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Title: Evidence for the effectiveness of pomegranate supplementation for blood pressure management is weak: a systematic review of randomized clinical trials

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ABSTRACT:

Hypertension is one of the most important preventable causes of premature death. Studies have been conducted assessing the impact of pomegranate on blood pressure, with varying results. The aim of this review was to critically appraise and evaluate the effect of pomegranate on blood pressure in adults, using evidence from randomized clinical trials (RCTs). We conducted electronic searches in Medline, Embase, Amed and The Cochrane Library, and included RCTs assessing the effectiveness of pomegranate on blood pressure. We assessed the reporting quality using the Cochrane criteria. We included eight RCTs comprising 619 participants. The studies varied in their reporting quality, and compared pomegranate juice or capsules with a control. Two studies reported significant reductions in systolic blood pressure favoring pomegranate: $p=0.002$ and $p<0.001$ respectively; three studies reported no significant differences between groups; and three studies failed to report between-group differences. Two studies reported significant reductions in diastolic blood pressure favoring pomegranate: $p=0.038$, $p<0.001$, respectively; four studies reported no significant between-group differences; and two studies did not report between group differences. No adverse events were observed. The limited evidence from clinical trials to date fails to convincingly show a beneficial effect of pomegranate on blood pressure. We have identified evidence gaps and highlight areas for future research to be conducted, including performing studies of high quality and longer duration.

Key Words: Pomegranate; blood pressure; cardiovascular disease; systematic review; fruit

1. Introduction

Hypertension is a major risk factor for cardiovascular disease and one of the most important preventable causes of premature morbidity and mortality [1]. Clinical management of hypertension is one of the most common interventions in primary care, accounting for approximately £1 billion in drug costs annually in the UK alone [1]. Hundreds of dietary supplements are currently marketed for the management of hypertension, but the evidence for their effectiveness is mixed [2]. One such supplement presently promoted for CVD management is pomegranate.

Pomegranate, *Punica granatum*, is a fruit-bearing shrub native to the Middle East [3], but is cultivated in several regions globally [4]. The fruit is widely touted as a functional food, and commonly used as a supplement in various forms [5]. Pomegranate peel is also used as a food preservative [6]. Phytochemically, pomegranate possesses a high polyphenolic content [7], and this property has been utilised in the prevention and/or treatment of various medical conditions including diabetes [8], cardiovascular disease (CVD), cancer [9] and osteoporosis [10].

Pomegranate decreases lipid peroxidation and protein oxidation, increasing the concentration of glutathione (GSH), and enhancement of nitric oxide activity [11,12]. These antioxidant actions have been reported to be responsible for its purported protective effects against atherosclerosis [13,14]. Results of animal research have suggested that pomegranate juice inhibits angiotensin converting enzyme (ACE) [15,16], and in humans consumption of pomegranate juice reduces the activity of ACE by as much as 36%, leading to reductions in systolic blood pressure [17].

Pomegranate is usually marketed either as juice, syrup concentrate, or pills. Several clinical trials of pomegranate on blood pressure have been conducted; however, the results of these have not been systematically reviewed. Therefore, the objective of this review was to systematically appraise and evaluate the evidence from randomized clinical trials (RCTs) investigating the effects of pomegranate consumption on blood pressure in adults.

2. Approach

2.1 Search Strategy

We conducted electronic searches on the following databases: MEDLINE, Embase, AMED, and The Cochrane Library. Each database was searched from inception up to October, 2016. Search terms used included pomegranate, Punica granatum, blood pressure, and derivatives of these. [See web appendix A for the full MEDLINE search strategy]. No time or language restrictions were imposed. We also searched Google Scholar for relevant internet proceedings, and we hand searched the bibliography of located articles. No time or language restrictions were imposed.

2.2 Eligibility criteria and study selection

Included RCTs had to test the effect of pomegranate juice, extract or capsules on blood pressure in subjects aged 16 years and above and lasted at least two weeks. RCTs were included irrespective of lifestyle modification incorporated into the trial regimen. The included studies needed to report blood pressure as an outcome measure. Studies in which pomegranate was combined with other types of dietary supplements were excluded.

The primary outcomes were systolic and diastolic blood pressure. Our secondary outcome was adverse events. Data from each study was extracted according to participant characteristics, type of intervention and comparator, and results. Two reviewers [OAG and IJO] independently extracted the data, with disagreements resolved through discussion.

2.3 Quality assessment

The reporting quality of all included studies was assessed using the Cochrane risk of bias criteria [18] which examines the following domains: method of randomization, concealment of allocation, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data (attrition and ITT analysis), selective outcome reporting, and other bias, such as conflict of interest and funding disclosure. Two reviewers [OAG and IJO] independently assessed the risk of bias in the included studies. Disagreements were resolved through discussion.

2.4 Data synthesis

Mean changes in systolic blood pressure and diastolic blood pressure were used as primary endpoints to assess the differences between the intervention (pomegranate juice) and comparison (placebo or identical control) groups. We reported risk of bias across the studies graphically, and used summary tables to present the results of included studies. We had planned to statistically combine the data across studies, however, due to significant heterogeneity in the included studies meta-analysis was considered inappropriate (see below). We had intended to use funnel plots to test for publication bias; however, because fewer than ten studies were included in the review, funnel plots were deemed inappropriate [19].

3. Results

3.1 Study screening

We identified 35 non-duplicate citations, out of which 17 eligible studies were identified (Figure 1). One study was excluded because it was a single-arm trial [20], another because of insufficient duration [21], and a third because it had a quasi-experimental design [22]. Two studies [23,24] were excluded because they did not report blood pressure as an outcome, two [25,26] because they compared pomegranate with grapefruit, one because both comparator arms consumed pomegranate [27], and one because pomegranate was combined with another dietary supplement [28]. Thus, eight studies (Asgary et al [29], Davidson et al [30], Mirmiran et al [31], Lynn et al [32], Shema-Didi et al [33], Sumner et al [34], Tsang et al [35], and Wu et al [36] comprising 619 participants were included in the review. Three studies were conducted in the USA [30, 34, 36], two in the UK [32, 35], two in Iran [29, 31], and one in Israel [33].

3.2 Study characteristics

The minimum age of included participants was 30 years (Table 1). Selected participants had varying baseline characteristics across the studies; for inclusion, some were required to have hypertension [29], or at least one cardiovascular risk factor, such as hypertension, or taking medications to treat hypertension [30]. One study excluded participants on treatment for hypertension [32]. Two studies included exclusively participants undergoing haemodialysis [33, 36].

Five of the eight studies compared pomegranate juice consumption with a control beverage, whilst three studies compared pomegranate capsule consumption with ingestion of a control

capsule (Table 1). All of the studies had a single experimental arm versus a control arm. Shema-Didi et al [33] administered the intervention/control to participants thrice weekly, but all other studies involved daily interventions. The study durations ranged from 2 weeks to 18 months. Six studies clearly reported the constituents of their placebo [29, 30, 32, 33, 35, 36].

3.3 Risk of Bias

The included studies varied in their risk of bias (Figures 2a and b). Each of the studies reported on outcomes as specified in their methods. By contrast, none of the studies had a low risk of selection bias. One RCT [34] had a low risk of allocation bias; and three studies reported adequate blinding of participants and personnel [31, 33, 34]. Three included trials had a low risk of attrition bias [29, 34, 35], and three reported adequate blinding of outcome assessment [29, 33, 34].

3.4 Blood pressure

3.4.1 Systolic blood pressure (SBP)

Six studies reported adequate data for statistical pooling. However, because of the significant heterogeneity in the results, meta-analysis was considered inappropriate (see Figure 3). The results have therefore been presented narratively.

The impact of pomegranate on SBP across the studies varied (Table 2). Asgary et al [29] found that pomegranate juice consumption compared with control was associated with a significant reduction in mean systolic blood pressure (pomegranate versus control: -6.36 mmHg (SD 5.05) versus 0.00 mmHg (SD 0.00); p=0.002 between groups). Lynn et al [32] similarly found a significant reduction in SBP in the pomegranate group, compared with

controls (pomegranate versus control: -3.14 mmHg (SD 5.83) versus 0.38 mmHg (SD 6.76); p <0.001 between groups). By contrast, Sumner et al [34] did not find a significant difference in SBP between pomegranate and control groups (pomegranate versus control: -1 mmHg (SD 2) versus – 2 mmHg (SD 12)).

Tsang et al [35] found a significant within group reduction in SBP associated with pomegranate juice ingestion (pomegranate group: -7.3 mmHg (SD 1.17); p = 0.034), which was not found in the control group (Control: 1.2 mmHg (SD 1.9); p = 0.498); no between group comparisons were offered. Another study [33] reported that the mean SBP among patients in the pomegranate group was reduced after one year of intervention by 6.8% (p=0.01). The authors state that no significant changes were demonstrated in the placebo group (no values reported). They mention, however, that the number of antihypertensive drugs decreased in 22.7% of pomegranate group participants, compared to 8.6% in the placebo group, while an increase was documented in 10.6% of the pomegranate juice patients compared with 31.4% in the placebo group.

Wu et al [36] report a significant within group reduction in SBP in the group consuming pomegranate capsules (pomegranate group versus placebo: - 24 mmHg (SD 5.05), p<0.05 versus 6 mmHg (SD 7.86)). However, the authors state that the reduction in SBP was not significant when baseline blood pressure was adjusted for. No between-group comparisons were offered. Davidson et al [30] and Mirmiran et al [31] reported that there was no difference between pomegranate and control groups for changes from baseline in blood pressure. No within or between group statistics are reported by either paper.

3.4.2 Diastolic blood pressure (DBP)

Six studies reported adequate data for statistical pooling. However, because of the significant heterogeneity across the studies, meta-analysis was considered inappropriate (see Figure 4). The results have therefore been presented narratively.

The pattern of findings across the studies for impact of pomegranate on DBP was similar to that for its effect on SBP. Asgary et al [29] found a significant reduction in mean DBP in the pomegranate juice group, compared with the control group (pomegranate juice versus control: -3.64 mmHg (SD 5.05) versus 0.00 mmHg (SD 0.00), p=0.038 between groups). Similarly, Lynn et al [32] found a significant reduction in DBP in those consuming pomegranate juice (pomegranate juice versus control: -2.33 mmHg (SD 3.97) versus 0.31 mmHg (SD 3.72), p<0.001 between groups).

One study [35] found a significant reduction in DBP within the pomegranate juice group (pomegranate group: -4.07 mmHg (SD 0.6), p=0.039), which was not found in the control group (Control group: 2.0 mmHg (SD 0.2), p=0.397). No between-group comparisons were reported. Wu et al [36] found a significant within-group reduction in DBP in those consuming pomegranate capsules (pomegranate group: -11 mmHg (SD 1.44), p<0.05), however, the authors reported that this result was no longer significant after adjusting for differences in baseline DBP.

Sumner et al [34] report no statistically significant difference in DBP between pomegranate and control groups (pomegranate versus control: -3 mmHg (SD 2) versus -5 mmHg (SD 1)). Shema-Didi et al [33] did not observe a significant difference in this outcome between groups

(p=0.38). Two studies [30, 31] found no difference between groups for this outcome, although they did not report data to support this.

3.5 Adverse events

Of the two studies that reported data on adverse events, neither found any harms associated with the intervention [33, 36]. In spite of the high drop-out rate (33.7% overall; 37.8% and 25.7% in the pomegranate and control groups, respectively), Shema-Didi et al [33] report that they did not observe any adverse events, such as gastrointestinal effects, amongst subjects.

3.6 Sources of funding

Three studies [30,35,36] received funding from private sources, while one [34] was funded by a charity organisation (Table 1). Three studies [29,31,33] received funding from public institutions, and one study [32] did not include a funding statement.

4. Discussion

There is mixed evidence for a beneficial effect of pomegranate consumption upon systolic blood pressure, with two studies reporting a significant between group reduction in this outcome [29, 32], and a further two studies [33, 35] reporting a significant within group reduction in this outcome. Similarly, there is mixed evidence for benefit of pomegranate consumption on reduction in DBP. To the best of our knowledge, this is the first systematic review that evaluates the effect of pomegranate consumption on blood pressure.

Pomegranate is a component of the Mediterranean diet [37], and such diets have been reported to be protective against a number of major, chronic diseases, including

cardiovascular disease [38]. The results of the studies included in this review have shown limited evidence of possible benefit on blood pressure. The cardiovascular benefits of pomegranate consumption have largely been linked to its anti-oxidant and therefore health-promoting properties. In a study conducted in Israel, ten participants with severe carotid artery stenosis were supplemented with pomegranate juice for a year, and a further five participants continued for three years [39]. Pomegranate juice was found to reduce systolic blood pressure, with maximal effect after one year of study. This effect was thought to be mediated through reduction in Angiotensin converting enzyme (ACE) levels, but also through reduction in levels of oxidative stress, mediated by pomegranate juice [17]; polyphenol constituents of pomegranate juice, such as punicalagin, are believed to have anti-oxidant effects that reduce oxidative stress [38].

In this review, the impact of pomegranate consumption on blood pressure, both systolic and diastolic, was not consistent across the trials that reported on this outcome. Indeed, in one of the studies included in the review, the reductions in blood pressure were not accompanied by a corresponding reduction in the activity of ACE [32].

We postulate that there could be a number of reasons for these differences; not least differences in study design. Wu et al [36] found that there was a significant reduction ($p<0.05$) in SBP and DBP following pomegranate consumption, however, after adjusting for differences in baseline blood pressure, the reductions were no longer significant. It is possible that, had the studies finding a reduction in blood pressure in the pomegranate arm performed such adjustments, the results may not have been so favorable. Furthermore, the two studies reporting significant, between group reductions in SBP and DBP, were of very short duration, conducted over two weeks [29] and four weeks [32], respectively. The mechanisms by which

pomegranate could cause a significant reduction in blood pressure in such a short duration of time are unclear to us.

In spite of these inconsistent results, proponents of this intervention might cite that consumption of fruit, such as pomegranate, is considered part of a healthy diet and actively promoted to all [40]. Any beneficial effect of pomegranates on blood pressure might be considered an additional bonus.

One study [33] reported a significant, within-group reduction in SBP in the pomegranate group. However, they also noted that the number of antihypertensive drugs decreased in 22.7% of the participants in the pomegranate juice group, compared to 8.6% in the placebo group. In addition, 10.6% of the pomegranate juice group compared to 31.4% in the placebo group had a documented increase in anti-hypertensive medication. The impact that this may have had on the blood pressure of the participants is unclear.

4.1. Strengths and Limitations

We used a robust search strategy to identify studies, and we accounted for the reporting quality of the included studies. In addition, we tried to contact authors when necessary to clarify details in the papers being screened for inclusion. We recognize, however, a number of limitations to this review. We may not have identified all of the studies evaluating the effect of pomegranate consumption on blood pressure, especially unpublished studies. Due to the small number of included studies and the heterogeneity between them, we were unable to perform meta-analysis for SBP or DBP. As the maximum duration of the included studies is 72 weeks, the effects of Pomegranate consumption in the long-term are unknown.

4.2 Implications for future research

In order to make robust conclusions about the purported benefits of pomegranate consumption on blood pressure, more trials of longer duration and of high quality need to be conducted. Trials should appropriately report their results, reporting between group comparisons, not simply within-group comparisons over time, as the latter can be misleading [41]. Investigators of future studies should also incorporate harms reporting into their trial methodology. Further studies could help to define the minimum effective dose of pomegranate required for beneficial effects, the minimum effective duration of consumption, as well as the best preparation (whole fruit versus juice versus extract in capsule) for maximal beneficial effect. However, given that the evidence to date does not support a significant impact of pomegranate on blood pressure, research efforts may be better directed towards alternative interventions.

4.3 Implications for clinical practice

The limited evidence to date does not support the benefit of pomegranate juice in lowering blood pressure indices in the short to medium term. At present there is insufficient evidence to support a change in clinical practice. However, the impact in the long-term is unknown. If there is a real, beneficial effect of pomegranate consumption on blood pressure, this could prove a useful adjunct to more conventional anti-hypertension treatments. However, before this could be proposed, the adverse effects of pomegranate consumption, if any, must be clearly evaluated.

5. Conclusion

The limited evidence from published clinical trials does not convincingly suggest that pomegranate consumption has beneficial effects on blood pressure. Few clinical trials examining the effect of pomegranate on blood pressure have been conducted. They vary in reporting quality, and are characterized by small sample sizes. Future studies in this area should be better designed, well reported, and should be of longer intervention duration.

Acknowledgement

We would like to thank Professor Carl J Heneghan for helpful comments on the manuscript.

Conflict of interest

OAG, IJO and EAS have no conflicts of interests to disclose.

Funding

OAG is funded by the National Institute of Health Research School for Primary Care Research (NIHR SPCR). This research is independent of the funder: the funder had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. This research did not receive any specific grant funding from agencies in the public, commercial, or not-for-profit sectors.

Authors' contribution

OAG – Protocol development, data extraction and analysis, risk of bias assessment, and co-drafting of the review.

IO - Protocol development, screening of abstracts, data extraction and analysis, risk of bias assessment, and co-drafting of the review.

ES – Protocol development and co-drafting of the review.

Figure captions:

Figure 1 **–** Flow chart showing the process for identification of RCTs examining the effect of pomegranate on blood pressure

Figure 2a - Risk of bias summary for RCTs examining the effect of pomegranate on blood pressure

Figure 2b - Risk of bias graph for RCTs examining the effect of pomegranate on blood pressure

Figure 3 – Effect of pomegranate consumption on systolic blood pressure

Figure 4 – Effect of pomegranate consumption on diastolic blood pressure

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