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Is Vitamin E Supplementation Effective in Reducing Mortality Related to Cardiovascular Events in People with Type 2 Diabetes Mellitus?

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Is Vitamin E supplementation effective in reducing mortality related to cardiovascular events in people with Type 2 Diabetes Mellitus?

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Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this systematic review is to determine whether or not Vitamin E is effective in reducing the mortality related to cardiovascular event in patients with Type 2 Diabetes mellitus.


DATA SOURCE: Randomized, double blind, placebo-controlled trails comparing Vitamin E to Vitamin C, n-polyunsaturated fatty acid and placebo were found using Ovid MEDLINE and Cochrane database.

OUTCOME MEASURED: The primary outcomes measure by all three studies included 30-day cardiac mortality, mortality due to CHF and nonfatal myocardial infarction and stroke. The secondary outcomes measured in the studies included hospitalization for CHF and coronary revascularization.

RESULTS: Three double-blind randomized controlled trails were incorporated in this review. Study by Milman et al showed that Vitamin E supplementation is beneficial compared to the placebo group. The second study by Jaxa-Chameic et al. showed that Vitamin E is beneficial along with Vitamin C but is not effective when used alone. The third study by Marchioli et al. showed that Vitamin E treatment has a statistically nonsignificant (p = 0.18) increased risk of developing CHF.

CONCLUSIONS: The result of one of the three RCT’s showed that use of Vitamin E supplementation provides cardiovascular benefits in diabetic population with Hp 2-2 genotype. The other two studies showed worse effects or no conclusive effects with Vitamin E supplementation. The study population with favorable outcome with Vitamin E supplementation included Diabetic patients with Hp 2-2 genotype. Hence, further studies must be conducted in population with Hp 2-2 genotype to conclude the effects of Vitamin E.

KEY WORDS: Vitamin E, antioxidants, Myocardial Infarction, Diabetes Mellitus, Prophylaxis
INTRODUCTION

Cardiovascular disease is a major cause of morbidity and mortality in patients with Type 2 Diabetes Mellitus (T2DM). T2DM is the most common form of metabolic disorder commonly seen in obese population. Diabetic patients are chronically exposed to high blood glucose levels which in the long run leads to increased deposits of lipids in the intima of the blood vessels. These deposits lead to narrowing of the vessel, affecting the blood flow and ultimately resulting in an increased risk of clogging and hardening of the vessels. Hyperlipidemia, also commonly seen in diabetic patients, leads to atherosclerotic changes of the arteries of the heart causing coronary artery disease (CAD), the most common cause of acute myocardial infarction (AMI) and congestive heart failure (CHF).

Diabetes Mellitus is an independent risk factor of cardiovascular diseases and tends to develop heart disease and stroke at an earlier age. In the article by Jaxa-Chamiec, it is proposed that reactive oxygen species (ROS) along with hyperglycemia plays a crucial role in endothelial dysfunction, ischemia reperfusion injury and pathogenesis of DM. Endothelial dysfunction leads to decreased production of nitric oxide (NO). NO is an endothelium-derived relaxing factor (EDRF) which signals smooth muscle to relax causing vasodilation of the blood vessel. Hence, decrease in NO causes vasoconstriction and decrease perfusion to organs and tissues. Population with diabetes, hypertension and atherosclerosis are noted to have decreased amount of NO. In 2004, death due to cardiovascular complication in diabetic population of ages 65 years or older was around 68%.

Diabetic population has atypical presentation of AMI or no symptoms due to autonomic nerve dysfunction known as “silent heart attack”. The classic presentation of
AMI includes symptoms of severe substernal chest pain/pressure sometime radiating to the left upper extremity, jaw or shoulder; nausea, vomiting, diaphoresis, dizziness, shortness of breath or general malaise. The heart myocardium is damaged in MI leading to decreased compliance of the heart ultimately reducing the contractility and stroke volume. AMI is the common cause of heart failure. The population with CHF requires frequent hospitalizations increasing the cost of care. In United States, between 2009 – 2034, cost of care for cardiovascular disease is estimated to increase from $113 billion to $336 billion.¹ Since there is no definite treatment for cardiovascular complications in diabetic patients, most of the money is spend to prevent further complications and to stabilize patient’s condition.

T2DM is a chronic disease that requires constant monitoring and drug intervention. T2DM population receives aspirin, clopidogrel, B-blocker to prevent AMI or stroke and receive Angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), B-blockers, digoxin, and diuretics in various combinations to control the severity of the heart failure.² However, the diabetic population is not treated to reduce the reactive oxidative species (ROS), which leads to endothelial damage. Vitamin E is known to have an antioxidant property that is theoretically known to decrease ROS levels and hence the study was proposed to see the effects of Vitamin E on cardiovascular disease in diabetic patients.

The topic of study is important to health care providers working in any specialty because diabetes is a common condition today with high rates of incidence and prevalence. It is proposed that between 2009-2034, diabetic patients will increase from 23.7 million to 44.1 million.¹ Also, if the study intervention shows to have positive effects in T2DM patients, the
cost associated with care in this population can be reduced. If supplemental Vitamin E shows to reduce the incidence of AMI and severity of CHF, it will reduce the cardiovascular related hospitalization cost in T2DM population.

**OBJECTIVE**

The objective of this systematic review is to determine whether or not the use of Vitamin E supplementation is effective in reducing the cardiovascular mortality in Type 2 Diabetes Mellitus (T2DM) patients.

**METHODS**

The three studies included in this review were based on a following criterion. The population included individuals with Type 2 Diabetes Mellitus and acute myocardial infarction with or without T2DM. Study by Milman et al. further classified the diabetic population depending on their genotype: Haptoglobin (Hp). The study included the diabetic patients with Hp 2-2 genotype only.

All studies excluded patients with uncontrolled hypertension, stroke within 1 month before enrollment, unwillingness to stop antioxidants supplements, known allergy to vitamin E. In addition, the study by Milman et al. excluded diabetic population with Hp 1-1 and Hp 2-1 genotype; Jaxa-Chamiec et al. excluded the death due to non-cardiac related cause and Marchioli et al. excluded population with baseline CHF managed by multiple drug regimen.

The intervention used in the studies was Vitamin E 300 mg/day (Marchioli et al.), 600 mg/day (Jaxa-Chamiec et al.) and 400 IU/day (Milman et al.). The treatment groups
were compared to the control groups who were given visually matched n-polyunsaturated fatty acid 1g/day (Marchioli et al.), Vitamin C 1200 mg/day (Jaxa-Chamiec et al.) and placebo. The main outcomes measured were mortality related to cardiovascular events, risk of developing CHF and hospitalization for cardiovascular complication (PEOM). The studies were double blind, randomized, and placebo-controlled.

The study performed by Jaxa-Chamiec et al. were given infusion and oral Vitamin E and Vitamin C together and other group on the study was given infusion of saline placebo.²

In the study performed by Marchioli et al. the population was divided into four groups who were given Vitamin E, n-polyunsaturated fatty acids, both or none respectively and were followed for 3.5 years.³ Echocardiographic measure of left ventricular ejection fraction was determined and patients developing CHF were defined as “hospitalization or death for CHF”.³

The study performed by Milman et al. took place within 47 primary health care clinics in the Haifa and Western Galilee district of Clalit Health Services.⁴ Hp phenotyping was performed by electrophoresis and diabetic population with Hp 2-2 were selected. A computer generated randomization was used to divide study population into 2 groups from with one group received Vitamin E and another group received placebo.⁴

Key words used in literature searches were vitamin E, antioxidant, congestive heart failure, myocardial infarction, diabetes mellitus and oxidative stress. All articles were published in English language in the peer-reviewed journals. Articles used in the review were searched and selected by the author using literature searches like Ovid, Medline and Cochrane. Articles were selected based on their relevance and outcomes. The studies included are conducted in randomized, controlled fashion in a prospective, intention to
treat basis, date after 2004 or later. The statistics utilized in the studies were p-value, confidence interval (CI), relative risk reduction (RRR), absolute risk reduction (ARR) and number needed to treat (NNT).

Table 1 - Demographics & Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>#Pts</th>
<th>Age (yrs)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaxa-Chamiec, 2005 (1)</td>
<td>Randomized, placebo-controlled double-blind clinical study</td>
<td>800</td>
<td>50 - 75</td>
<td>In-hospital or out-hospital cardiac mortality in patients with or without diabetes mellitus</td>
<td>Documented non-cardiac cause</td>
<td>0</td>
<td>Vitamin E 600 mg/day; Vitamin C 1200 mg/day</td>
</tr>
<tr>
<td>Marchioli 2006 (2)</td>
<td>Open label, randomized, clinical trial</td>
<td>8415</td>
<td>45 - 70</td>
<td>No diagnosis of heart failure and an echocardiographic measurement of Ejection Fraction (EF) at baseline</td>
<td>Heart failure at baseline; use of angiotensin-converting enzyme inhibitors, B-blockers, diuretics or nitrates for CHF management.</td>
<td>220</td>
<td>Vitamin E 300 mg/day; n-3 polyunsaturated fatty acids 1g/day</td>
</tr>
<tr>
<td>Milman, 2008 (3)</td>
<td>Prospective, Double-blinded clinical trial</td>
<td>1434</td>
<td>≥55 yo T2DM and Hp 2-2 genotype,</td>
<td>≥55 yo T2DM and Hp 2-2 genotype, Uncontrolled hypertension; MI or stroke within 1 month before enrollment; unwillingness to stop antioxidant supplements; Known allergy to Vitamin E</td>
<td>136</td>
<td>Vitamin E 400 IU/day;</td>
<td></td>
</tr>
</tbody>
</table>
OUTCOME MEASURED

The primary outcome measured was incidence of the cardiovascular morbidity and mortality in the study population. Jaxa-Chamiec et al. measured the primary outcome based on 30-day cardiac mortality in-hospital or out-hospital. Marchioli et al. measured the risk of developing congestive heart failure by performing echocardiogram measurement of the ejection fraction and defined the population developing CHF during the study as “death or hospitalization due to CHF”. Study performed by Milman measured primary outcome based on composite of cardiovascular death, nonfatal myocardial infarction and stroke. Milman also measured the secondary outcomes, which included total mortality, hospitalization for congestive heart failure and coronary revascularization.

RESULTS

The results pertaining to the primary outcome were documented as dichotomous data in all three studies. The data from the studies was published as an intention to treat analysis with the exception of participants who did not participate till the end of the study or those who were lost to follow-up or incompliant.

Jaxa-Chamiec et al. reported cardiovascular mortality of 8% and 22% in the Vitamin E and control groups (Vitamin C), respectively. This difference is statistically significant (p = 0.036). The absolute risk reduction (ARR) was calculated to be 14% and the relative risk reduction (RRR) was 175%. This study determined that number needed to treat (NNT) was 7 patients using the dosage of 600 mg/day (Table 2).

Marchioli et al. reported hospitalization and death due to congestive heart failure of 4.7% and 2.2% in the Vitamin E and control groups (n-polyunsaturated fatty acid), respectively. This difference is statistically nonsignificant (p = 0.18). The treatment with Vitamin E in this study
showed increased risk of developing CHF. The absolute risk reduction (ARR) was calculated to be 2.5% and the relative risk reduction (RRR) was 53%. This study determined that number needed to treat (NNT) was 40 patients using the dosage of 300 mg/day (Table 2).

Milman et al. reported cardiovascular death, nonfatal myocardial infarction and stroke of 1.6% and 4.6% in the Vitamin E and control groups, respectively. This difference is statistically significant (p = 0.003). The absolute risk reduction (ARR) was calculated to be 3% and the relative risk reduction (RRR) was 187.5%. This study determined that number needed to treat (NNT) was 33 patients using the dosage of 400 IU/day (Table 2).

Table 2- Efficacy of Vitamin E in cardiovascular mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Vitamin E group (CER)</th>
<th>Control group (EER)</th>
<th>p-value</th>
<th>95% CI</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaxa-Chamiec</td>
<td>8%</td>
<td>22%</td>
<td>0.036</td>
<td>0.51 to 1.85</td>
<td>175%</td>
<td>14%</td>
<td>7</td>
</tr>
<tr>
<td>Marchioli</td>
<td>4.7%</td>
<td>2.2%</td>
<td>0.18</td>
<td>0.92 to 1.56</td>
<td>-53%</td>
<td>-2.5%</td>
<td>-40*</td>
</tr>
<tr>
<td>Milman</td>
<td>1.6%</td>
<td>4.6%</td>
<td>0.003</td>
<td>0.16 to 0.70</td>
<td>187.5%</td>
<td>3%</td>
<td>33</td>
</tr>
</tbody>
</table>

CI = Confidence Interval, RRR = Relative Risk Reduction, ARR = Absolute Risk Reduction, NNT = Number Needed to Treat

*Since the outcome measured was incidence and severity of cardiovascular disease, the negative value for NNT indicates that for every 40 participants who took Vitamin E, there was one fewer incidence of cardiovascular complication than in the group of participants taking placebo.

As seen in table 2 the Relative Risk Reduction (RRR) is high in both the Jaxa-Chamiec and Milman studies with 175% and 187.5% respectively, however the Marchioli study did not show a similar reduction in cardiac mortality with a RRR of 53%. It is also reflected in numbers needed to treat (NNT) for Marchioli study is higher compared to the other two studies.

If compared the doses of Vitamin E used in the three studies, it appears that Jaxa-Chamiec utilized dose of 600 mg/day is approximately five to six times more effective with a
NNT value of 7 compared to dose of 300 mg/day and 400 IU/day used by Marchioli and Milman with a NNT value of 40 and 33 respectively. However, there is no data in study that mentions compares the dosage of Vitamin E.

Secondary end points measured in the study by Milman et al. did not show significant difference in the group treated with Vitamin E compared to the placebo. The results for the secondary end points are listed in Table 3.

<table>
<thead>
<tr>
<th>End points</th>
<th>Vitamin E</th>
<th>Placebo</th>
<th>P Value</th>
<th>RRR</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revascularization</td>
<td>11 (1.5%)</td>
<td>18 (2.5%)</td>
<td>0.17</td>
<td>66%</td>
<td>1%</td>
<td>1</td>
</tr>
<tr>
<td>Congestive Heart Failure</td>
<td>8 (1.1%)</td>
<td>8 (1.1%)</td>
<td>0.96</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>11 (1.5%)</td>
<td>12 (1.7%)</td>
<td>0.77</td>
<td>13%</td>
<td>0.2%</td>
<td>5</td>
</tr>
</tbody>
</table>

The studies chosen for this review had certain limitations. The study did not include all the participants in the results as some were excluded from the study. In the study by Milman et al. 136 were not included in the results: two were lost to follow up; seven due to their physician’s advice; eleven due to side effects, 116 were noncompliant based on telephone interviews. Also, in this study, no attempt was made to optimize or manage the medication prescribed by the primary care physician. Limitation to Jaxa-Chamiec et al. study is the retrospective mode of analysis performed on the diabetic patient subgroup and the secondary analysis (effects of antioxidant Vitamins on patients older than age 70, anterior myocardial infarction, and symptoms of AMI for >12) did not reach significance and hence failed to support the primary hypothesis of the study.

All the clinical trials have failed to test the basic foundation underlying the hypothesis, which is the capacity of the antioxidant to reduce the oxidative stress. None of the studies
measure the oxidative states in the study population, it is impossible to determine the effect of antioxidant supplement without knowing the initial oxidative stress a person is experiencing. It is hard to show the effect of a substance without determining what it is actually having the effect on in the first place.

**DISCUSSION**

Oxidative modification by reactive oxidative species (ROS) of low-density lipoprotein is an important step in the development and progression of atherosclerotic plaque. ROS are found in high quantity in hyperglycemic state of diabetic patients. Increased oxidative stress has been linked to impaired endothelial function. Vitamin E has antioxidant properties that help reduce ROS formation, in turn inhibit the formation of atherosclerotic plaque. Reduction in the formation of atherosclerotic and endothelial damage can reduce cardiovascular damage in diabetic population.

According to the study Marchioli et al., there is a significant relation between plasma oxidized low-density lipoprotein and severity as well as worsening ejection fraction and higher level of neurohormonal activation in patients with CHF. However, it’s effect were not reproducible in the study which concluded that Vitamin E leads to depression of myocardial function and hospitalization and death in CHF. Hence, Vitamin E did not show a beneficial role in prevention of congestive heart failure after a myocardial infarction.

However, the study on Diabetic population with Hp 2-2 genotype by Jaxa-Chamiec et al showed cardiovascular benefits form Vitamin E supplementation. It was concluded that Vitamin E reduced cardiovascular death and AMI in the specific population with Hp 2-2 genotype.
CONCLUSION

According Marchioli et al. Vitamin E has deleterious effect on cardiovascular outcomes, particularly late-onset heart failure. The study showed a statistically nonsignificant increased risk of developing CHF due to depression of left ventricular function with addition of Vitamin E supplementation to their therapy. According to Jaxa-Chamiec et al. antioxidative property of Vitamin E significantly reduces a 30-day mortality in diabetic patients with recent MI but the secondary analysis in a trail failed to support its primary hypothesis and the validity of the trail is questionable. However, according to Milman et al. Vitamin E provides cardiovascular benefit to diabetic individuals with the Hp 2-2 genotype. Vitamin E supplementation in this population has shown to reduce cardiovascular death and myocardial infarction.

Hence, it can be conclude that Vitamin E is effective in diabetic patients with Hp 2-2 genotype and can have adverse effect in non-diabetic population. Future research should be designed to study the effect of Vitamin E in Hp 2-2 genotype diabetic patients. The research of further studies will implement the use if Vitamin E in specific diabetic population. The use of Vitamin E in this population can reduce the cost and cardiovascular complications in diabetic population.
References:


