Chronic antioxidant use and changes in endothelial dysfunction: a review of clinical investigations

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Authors' objectives
To review information from patient studies that have assessed the effect of chronic antioxidant use on endothelial dysfunction.

Searching
The entire MEDLINE database was searched for trials dealing with endothelial function in patients and investigating the effects of antioxidants. This search was augmented by a similar search of Current Contents. Finally, the references within the identified citations were carefully examined to locate other papers of potential relevance that were not identified by computer searches. No attempt was made to identify unpublished studies.

Study selection
Study designs of evaluations included in the review
Prospective studies, placebo-controlled trials and randomised controlled trials (RCTs) are included. Studies reported in abstract and unpublished studies are not included in this review, nor are studies based solely on low density lipoprotein (LDL) oxidation as an end point.

Specific interventions included in the review
Antioxidants (300-1200mg Vitamin E (D-alpha or alpha-tocopherol acetate), once or twice a day, alone or with diltiazem or simvastatin; or 150-2000mg vitamin C, once or twice daily; or 4.8g omega-3 fatty acids; or 200 mg troglitazone; or probucol, alone or with lovastatin; or 15-30mg beta-carotene a day; or 25-50mg carvedilol; or 4-8mg perindopril) versus placebo, alone or with diltiazem, simvastatin or lovastatin and cholestyramine, or the American Heart Association step 1 diet.

Duration of studies was between 10 days and 1 year.

Participants included in the review
Patients treated with oral antioxidants to modify endothelial dysfunction. Patient populations recruited by individual studies included the following: coronary spastic angina (CSA) patients, hypercholesterolemia patients, patients with chronic heart failure, patients with hypercholesterolemia and coronary artery disease, patients with postmyocardial infarction, noninsulin-dependent diabetes mellitus (NIDDM, some also had mild hypertension), smokers, smokers with hyperlipidemia, non-smokers and healthy control subjects. No a-priori patient inclusion criteria were specified.

Outcomes assessed in the review
The a priori outcomes looked at include: vascular dilatory function, and other end points with relatively direct relationships to endothelium-mediated processes.

Outcome measures used by the included studies were: endothelial dysfunction, monocyte function, endothelial cell markers, platelet aggregation, and P- and E-selectin.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection. [A:Two researchers reviewed all potential studies to ensure that the studies pertained to humans/clinical patients and that the therapy had been given as an infusion or as a single, acute dosage study. The end-points needed to be acceptable as defined above.]

Assessment of study quality
The authors do not state that validity was assessed. [A: Studies were assessed with respect to the clarity of the duration of treatment, the specific drug, and the acceptability of the end point as being directly and unambiguously related to endothelial dysfunction. Two independent investigators applied the above criteria and came to a consensus. Due to the paucity of studies, studies other than RCT were included if described in enough detail to meet the aforementioned criteria.]

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction. [A: Data was extracted using a pre-specified spread-sheet to collate the key features, treatments, vascular beds and outcomes of the study. Only the published data in each report was summarized. Primary authors were not contacted for primary data.]

Methods of synthesis
How were the studies combined?
Studies were combined in a narrative way.

How were differences between studies investigated?
Not stated. [A: Differences among studies were categorized on the basis of the type of intervention and the type of end-point. In particular, studies in conduit versus resistance vessels were of key interest and these were contrasted to those using non-dilatory end-points (e.g. adhesion molecules).]

Results of the review
In total 17 studies, including 401 subjects were included in the review: 5 studies (2 RCTs, 1 placebo-controlled trial and 2 prospective studies) regarding the effect of antioxidants on conduit vessel endothelial dysfunction, 6 studies (2 double-blind RCTs, 2 placebo-controlled trials and 2 prospective studies) regarding the effect of antioxidants on resistance vessel endothelial dysfunction, and 6 studies (3 RCTs and 3 prospective studies) regarding the effect of antioxidants on thrombotic and adhesive markers of endothelial dysfunction.

Studies assessing resistance vessel function were negative with only one exception, this may be due to the insensitivity of venous plethysmography to detect the effect of chronic antioxidant.

All studies of conduit vessel function were positive. However, all but 2 of these studies were undertaken in hypercholesterolemic patients.

All but one study pertaining to endothelial cell-monocyte interaction, adhesion molecules and endothelial cell markers were positive.

Authors' conclusions
Authors conclude that the likeliest reason for the preponderance of negative studies is the lack of major nitric oxide dependency within resistant vessels.

Improvement in resistance vessel function has not been definitely demonstrated, but there is consistent evidence to suggest that chronic antioxidant therapy can improve conduit vessel endothelial dysfunction, some measures of monocyte endothelial interaction and circulating levels of markers of endothelial cell activation. No published studies directly linked these effects to any of the positive (or negative) effects in the few clinical outcome or regression studies to date, and therefore endothelial dysfunction cannot be used as a surrogate end point.

CRD commentary
The inclusion criteria seem well chosen. The population under study was not specified in the review question. The databases searched were restricted to MEDLINE and Current Contents and, therefore, the possibility of publication
bias cannot be excluded. The authors did, however, examine the references of identified citations. Authors did not report on the way decisions on the inclusion or exclusion of studies were made and how the data extraction was done. There is no information on the quality of studies included.

The authors did not attempt to generate a summary estimate of effect across studies. Instead they described the results of primary studies in a narrative way, which seems appropriate given the heterogeneity of interventions although differences between studies were not investigated.

The conclusions of the review author seem to follow from the evidence presented although, due to the limitations mentioned above, they should be treated with caution.

**Implications of the review for practice and research**
The authors state that further trials are required to clarify and define the impact of these findings on clinical outcome.

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**Record Status**
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.