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Tomato and lycopene supplementation and cardiovascular risk factors: A systematic review and meta-analysis

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ABSTRACT

Background and aims: Epidemiological evidence suggests an association between consumption of tomato products or lycopene and lower risk for cardiovascular diseases (CVD). Our aim was to evaluate the state of the evidence from intervention trials on the effect of consuming tomato products and lycopene on markers of cardiovascular (CV) function. We undertook a systematic review and meta-analysis on the effect of supplementing tomato and lycopene on CV risk factors.

Methods: Three databases including Medline, Web of science, and Scopus were searched from inception to August 2016. Inclusion criteria were: intervention trials reporting effects of tomato products and lycopene supplementation on CV risk factors among adult subjects >18 years of age. The outcomes of interest included blood lipids (total-, HDL-, LDL-cholesterol, triglycerides, oxidised-LDL), endothelial function (flow-mediated dilation (FMD), pulse wave velocity (PWV)) and blood pressure (BP) inflammatory factors (CRP, IL-6) and adhesion molecules (ICAM-1). Random-effects models were used to determine the pooled effect sizes.

Results: Out of 1189 publications identified, 21 fulfilled inclusion criteria and were meta-analysed. Overall, interventions supplementing tomato were associated with significant reductions in LDL-cholesterol (−0.22 mmol/L; $p = 0.006$), IL-6 (standardised mean difference −0.25; $p = 0.03$), and improvements in FMD (2.53%; $p = 0.01$); while lycopene supplementation reduced systolic-BP (−5.66 mmHg; $p = 0.002$). No other outcome was significantly affected by these interventions.

Conclusions: The available evidence on the effects of tomato products and lycopene supplementation on CV risk factors supports the view that increasing the intake of these has positive effects on blood lipids, blood pressure and endothelial function. These results support the development of promising individualised nutritional strategies involving tomatoes to tackle CVD.

1. Introduction

Globally, behavioural risk factors including a range of dietary risks, e.g. low intakes of fruit and vegetables, have the greatest potential to promote disease and impair human health [1]. A wealth of epidemiological evidence indicates that, particularly, cardiovascular health is strongly influenced by a healthy diet; fruit and vegetables are considered an important element of a cardio-protective diet [2].

The benefit of consuming fruit and vegetables is often ascribed to specific components of food. Recent systematic reviews of the literature indicate that supplementation with dietary nitrates, or foods rich in these compounds such as beetroot, have the potential to lower blood pressure [3] and improve endothelial function [4], both regarded as early indicators of cardiovascular diseases (CVD). These benefits are valuable when developing effective nutritional strategies targeting specific key metabolic risk factors for the prevention and management of CVD.

Vegetables such as tomato are ubiquitous in most dietary patterns across the world and their contribution to health has been documented in longitudinal epidemiologic studies. High self-

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reported intakes of tomato and tomato products, and of dietary lycopene (a carotenoid compound) are associated with lower risk for CVD [5,6]. Lycopene is one of the most potent antioxidants and the most predominant carotenoid in human plasma and it is assumed to be one of the active compounds responsible for the health benefits of tomato [7]. While the epidemiological evidence indicates a consistent association between tomato products and/or lycopene and lower CVD risk [5,6], the effect of nutritional interventions on tomato products and lycopene have been studied only recently and their efficacy on improving vascular function remains to be evaluated. The evidence from human intervention trials on the efficacy of tomato products or lycopene supplementation on cardiovascular risk biomarkers, such as blood lipids (total-, HDL-, LDL-cholesterol, triglycerides, Oxidised-LDL) and endothelial function (FMD, PWV), has not been meta-analysed and systematically reviewed previously and a critical appraisal of the literature should be useful in testing this hypothesis. Here, we report the findings of a systematic review and meta-analysis of the evidence from intervention trials investigating the efficacy of tomato products or lycopene supplementation on cardiovascular (CV) risk factors in adult human individuals. In this review we focused particularly on blood lipids (total-, HDL-, LDL-cholesterol, triglycerides, Oxidised-LDL), endothelial function (FMD, PWV), inflammatory factors (CRP, IL-6) and adhesion molecules (ICAM-1).

2. Materials and methods

This systematic review was undertaken in adherence with guidance from Cochrane [8] and the Centre for Reviews and Dissemination guidelines [9] and is reported according to PRISMA guidelines [10] (Fig. 1 and Supplementary Table 1). The protocol of this systematic review has been previously registered with PROSPERO, the International Prospective Register of Systematic Reviews (Registration number CRD42016042092).

In August 2016, Medline, Web of science, and Scopus were searched systematically from inception. Reference lists of identified publications were hand searched to identify other studies potentially eligible for inclusion.

The search strategies included the following terms 1) tomato; 2) lycopene; 3) trial/clinical trials; 4) vascular risk factors; 5) biomarkers; 6) vascular function; 7) endothelial function; 8) blood lipids. The systematic review was restricted to articles published in English.

Two researchers (HMC, JL) assessed articles independently for eligibility. The decision to include studies was hierarchical and was made initially on the basis of screening the studies' titles and abstracts, and if a decision was not reached at this stage, then the full-text of the article was evaluated to make such a judgement. The full text of the selected articles was independently assessed by the same researchers.

2.1. Inclusion/exclusion criteria

The selection of references during the search strategy and the data extraction was performed according to specific criteria which are delineated below:

Inclusion criteria included: 1) Study Design: intervention studies; 2) Subjects: adult subjects >18 years of age; 3) Interventions: nutritional/dietary interventions (tomato and tomato-based products or lycopene supplements versus a control or placebo group); 4) Outcomes: CV health-related outcome measures (described below). Exclusion criteria included 1) Study Design: non-interventional studies; 2) Subjects: subjects <18 years of age; 3) Interventions: interventions not involving tomato or lycopene, or interventions combined interventions in which the effects of tomato and lycopene cannot be singled out; 4) Outcomes: non-vascular outcome measures.

2.2. Data extraction

A standardised, pre-piloted form was used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information included: study design, country of origin, randomization, duration and length of follow-up, methods of analysis, completion rates; participant characteristics (population, settings of interventions, baseline characteristics); outcome measures (dietary and/or nutritional intake, body mass index, CV biomarkers); intervention details (i.e. tomato or lycopene). Study quality was assessed using the Cochrane risk of bias tool [18].

2.3. Outcome measures

The primary outcomes of this review were changes in CV risk factors after tomato or lycopene supplementation. Measures included blood lipids (total-, LDL-, and HDL-cholesterol, triglycerides, oxidised-LDL), assessment of endothelial function by flow-mediated dilation (FMD), pulse wave velocity (PWV), resting blood pressure, systolic (SBP) and diastolic (DBP), inflammatory factors (CRP, IL-6) and adhesion molecules (ICAM-1).

2.4. Statistical analysis

The Review Manager (RevMan Version 5.1 for Windows Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011) was used to synthesise and meta-analyse results from the individual studies. Pooled results are mostly reported as weighted mean differences with 95% CI and with two-sided p-values. However, when variables (such as IL-6 or CRP, and ICAM) were reported on different scales, standardised mean differences (SMD) were used as a summary statistic for comparing effect sizes across studies.

A random effects model accounting for inter-study variation was used. Multiple dietary intervention arms from three studies were included in the meta-analysis. Following previous guidance [8], excessive weightings from “double counts” arising from the “shared” group (in this case, the control group) were controlled by splitting the sample size of the shared group into approximately equal smaller groups for the comparisons. In this analysis we sought to extract and analyse adjusted results from multivariate models, if reported in the studies.

Heterogeneity was evaluated using the I^2 statistic [8,9]. Levels of heterogeneity are commonly regarded as high when I^2 values are >50%. Publication bias was appraised by visually inspecting the funnel plot, and supplemented with calculations of the Egger's regression test [11]. Quality of studies was assessed using the Jadad system [12].

3. Results

The searches yielded 1189 publications after de-duplication and results of the screening process are described in Fig. 1. Twenty-two publications that met our inclusion criteria were included in the present systematic review (Table 1) [13–34], and 21 of those publications were included in the meta-analysis [13–32,34].

3.1. Study characteristics

Fifteen studies used a RCT design while seven were controlled trials using a non-randomised design. These 22 studies originated from the USA (n = 4), UK (n = 2), Greece (n = 3), Israel (n = 5), and