissolver along with coumadin and may be tapering down to just Natto. The claim is that it enhances the body's natural ability to fight blood clots in several different ways. Because it so closely resembles plasmin, it dissolves fibrin directly. Do you have any opinions on this soy product?"

A2: While Nattokinase may have some potential to protect from blood clots, it has not been appropriately studied. Any comments and conclusions that "it is effective in preventing blood clots in humans" are, at present, speculation, and any claim that one should consider "using warfarin and Nattokinase together and titrate the warfarin downward" to "decrease the harmful effects of warfarin while maintaining a safer level of anticoagulation with the positive effects of nattokinase" (reference 8) are clinically and scientifically unsound. Nattokinase is not a substitute for warfarin. If an individual takes it, he/she should not count on it having any clinical effect. It is also not know whether it is safe, particularly in people on warfarin.

Q3: "Combination therapy with both warfarin and nattokinase can provide increased prophylaxis and minimize the negative attributes of solitaire warfarin treatment".

A3: This comment (reference 8) lacks backing by scientific clinical data and is, in my opinion, inappropriate and irresponsible.

Q4: "I want to start taking Nattokinase. I have been on warfarin/Coumadin® for 4 1/2 years due to two-time DVT/PE. Will this enzyme affect my INR? How do I know if I am taking a safe amount of it while still on Coumadin®?"

A4: With any new drug or herbal product that a person on warfarin (coumadin®) starts taking it is a safe approach to think that the new drug/product may influence the INR - either make it go down or up. Many drugs influence the metabolism of warfarin, some herbal products may also influence the metabolism or contain vitamin K. It is, therefore, advisable to have an INR checked approximately 3-4 and again 7-10 days after having started a new drug/product. The safety of Nattokinase, particularly when taken together with warfarin or aspirin, has not been formally studied. It is, therefore, impossible to answer the second part of the question above, "how do I know if I am taking a safe amount of Nattokinase while still on coumadin®.

Q5: "I would like to know whether anybody has heard of Lumbrokinase. It's derived from an earthworm for treating hypercoagulability - reducing blood clots much like nattokinase. It supposedly has gone through phase III clinical trials in China. I'd be interested in an opinion on this product."

A5: I had not heard of it. The medical literature search system "Pubmed" reveals 26 publications about Lumbrokinase; only one of these is a clinical trial; it was published in a low impact-factor journal, Clinical Hemorheology and Microcirculation (impact factor 0.63). By abstract this appears to be a small phase II/III study. I would not conclude anything from this one study, but wait for publication of follow-up clinical studies..

Q6: "Is it true that there are two different types of Nattokinase, (1) NKCP type of Nattokinase and (2) NSK-SD type of Nattokinase? What is the difference and do they differ in their safety and efficacy?"

A6: NKCP® and NSK-SD™ are Nattokinase preparations from two different companies - NKCP® by Daiwa Pharmaceutical Co and NSK-SD™ from "Japan Bio Science Laboratories". They are produced by different methods, and, thus, their make-up is somewhat different, but they both contain Nattokinase, which is the compound said to have blood clot-dissolving properties. Clinical studies investigating whether these preparations have any clinically relevant beneficial effect are lacking for both of these products.

Nattokinase is a soybean food content, produced by the bacterium *Bacillus subtilis* (natto) during fermentation of soybeans. It is a 275 amino acid peptide. It is also called "Subtilisin NAT" (ref. 4). It is said to have similar clot-dissolving abilities as does plasmin, an enzyme that we all have in our blood as our natural defense mechanism to

dissolve unwanted blood clots. The "clot busters" used in clinical medicine (tPA=tissue plasminogen activator, streptokinase, urokinase, etc) to dissolve blood clots that have led to heart attacks, strokes, pulmonary embolism or deep vein thrombosis, all work through enhancing plasmin's action. They have to be given intravenously, because they are not active when given orally.

There are some research data that indicate that orally taken Nattokinase increases the clot dissolving activities (= fibrinolytic activity) of blood in animals and human volunteers and that it suppresses clot formation and enhances clot resolution in animals. However, to my knowledge, only one clinical study has been performed to assess whether Nattokinase has any real benefit in the prevention of blood clots in humans. In that study (reference 7) Nattokinase or placebo were given to individuals prior to long distance (7-8 hours) flights. Of the 92 individuals in the placebo group 7 developed a clot, all without symptoms, discovered by ultrasound; of the 94 individuals in the Nattokinase group none developed a clot. Main flaw of the study, limiting the usefulness of its conclusions, is, that the publication does not indicate whether this was a double-blinded study, or, at least, an investigator-blinded study. A non-blinded study has the potential for bias, limiting the validity of its findings and conclusions.

I think it is fair to conclude at present that Nattokinase may have some potential to protect from blood clots. However, it has not been appropriately studied in humans. Nattokinase is not a substitute for warfarin! If you take it - don't count on it having any clinical effect. It has also not been studied regarding its safety profile, particularly when it is taken together with warfarin or aspirin. The FDA concluded in 2002 that there is no "adequate basis to conclude that NKCP [Natto extract] containing 0.01 % of Nattokinase enzyme is reasonably expected to be safe" and that "there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury" [reference10]. Furthermore, the FDA has warned as recently as September 21,2006, that unsubstantiated and illegal claims are being published about the effectiveness of NSK-SD Nattokinase (ref. 11). Other health care professionals have also concluded that there is an absence of data at this time that Nattokinase has clinical effectiveness (ref. 12).

References:

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