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Is vitamin E supplementation effective in reducing mortality related to cardiovascular events in people with type 2 diabetes mellitus? A systematic review

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ABSTRACT

Objective: To determine the effect of vitamin E in reducing cardiovascular mortality in diabetic patients.
Data source: Review of several English language primary studies published from 2004 to 2015.
Outcome measured: The primary outcomes measure by all studies included 30-day mortality due to congestive heart failure, myocardial infarction, stroke, and HDL function as it relates to cardiovascular outcomes. The secondary outcomes included hospitalization for CHF and coronary revascularization.
Results: Five Randomized, double-blind, placebo-controlled trials and 11 studies were used for this review. The study published by Jaxa-Chamiec et al. showed that vitamin E is beneficial along with vitamin C but is not effective when used alone. The study facilitated by Marchioli et al., showed that vitamin E supplementation is associated with a statistically non-significant ($p = 0.18$) increased risk of developing CHF. Finally, a study by Milman et al. showed that vitamin E supplementation is beneficial compared with a placebo group. This was a recurring theme and common finding among the studies explored within the context of this review.
Conclusions: Although, two studies showed no benefit from vitamin E supplementation, the remaining studies demonstrated that vitamin E supplementation provided cardiovascular benefits in a specific diabetic subpopulation. The study population that derived a favorable outcome from vitamin E supplementation consisted of diabetic patients with the Hp 2–2 genotype. Hence, further studies should be conducted in diabetic populations with the Hp 2–2 genotype for identifying the definitive effects of vitamin E.

1. Introduction

Cardiovascular disease is a major cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). In 2004, death due to cardiovascular complication in the diabetic population aged 65 years or older was around 68% [1]. Clearly, there is an urgent need for interventions that can reduce the morbidity and mortality associated with cardiovascular disease in patients with T2DM.

There are several factors responsible for this increased risk. Various authors have suggested that reactive oxygen species (ROS) contribute to the increased burden of cardiovascular disease in people with T2DM, due to an increased production of reactive oxygen species that produce structural changes in lipoproteins that markedly increase their atherogenic potential.

Vitamin E is known to have an antioxidant property that decreases ROS levels. In the past, preclinical and observational studies motivated some cardiologists to prescribe vitamin E for patients with T2DM. Clinical trials did not support the ability of vitamin E supplementation to provide cardiovascular protection in genetically unselected populations with T2DM. However, some investigators have suggested that vitamin E can reduce cardiovascular disease events in subpopulations of patients with T2DM.

The topic of this review is important because diabetes is a common condition with high rates of incidence and prevalence. It is estimated that between 2009 and 2034, the number of diabetic patients in the United States will increase from 23.7 million to 44.1 million [5]. Also, if the use of vitamin E is shown to have positive effects in a clearly identified group of T2DM patients, the cost associated with care in this population can be significantly reduced.

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2. Objective

The objective of this systematic review is to determine whether the use of vitamin E supplementation is effective in reducing the cardiovascular mortality in T2DM patients, including any relevant subpopulations.

3. Methods

The studies included in this review were based on the following criterion. The population included individuals with T2DM and acute myocardial infarction with or without T2DM. A study by Milman et al. [10] further classified the diabetic population depending on their genotype: haptoglobin (Hp). The study only included diabetic patients with the Hp 2–2 genotype. This method of genotype classification was also present in Blum et al., Costacou et al., and Koren et al. [1,2,7], which explored alternative medicinal interventions among patients with T2DM, Lee et al. [8], which focused on females in the Women's Health Study, as well as the meta-analytic study of Vardi et al. [12]. Genotype classification was also evident in the review articles published by Goldenstein et al. [4] and Sarmento et al. [11], which shared this similarity with the aforementioned studies, focusing on the subgroup of individuals with the Hp 2–2 genotype. Meanwhile, Farbstein et al. [3] classified participants, according to genotype, utilizing the inclusion of DM patients with both Hp 2–2 and Hp 2–1 genotypes within the analysis.

All studies excluded patients with uncontrolled hypertension, stroke within 1 month before enrollment, unwillingness to stop antioxidants supplements, or known allergy to vitamin E. In addition, the study by Milman et al. [10] excluded the diabetic population with Hp 1–1 and Hp 2–1 genotypes; Jaxa-Chamiec et al. [6] excluded death due to non-cardiac related cause and Marchioli et al. [9] excluded populations with baseline CHF managed by a multiple drug regimen.

The intervention used in the studies was vitamin E 300 mg/day [9], 600 mg/day [6], and 400 IU/day [1,2,8,10]. This was with the exception of Koren et al. [7], which implemented a survey approach in obtaining data related to participants' existing regimen of medication and, therefore, was not reliant on the execution of an intervention, as was also the case with the reviews authored by Goldenstein et al. [4] and Sarmento et al. [11]

The treatment groups were compared with control groups, who were given visually matched n-polyunsaturated fatty acid 1 g/day [9], vitamin C 1200 mg/day [6] and placebo.

The main outcomes measured were mortality related to cardiovascular events, risk of developing CHF, and hospitalization for cardiovascular complication. One other outcome measure was HDL function as it pertains to the risk for CVD, thereby proving relevant within this context, based upon its response to vitamin E (or, the lack thereof). The studies were double blind, randomized, and placebo-controlled with the exception of the meta-analyses and reviews. In addition, Costacou et al. [2] and Farbstein et al. [3] employed a crossover design, supplementing the aforementioned study design characteristics.

The study facilitated by Blum et al. sought to validate the prior findings of the ICARE study or Israeli Cardiovascular vitamin E study and the Heart Outcomes Prevention Evaluation study (HOPE) [1]. Participants were further characterized as presenting with a diagnosis of DM and Hp genotype, which was evaluated through gel electrophoresis [1]. Individuals with the Hp 2–2 phenotype were then randomized and assigned to either the vitamin E or the placebo group [1].

Established upon the relationship between HDL function and risk of CVD, Costacou et al. examined the effect of vitamin E on HDL function compared to placebo. Participants were derived from Allegheny County diabetes registries and 30 individuals randomly assigned to each of 3 genotype groups (Hp 1–1, Hp 2–1 and Hp 2–2) and administered daily α-tocopherol or placebo for a period of 8 weeks [2]. This was followed by a 4-week "washout" period, which then led into the crossover in which those given vitamin E were provided with placebo and vice versa [2].

In the research conducted by Farbstein et al., 59 DM participants were categorized as presenting with either the Hp 2–1 or Hp 2–2 genotype. Participants in this double-blind design were administered vitamin E or a placebo for a 3-month period of duration [3]. The groups then crossed over and the original vitamin E group then received placebo and vice versa for another 3-month study period [3]. HDL functionality was measured at baseline and upon the completion of each 3-month study period [3].

Patients in the study by Jaxa-Chamiec et al. were given infused and oral vitamin E and vitamin C together, and the other group in the study was given infusion of saline placebo [6].

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 neither, and were followed for 3.5 years [9]. Echocardiographic measurement of left ventricular ejection fraction was determined and patients developing CHF were defined as "hospitalization or death for CHF" [9].

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 [10]. Hp phenotyping was performed by electrophoresis and the diabetic populations with Hp 2–2 were selected. A computer generated randomization was used to divide study population into two groups from with one group received vitamin E and another group received placebo [10].

Koren et al. [7] was a cross-sectional study established upon questionnaire data retrieved from T2DM patients at Assah Harofeh Medical Center in Israel. Finally, Goldenstein et al. [4] and Sarmento et al. [11] employed a meta-analytic and systematic review approach, identifying the impact of vitamin E on CVD in patients with diabetes.

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 the English language in 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 were conducted in a randomized, controlled fashion in a prospective, intention to treat basis, and dated after 2004. 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).

4. Outcomes measured

The primary outcome measured was incidence of cardiovascular morbidity and mortality in the study population, supplemented with HDL function as it relates to CVD. Blum et al. [1] examined myocardial infarction and cardiovascular death, which also served as endpoints in Vardi et al. [12], while Costacou et al. [2] examined risk for CVD and cardiovascular complications. Farbstein et al. [3] evaluated HDL function and HDL oxidation and inflammation markers. Jaxa-Chamiec et al. [6] measured the primary outcome based on 30-day cardiac mortality in-hospital or out-hospital. Lee et al. [8] included total mortality and ischemic stroke among CVD endpoints. Marchioli et al. [9] 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". In the study performed by Milman et al. [10], investigators measured primary outcome based on a composite of cardiovascular death, nonfatal myocardial infarction, and stroke. Milman et al. also measured secondary outcomes, which included total mortality, hospitalization for congestive heart failure, and coronary revascularization.

5. Results

The results pertaining to the primary outcome were documented as dichotomous data in Jaxa-Chamiec et al. [6], Marchioli et al. [9], and