Vitamin E's lack of heart benefit linked to dosage

August 22 2007

The reported failure of vitamin E to prevent heart attacks may be due to underdosing, according to a new study by investigators at Vanderbilt University Medical Center.

The findings, published early online in *Free Radical Biology and Medicine*, suggest that these earlier studies all had a fundamental flaw – the doses used weren't high enough to have a significant antioxidant effect. In fact, no studies have ever conclusively demonstrated the dose at which vitamin E can be considered an antioxidant drug, the researchers report.

Oxidant injury, or oxidative stress, occurs when highly reactive molecules called free radicals attack and damage cellular proteins, lipids (fats) and DNA. Free radicals, which are byproducts of normal metabolism, are produced in excess in certain disease states, including heart disease.

Epidemiological data and animal studies suggested that antioxidant compounds like vitamin E, vitamin C and beta-carotene might offer some protection against heart attack in individuals at risk.

But subsequent controlled clinical trials of vitamin E – which showed little to no benefit from the vitamin – stymied that hope.

"Multiple human trials looking at the effect of vitamin E supplementation on coronary events and atherosclerosis have all failed,"

said Jack Roberts, M.D., the T. Edwin Rogers Professor of Pharmacology, professor of Medicine, and lead author on the study.

“We’re talking about trials that examined quite high doses,” added Jason Morrow, M.D., F. Tremaine Billings Professor of Medicine & Pharmacology and chief of the Division of Clinical Pharmacology. “Short of a couple of studies, there was no benefit in terms of prevention of cardiovascular events and deaths.”

These results caused many to discount vitamin E supplementation as a cardioprotective treatment, but Morrow and Roberts suspected that the studies had been poorly designed. All of the trials simply gave a dose of vitamin E and looked for end points such as heart attack occurrence. But Morrow and Roberts found a critical piece of information missing.

“All of these studies were designed in a way that they never assessed the ability of the dose of vitamin E tested to effectively reduce oxidant stress,” Morrow said.

Without determining whether the dose of vitamin E given was exerting sufficient antioxidant effects, the previous clinical trial results were flawed, the researchers said.

In the new study, Morrow and Roberts determined the optimum antioxidant dose of vitamin E using an assay they developed to measure compounds formed by oxidative stress processes, called F2-isoprostanes. This measure, said Roberts, “has been independently validated as the best measure of oxidative stress status in vivo.”

The researchers first determined how long it took for a very high dose of vitamin E – 3200 IU/day – to suppress oxidative stress in individuals at risk for cardiovascular disease.

To their surprise, it took 16 weeks for this dose – which is more than 100 times the recommended daily intake and about four times higher than doses used in most previous clinical studies – to maximally suppress F2-isoprostane formation.

In another group with similar cardiovascular risk factors, the researchers administered varying doses (0, 100, 200, 400, 800, 1600, and 3200 IU/day) over the 16-week period to find the minimum effective dose.

They found that it was necessary to give at least 1600 IU per day to cause a significant reduction in oxidative stress – twice that used in some of the previous clinical trials.

“It was clear that large doses – and doses in excess of what all clinical studies had used – were necessary,” Morrow said.

“Even with this massive dose of vitamin E, you only observe a 50 percent reduction in F2- isoprostanes,” added Roberts. “So in my opinion, vitamin E is not the spiffy antioxidant everybody thinks it is – it’s a pretty poor antioxidant.”

Because the long-term safety of such high doses is unknown, “we are not touting taking vitamin E in large doses,” Morrow said. “We are saying that, in the design of clinical trials, one needs to have good surrogate biochemical markers.”

Based on their findings, the investigators suggest that measures like F2-isoprostane measurement should be incorporated into any future studies of antioxidants in atherosclerosis prevention.

And since oxidative stress has been linked to numerous other diseases, including Alzheimer’s disease, Morrow suggests that F2-isoprostane measurement “really ought to be incorporated into studies assessing

disease prevention by antioxidants in general."

Source: Vanderbilt University Medical Center