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INTERVIEW

E VITAMIN E

Revitalizing Your
Immune System

Simin Meydani's compelling research has discovered much of what vitamin E is good for . . . and what it doesn't do as well. A foremost researcher discusses her science and your health.

Simin Nikbin Meydani, D.V.M., Ph.D., and her colleagues, including her husband Mohsen Meydani, Lynette Leka, and seven other authors, created quite a stir with the publication of a paper entitled "Vitamin E Supplementation and In Vivo Immune Response in Healthy Elderly Subjects: A Randomized Controlled Trial," in the May 7, 1997, issue (vol. 277, pp. 1380-1386) of the *Journal of the American Medical Association*. The results showed that a variety of age-related changes in human immune system function could be reversed by ingesting more vitamin E than can be consumed in any reasonable human diet. As a result of the study, Dr. Meydani was interviewed by NBC Nightly News, CNN, National Public Radio, the Discovery Channel, and many other national media.

Dr. Meydani is chief of the Nutritional Immunology Laboratory, the Jean Mayer USDA Human Nutrition Research Center on Aging, at Tufts University, in Boston. For the complete abstract of Dr. Meydani's JAMA paper, see the Abstracts section in this issue of Life Extension. This updated interview is adapted from one originally conducted by AGE News, the newsletter of the American Aging Association, and is republished with permission.



Congratulations on your successful study and on all the attention it has attracted. How would you summarize the results of your study?

Simin Meydani: Well, basically, we found that if you supplement the elderly with vitamin E, you can enhance their immune response, and in particular aspects of their immune response that are representative of T lymphocyte function.

Is it fair to say that supplementation with vitamin E actually reversed some of the age-related changes in immune system function?

Meydani: It did, but it did not reverse them completely. It certainly brought them up from the previously existing level. In elderly humans there is such a heterogeneity of response that, with 20 people in each group, it's difficult to say how close we came to youthful levels. We had some elderly who were, at the beginning, close to having a youthful immune response, and some who were

far from it for whom we enhanced their response.

But in this study, we didn't have young controls for comparison to see if we totally reversed and brought the elderly back to the level of the young. In our previous studies, especially with animals, when we've had young controls, vitamin E had partially restored the decline in immune response, but it didn't bring it up exactly to the young level.

Why does cell-mediated immunity decline with age?

Meydani: There are intrinsic defects in the T cells themselves, and we and others have proposed that, in addition, the production of suppressive factors like prostaglandin E2 can contribute to the decline in T-cell function.

Why should vitamin E be able to reverse rather than merely slow or arrest immune system damage?

Meydani: The immune cells are very dynamic. There is a lot of new material being synthesized constantly, so I think it would make sense for vitamin E to be effective because it would allow newly synthesized molecules, which are not damaged, to replace older, damaged molecules. Besides, if vitamin E reduces the production of suppressive mediators, the unsuppressed responses should be higher.

Do you have any comments as to the optimal time of day, the optimal form, or the optimal dose of vitamin E?

Meydani: In this study, we tested three levels. For the synthetic vitamin E that was used in this study, milligrams are almost equivalent to international units. For the synthetic form, 1 mg is 1.1 IU, and for the natural form, 1 mg is 1.43 IU. So we used 60 mg, 200 mg, and 800 mg per day, and of these three doses, the 200 mg was the optimal dose. As far as synthetic versus natural vitamin E, we've never done a side-by-side comparison of the exact dose to be able to see if there's a difference in their benefits. There are studies that have shown the body tends to pick up the natural form of vitamin E over the synthetic form. But, obviously, with the doses we were giving, we were able to increase the serum level of vitamin E, and in our previous studies there was an increase in the level of vitamin E in the white blood cells.

At this point, I can't say whether there's an advantage in consuming the natural form over the synthetic form as far as the immune response is concerned.

As for time of day, in this study people were taking it with their dinner mainly because we wanted to make sure they developed a routine. It was more for compliance purposes than anything else. Vitamin E is a fat-soluble vitamin. Taking it with lipid [fat]-containing food should help its absorption, but whether you take it in the morning or evening should not make any difference.

Is it possible to obtain the amount of vitamin E you found to be optimal by eating a healthy, normal diet?

Meydani: It's possible to get this from the diet, but it would be an unusual diet. Even then you'd need to be using cereals supplemented with vitamin E, in addition to a lot of plant oils and wheat germ oil.

So, in other words, there's really no way to get all of this vitamin E in a natural diet. You must take supplementation in some form.

Meydani: Right. It would be very difficult, very difficult, and especially considering that it would be a high-fat diet, it wouldn't make sense.

Would increasing vitamin E intake affect the dietary recommendations for other nutrients?

Meydani: Not that we can think of. We haven't finished analysis of all of the nutrients, but so far it does not seem to have an effect on the status of other nutrients.

Status meaning concentration?

Meydani: Yes.

I was thinking whether, if you take more vitamin E, you should reduce your selenium intake or the like, because you might change the function of selenium or the function of other nutrients. Do we have any information of that sort?

Meydani: The only information we have is that we looked at selenium status or vitamin C status, and vitamin E did not have an effect.

You mentioned that you've improved T-cell function in this study, but to the average person in the street that may not mean too much. Can you comment about the relationship between T-cell function and the chances of getting sick as you're getting older?

Meydani: Right. T cells are mostly involved in fighting against viral infections and killing tumors. They also provide help to other cells of the immune system, for example B cells and macrophages and cells involved in bacterial killing. There's preliminary evidence that they may themselves be involved in bacterial killing, but their main functions are to fight against viral infections and tumors and to provide help, or to serve in a sort of regulatory role, for other cells of the immune system.

I believe you measured T-cell function in part through a delayed type hypersensitivity (DTH) test. Can you comment on the connection between this measurement you have made and the rates of sickness and mortality?

Meydani: This test basically administers several antigens that people have been exposed to before, things like TB, tetanus, diphtheria, strep, staph, and things like that, things that we've all been exposed to, either through vaccination or in other ways. So you administer this and you look to see how well the body is able to respond to these antigens. It's used as a test of cell-mediated immunity, and T cells in particular play an important role here. This device we used had seven recall antigens in it. If there's no response to any of those antigens, it's called energy, and that has been shown to be associated with increased mortality in the elderly.

There is also "partial energy" in the elderly. In other words, if you have a response to some but not all of the antigens, or a lower response, that can have an effect on the ability of the body to respond to, for example, sepsis. So there is a semi-quantitative relationship between the DTH test and mortality and morbidity [sickness], but there's not a lot of data available on the quantitative relationship.

But there's certainly an overall trend for improvement in health with improvement in DTH score.

Meydani: Right.

Since you've given vitamin E, and that improves the immune-system score, and given that higher immune-system scores are indicative or associated with higher health, the logical inference would be that vitamin E improves the health of the elderly, and would be expected to reduce the chances of death and the chances of getting an infection. Is that a correct conclusion?

Meydani: Yes and no. If things in biological systems had a linear relationship, that would be a correct prediction. The problem is, we don't really know whether, for example, a 50% improvement in DTH or in response to a vaccine will cause a 50%, or even a 10% or a 20%, decrease in incidence of infectious diseases. Those relationships have not been developed. It would require doing much larger studies than have already been done. That's one of the reasons why we can't say all elderly people should be supplementing with 200 mg per day of vitamin E. We don't in fact know if the degree of improvement that we saw in immune response would be associated with a significant clinical benefit for the elderly.

We do have preliminary data, however, that suggest a benefit. In this study we asked the people to report their incidence of infectious diseases, but the study was not really designed to look at this question, and the collection of data was not done rigorously. But we did see a very nice trend, that people who had a higher serum level of vitamin E had a lower incidence of self-reported infections. But we need to confirm that with a larger study. We also have data from animal studies looking at influenza in older animals showing that vitamin E decreases lung viral "titer" [the quantity required to produce a reaction] in old animals who have been exposed to influenza virus. That was published in the Journal of Infectious Disease.

Have you ever noticed any differences in the way men and women respond to vitamin E?

Meydani: No, we've never had large enough numbers to be able to do such a study. But just by looking at the numbers from the studies we've done, we don't see a big difference.

Could you enlighten us as to what any possible risks there might be, contraindications, side effects, and any possible negative factors associated with taking vitamin E supplements?

Meydani: We really did not observe any side effects, so I would say it's fairly safe at the levels we have used. But this was done in healthy elderly people who were not on anticoagulants, and who were not using drugs like aspirin and indomethacin that might interfere with platelet aggregation [blood clotting]. Also, they were not consuming any other prescription medication, they did not have acute or chronic diseases, and so forth. So in the healthy elderly, the risk seems to be low or nonexistent.

And vitamin E is very cheap. I did calculate at one point that we might be able to save millions of dollars in Medicare and Medicaid costs in treating infectious diseases in the elderly.

So if cost isn't an issue and the side effects and risks are minimal, and the preponderance of evidence is for a benefit, then it seems that those who make recommendations for people should consider this. For many years it was known that high levels of cholesterol were associated with heart disease, but nobody was willing to recommend reducing cholesterol levels. We now know that if you reduce cholesterol levels, sickness and mortality go down, so it appears that excessive conservatism may have caused many people to die prematurely. Do you think recommendation of vitamin E supplementation for the elderly will be considered?

Meydani: I'm waiting to see how this data will be used. I'm sure it will be considered and evaluated, but whether it will be recommended that the elderly supplement themselves with vitamin E, I'm not sure. They might want to wait until our current study on infection is finished before they will go ahead and make such a recommendation.

Can you tell us more about this study on the incidence of infections?

Meydani: We will be supplementing the elderly with placebo or 200 mg of vitamin E for a year in a large clinical study, and we will be looking at the incidence of respiratory infections. That study probably will take four years to complete because we're enrolling a large number of people. This will be nursing home residents, as healthy as possible, but we can't be as rigorous in excluding nursing home residents as we were with free-living elderly, so they won't be as healthy a population as we used before. But they're not going to be suffering from acute diseases.

What led you to choose vitamin E for your studies, as opposed to some other nutrient?

Meydani: Well, several reasons. For one thing, it's an antioxidant nutrient, and our original hypothesis was that with aging there's an increase in the formation of free radicals, and in particular, oxidative products of arachidonic acid, things like prostaglandin E2, which have been shown to have a suppressive effect on T-cell function.

With aging, there is a decrease in enzymatic antioxidant activity, things like superoxide dismutase and catalase. It makes sense, then, that maybe the need for other antioxidants will be increased. We've also generated a lot of data supporting the notion that with aging there's an increase in PGE2 production, that the increase in production of PGE2 contributes to the decline in T-cell function, and that the effect of vitamin E seems to be mediated, at least in part, by decreasing the production of PGE2.

So our original hypothesis was that the increase in production of these oxidative products with aging contributes to the decline in T-cell mediated function. And because vitamin E had been shown to decrease formation of PGE2, and is also a very good biological antioxidant, we thought that it would be a good candidate for our studies.

There are also other factors. In animal models, investigators had shown that if you supplement with high levels of vitamin E, you can actually improve the immune response, and that was associated with increased resistance to infectious diseases. And it's a fairly safe nutrient.

How does vitamin E reduce the production of PGE2?

Meydani: That's a very interesting question. It actually does that by decreasing the activity of the enzyme cyclooxygenase, which is a main regulatory enzyme in the formation of prostaglandin E2. Cyclooxygenase needs lipid hydroperoxide for its activation, so we think that perhaps the effect of vitamin E is by decreasing the level of peroxides that are needed for the activity of the enzyme.

How does the dose of vitamin E that reduces PGE2 level compare with the dose that improves immune system function?

Meydani: The levels that cause an improvement in immune function also reduce PGE2, but we haven't done a dose response study in animals or humans to see whether there's a linear relationship between the two.

It sounds as though in the case of cyclooxygenase, the hydroperoxides are acting as a signal to regulate the enzyme, which sounds like a defensive mechanism. I wonder about the possibility that antioxidants like vitamin E might actually reduce the endogenous free radical defenses, as some have sometimes worried about.

Meydani: Well, from what we've done in this study, we don't have any evidence of that. We looked at other antioxidant nutrients, like vitamin C, carotenoids, and things like glutathione peroxidase as an indicator of selenium status, and I believe we also looked at superoxide dismutase, and we did not see any effect of vitamin E on these other antioxidant systems. So, from what we can see in humans, with the levels we used that does not seem to be a problem.

These were part of the safety study. Our concern, obviously, was that with high levels of a nutrient might come some side effects. So we did a very detailed safety evaluation, looking at the status of several nutrients, looking at liver enzyme function and kidney function and some of the hormones, and many, many other indices, too, to make sure that there was not a side effect.

None of that data was presented in your paper. Are you planning to publish the safety data separately?

Meydani: Yes. We already presented an abstract on it at FASEB [a large scientific society]. It was probably one of the most boring presentations I've ever given (laughs), because there was no toxicity data. I mean, I showed miles and miles of safety data and just kept on saying there's no adverse effect. (The full paper was recently presented in *Am. J. Clin. Nutr.* 1998; 68: 311-318.)

I think that's a very important boring paper, because it shows you can get a net benefit, a net increase in antioxidant status, presumably. You don't have to give up something in order to get something.

Meydani: Right.

Is vitamin E unique? Do you think you could achieve similar benefits by taking other antioxidants, like coenzyme Q10 or melatonin, for example?

Meydani: We haven't done anything with coenzyme Q10 or melatonin in humans. We did do a study with melatonin in animals in collaboration with my husband, Mohsen, and others, and we didn't see an effect of melatonin on immune response.

It's supposed to be a wonderful antioxidant.

Meydani: When we fed it to the animals, it really wasn't.

There appears to be at least one study that contradicts your own. Prasad found that giving adults 300 mg of vitamin E per day for three weeks actually reduced bactericidal activity and reduced the PHA response. Can you explain this discrepancy?

Meydani: Well, Prasad's study was done in young people, and ours was done in the elderly, and I think they also had a small number of people. This was an older study, and I don't remember all the details, but with a small number of people, it's possible to see anything.

Bacterial killing depends on the generation of hydrogen peroxide by cells called neutrophils, but that response was not inhibited at all. Is there a good rationale for why that function might have escaped from being inhibited by vitamin E, whereas other kinds of peroxidation are presumably inhibited?

Meydani: The only speculation we have is that vitamin E probably decreased the formation of free radicals by neutrophils, but the free radicals can also damage the neutrophils' own cell membranes. Probably vitamin E decreased free radicals but at the same time protected the membrane of neutrophils from their own products and in that way preserved their function.

Is it known as a fact that neutrophil function actually is compromised by free radical damage associated with fighting bacteria?

Meydani: There is some evidence for that.

You found that the delayed type hypersensitivity test and the responses to hepatitis B and tetanus vaccines improved with vitamin E administration. But another cell-mediated immune response, the response to diphtheria vaccine, failed to change. Why?

Meydani: Vitamin E has an effect on certain aspects of the immune system, but not on every part of the immune system. We also did not see a response to pneumococcal antigen, which depends on B-cell function. Vitamin E has its effects mostly on the T cells.

Does vitamin E have physiological functions beyond simply reducing oxidative damage and suppressing PGE2 that might be able to explain some of its effects on immunity?

Meydani: It might. There have been some indications from the studies by Dr. Azzi and others that vitamin E has functions other than just being a pure antioxidant. That evidence was gathered by looking at analogues of vitamin E that don't have an antioxidant function and yet they were able to, for example, have an effect on signal transduction. So there is some evidence that vitamin E's effect might be mediated not just by reducing free radicals, and we are looking into that. But at the moment, I don't have any data.

What sort of signal transduction processes was he looking at? Were they immune related?

Meydani: He was looking at nuclear transcription factors in smooth muscle cells. So vitamin E might actually change gene expression. Very interesting.

Vitamin E vs. Cardiovascular Disease

In laboratory tests, vitamin E prevented the early stages of plaque formation by preventing white blood cells from sticking to cells that line the artery wall-another weapon in the antioxidant's attack on heart disease, according to research at the University of Texas Southwestern Medical Center at Dallas.

The study, the first to examine how vitamin E-enrichment of these white plaque-producing cells-called monocytes-affects adhesion to the cells that line arteries, was published in the November 24, 1998, edition of *Circulation: Journal of the American Heart Association*.

"This beneficial effect of vitamin E further strengthens its role as an adjunctive therapy in the management of atherosclerosis," said lead author Dr. Ishwarlal Jialal, a professor of pathology and internal medicine at UT Southwestern.

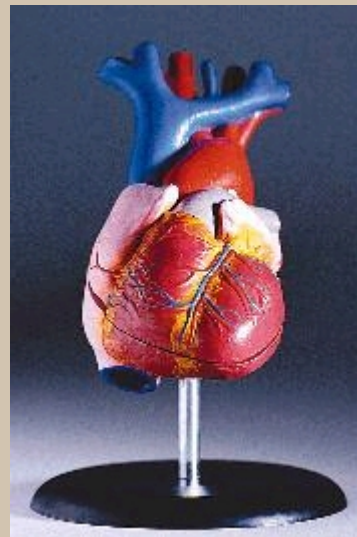
Scientists, including the UT Southwestern researchers, had already established that vitamin E can reduce susceptibility to atherosclerosis, or hardening of the arteries, because it inhibits the oxidation of low-density lipoprotein (LDL), or "bad" cholesterol. Two years ago, work by Jialal and Dr. Sridevi Devaraj, an instructor of pathology at UT Southwestern, showed the first intracellular effect of vitamin E-that it suppressed the function of monocytes.

The monocyte is the critical cell in early plaque development. An early stage of artery-clogging plaque involves the attachment of the monocyte to human endothelial cells-the artery wall. Preventing this step could be another important target in the treatment of atherosclerosis, according to Jialal.

While enrichment of monocytes with vitamin E decreased adhesion to endothelium, enrichment of both monocytes and endothelial cells resulted in greater inhibition of adhesion, the work showed.

"This is most likely what is occurring when one ingests vitamin E, since it gets in all cell membranes," Jialal said. This also represents the first demonstration that vitamin E has effects at the nuclear level on an important transcription factor. It inhibited the transcription factor NF-kappaB that is important for adhesion and inflammation. Jialal said they have elucidated the molecular events that cause vitamin E to decrease clogged arteries: It inhibits this transcription factor and decreases adhesion molecules, resulting in less adhesion of monocytes to the endothelium. These actions reduce plaque formation.

Humans can obtain this response by taking vitamin E supplements, the researchers concluded.



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