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Letters to the Editor

Systematic Review and Meta-analysis of Flaxseed

Dear Editor:

It was with great interest that we read the recent article by Khalesi et al. (1) on the effects of dietary flaxseed on systolic blood pressure (SBP) and diastolic blood pressure (DBP). Dietary flaxseed is, in our opinion, a potentially powerful antihypertensive strategy that deserves more research attention. However, our initial optimism in reading this article was lessened by a number of potential limitations in the published work that detract from its value to the scientific and lay communities. We identified 3 particularly important problems that were not addressed in this article that may result in either misleading or inaccurate conclusions.

First, the authors did not emphasize a major limitation of their review: the studies reviewed [with one notable exception (2)] were all conducted in normotensive or prehypertensive populations. Some of these studies included in the analysis actually excluded hypertensive patients or patients who were taking antihypertensive drugs (3). The value of investigating the efficacy of any compound that would reduce blood pressure (BP) in normotensive subjects may only be valuable from a safety perspective. This limitation of the meta-analysis is even more important because there are data that would suggest that the antihypertensive effects of dietary flaxseed are greater in a hypertensive population than in a normotensive population (2). The subgroup analysis of hypertensive patients at baseline in the Flaxseed and Peripheral Arterial Disease randomized controlled trial revealed that flaxseed induced a 15.2-mm Hg decrease in SBP and a 6.7-mm Hg decrease in DBP (2). Thus, the conclusion that "flaxseed may lower blood pressure slightly," as described in the Khalesi et al. review (1), may underestimate the antihypertensive effects shown by flaxseed in hypertensive patients included in a randomized controlled trial (2). We agree with the authors that this conclusion could be related to the small number of trials included in their analysis. The results of this systematic review as being primarily relevant to a normotensive/prehypertensive population should have been emphasized.

Second, the authors did not differentiate between whole flaxseed and ground flaxseed in this review. They are discussed interchangeably in the text and tables as if they are one and the same [e.g., page 761 (Results), page 763 (Discussion), Table 2]. They are not. Ground (milled) flaxseed added to the diet provides substantially more α-linolenic acid (4) and lignan metabolites (5) to the blood than does whole flaxseed. Because α-linolenic acid and lignans may be important bioactive compounds involved in the antihypertensive action of dietary flaxseed (2, 6), referring to the 2 forms as the same is incorrect.

Third, we have concerns about the quality of the data and the conclusions obtained from these data when combining very different interventions into the same meta-analysis. Using an oil supplement is quite different than using whole or milled seed [both in biological effects (7) and in taste and compliance (4)]. As stated elsewhere (8), "a meta-analysis of several RCTs with similar methods is of superior quality than one combining many studies with variable inclusion/exclusion criteria, time periods or treatment types."

Although lignins are present in flaxseed, their content is minor compared with that of lignans, and it is lignans that are the precursors to the bioactive compounds enterodiol and enterolactone (9). The study by Rodriguez-Leyva et al. (2) was carried out in Canada, not Cuba as indicated in Table 1, and patients were >40 y of age. This same study (2) was carried out for 52 wk, not just 24 wk as reported. There are errors in Table 1, but a more serious mistake occurs in Table 2, which indicates that the baseline mean BP of the participants was >130 mm Hg. We assume this actually means average SBP because a mean BP of 130 mm Hg would represent a hypertensive emergency.

In summary, although some of the problems identified above are of a relatively minor nature, we believe the importance of some of the issues as well as the number of problems identified were worthy of a letter here to ensure the conclusions as stated by Khalesi et al. (1) were appropriately qualified. Their meta-analysis is of interest and contributes to the area of research. However, it is also essential to highlight its limitations to correct inaccuracies and to ensure that proper conclusions are made.

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Reply to Pierce et al.

Dear Editor:

We thank you for the opportunity to discuss our recent article (1) and the concerns brought forward by Pierce and colleagues. We also thank Pierce et al. for bringing these issues to our attention.

Among the issues raised, Pierce et al. commented on the conclusion and its relevance given that the majority of studies consisted of normotensive/prehypertensive populations. We agree that the majority of publications in this systematic review included normotensive population groups and very few included prehypertensive/hypertensive participants (an issue that is analyzed and discussed in subgroup analysis results in the original article). However, it needs to be noted that the purpose of this systematic review (and all systematic reviews) was to include all relevant studies measuring changes in blood pressure (BP) after consuming flaxseed, whether BP changes were the primary outcome of the trial or not (2). We agree that more studies measuring the effects of flaxseed consumption on BP specific to hypertensive participants are required. However, we still feel that the initial conclusions of this systematic review (that flaxseed consumption may reduce BP) are relevant regardless of BP status.

With regard to the second issue raised by Pierce et al. that "the authors did not differentiate between whole flaxseed and ground flaxseed in this review," we also agree that digesting ground flaxseed may provide more bioavailable components compared with unground flaxseed (3). However, the term "whole flaxseed" was used to differentiate whole flaxseed from flaxseed extracts (oil, lignans, or fiber), not to differentiate between ground and unground flaxseed. This is further clarified in the "Information on supplement protocol" section of our article ("Four studies used whole or ground flaxseed for the intervention…"). With the exception of one study (4) that did not clarify if the flaxseed was ground, the remainder of trials in this subgroup used ground flaxseed. Given the small number of studies using unground flaxseed, a subgroup analysis was not considered appropriate.

Furthermore, it is well known that the similarity between the design and methods of trials and the characteristics of participants strengthens the power of the meta-analysis to draw more precise conclusions (2, 5). However, narrowing the inclusion criteria can lead to having sparse evidence (2). Sensitivity and subgroup analyses aim to measure the robustness of the meta-analysis outcome or outcomes and the effect or effects of different trial characteristics on outcome measures (2). These analyses have been conducted carefully and comprehensively in accordance with published guidelines (PRISMA) (6) in this systematic review to limit the possible influence of the observed variability between and among trials.

Subgroup analysis proposed slight, but pronounced, effects of flaxseed consumption as whole or ground compared with flaxseed extracts (as oil or lignans). The differences observed in the effect size of subgroups indicate a quantitative interaction rather than random chance (2). Therefore, it can be concluded with some confidence that the effects of whole and ground flaxseed on BP are similar to those of flaxseed extracts (oil, lignans). With regard to the difference between lignans and lignins, we agree with Pierce et al. that lignans are the major components available in flaxseed and are precursors to bioactive enterodiol and enterolactone compounds. This typographical error is noted in the Erratum in this issue. All reference to the term "lignins" throughout the original article should read as "lignans."

We have rechecked the published articles of each trial included in this meta-analysis and it is unfortunate that small mistakes in the presentation of characteristics from one study (7) are in Table 1. The corrections related to the placebo mixture, country in which the intervention was carried out, duration of intervention, and age of participants in the study by Rodriguez-Leyva et al. (7) are addressed in the Erratum in this issue. Although these minor mistakes should be avoided in high-quality reviews, the errors did not affect our meta-analysis, subgroup analysis, or interpretation of the results. Pierce et al. also suggested changing "baseline mean BP of participants" to "baseline mean SBP of participants" in column 1 of Table 2, which has been addressed in the accompanying Erratum. Nonetheless, we apologize for oversights in grammar and proofing of the article and associated tables.

Pierce et al. also commented that "although the problems identified are of a relatively minor nature…, they were worthy of a letter to ensure the conclusions as stated by Khalesi et al. (1) were appropriately qualified." Although we appreciate Pierce and colleagues' comments on this systematic review, and we thank them for pointing out these issues, we believe the conclusion made in this study that flaxseed consumption may reduce BP is accurate and justified. Although a number of minor errors have been correctly identified throughout the original article by Pierce et al., these have now been amended and these changes have no effect on the overall results or the conclusion of this study. Thus, the conclusions do not need to be revised.

We thank Pierce and colleagues for their letter regarding our publication and look forward to future research on this exciting topic.

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