The Influence of Fasting and Energy Restricting Diets on Blood Pressure in Humans: A Systematic Review and Meta-Analysis

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Short title: fasting, energy restricting and blood pressure

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Abstract

Purpose: To the best of our knowledge, no comprehensive meta-analysis has been carried out to investigate the effect of different approaches of fasting and calorie restriction on blood pressure. Thus, the present systematic review and meta-analysis was designed to examine the effect of fasting and energy restricting diets on blood pressure in adult subjects.

Methods: We searched PubMed/Medline, Scopus, the Cochrane Library, and Google Scholar up to June 2019. The clinical trials that examined the effects of fasting and energy restricting diets on Blood Pressure was identified using MESH and non-MESH terms.

Results: 23 studies, including a total of 1397 participants, reported SBP and DBP as an outcome measure. Overall results from the random-effects model indicated that fasting and energy restricting administration elicited significant changes in SBP (Weight Mean Difference (WMD): -1.88 mmHg, 95% CI: -2.50, -1.25) and DBP (WMD: -1.32 mmHg, 95% CI: -1.81, -0.84, p = 0.000). Subgroup analyses displayed that intervention duration ≤12 weeks more effectively reduced SBP (WMD: -3.26 mmHg) and DBP (WMD: -1.32 mmHg). In addition, these analyses showed that fasting regimens (WMD: -3.26 mmHg) more effectively reduced SBP than energy restricting diets (WMD: -1.09mmHg).

Conclusion: The principal finding of this study was that fasting and energy restricting diets elicited, overall, significant reductions in SBP and DBP. Subsequent subgroup analyses revealed that intervention duration ≤12 weeks and fasting regimens more effectively reduced SBP and DBP.

Keywords: Meta-analysis, Blood Pressure, fasting, energy restricting.

Introduction

Hypertension (HTN) is one of the leading causes of disability and mortality, due to cardiovascular disease, in the world, with an estimated 9.4 million deaths per year. The reported prevalence of HTN is about 40% in adults, and more than 70% in overweight and obese subjects, which indicates the global importance of prevention or management of HTN (Organization, 2013). Besides blood pressure lowering-medications, lifestyle modifications, including dietary alterations, weight loss, being physically active and keeping away from a stressful life, can improve blood pressure (Appel et al., 2006).

Weight loss, at any time, even if not maintained, is asserted to play a pivotal role in controlling HTN and modulating cardiovascular risks (Charakida et al., 2014, Fantin et al., 2019). A commonly applied approach to weight reduction is caloric restriction (Franz et al., 2007). Recently, intermittent fasting interventions among various calorie-restricted diets have drawn a great deal of contemporary popularity; which may be due to the acceptance and compliance of continuous caloric restriction is difficult in the long term (Moroshko et al., 2011). In addition, it seems that fasting may represent an alternative method for attaining benefits of conventional energy restriction while decreasing some other risk factors (Longo and Mattson, 2014). Most commonly utilised fasting approaches include the alternate day fasting, 5 days:2 days fast and intermittent energy restriction, or periodic fasting for 2 to 6 days per week that contains interspersing habitual energy intake with a short period of fasting/severe energy restriction (Moroshko et al., 2011, Horne et al., 2015, Headland et al., 2016, Harris et al., 2018a). It has been shown that fasting is associated with a decreased risk of heart disease, and it has been reported that weight loss of greater than six percent of body weight, following a fasting regimen, can yield positive influences on blood pressure (St-Onge et al., 2017). Furthermore, several experimental studies have shown that fasting, not only could have beneficial effects on body weight, but might improve blood pressure, insulin sensitivity, inflammation (Johnson et al., 2007, Castello et al., 2010, Wan et al., 2003, Wan et al., 2010, Li et al., 2017) and have some healthful ramifications related to longevity and cancer (Longo and Mattson, 2014). It is conceivable that increasing fat utilization and nutritional stress, which leads to cellular level repairs and functional optimization during fasting periods, may modify cardiometabolic risks including elevated blood pressure and thereby the advantages of intermittent fasting may be greater than conventional caloric restriction (Horne et al., 2015).

To date, the effect of fasting on weight management and cardiovascular risk factors has been addressed in some systematic reviews, with (Headland et al., 2016, Harris et al., 2018a, Harris et al., 2018b, Cioffi et al., 2018), or without meta-analysis (Barnosky et al., 2014, Seimon et al., 2015, Davis et al., 2016), indicating body weight reduction, improved insulin sensitivity, glucose homeostasis and blood pressure induced by fasting is nearly comparable to those resulted from CR diets. Furthermore, a meta-analysis by Alhamdan et al. (Alhamdan et al., 2016) suggested that alternate fasting day is associated with greater maintenance of lean body mass during weight loss in comparison with energy restriction. However, to the best of our knowledge, no comprehensive meta-analysis has been carried out to investigate the effect of different approaches of fasting and CR on blood pressure as a primary outcome. Thus, the present systematic review and meta-analysis was designed to examine the effect of fasting and energy restricting diets on blood pressure in adult subjects.

Material and methods

This systematic review was carried out in accordance with The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009).

Search strategy

We searched PubMed/Medline, Scopus, the Cochrane Library, and Google Scholar up to June 2019. The clinical trials that examined the effects of fasting and energy restricting diets on Blood Pressure was identified using MESH and non- MESH terms (see Supplementary Table 1).

Moreover, reference lists were reviewed, and hand searches of relevant journals and grey literature were performed.

Eligibility criteria

We included RCTs in adults (>18y) comparing fasting and energy restricting diets intervention with untreated controls. We included those that reported sufficient data on baseline and final trials of SBP or/and DBP in both fasting or energy restricting diets and control groups in more than two weeks intervention. If necessary, we emailed the investigators and the authors in order to retrieve the relevant information. We excluded studies conducted on children, pregnant women or animals, were not controlled trials, did not reported sufficient data for the outcomes in fasting and energy restricting diets and control groups, examined the effects of fasting and energy restricting diets along with other components. We did not include conference papers, Grey literature, dissertations, and patents.

Data extraction

Two of the contributors (ZM and AN-V) scanned articles based on title and abstract and selected relevant articles in full text reviewing based on eligibility criteria, in addition a head investigator helped to reach consensus where necessary (PM). In next stage, two of the contributors (A S-S and S-F) extracted data on study design, sample characteristics, intervention design and estimates of effect of fasting and energy restricting diets from each study, in addition a head investigator helped to reach consensus where necessary. The following data was extraction of each studies: first study author's name, age and gender of subjects, year of publication, follow-up period, study location, type of intervention (fasting and energy restricting), study design, health status of participants, sample size, mean and SD of SBP/DBP at baseline, post-trial and/or changes in SBP/DBP from baseline to the end-of-trial. We included only the most recent for studies reported multiple data at diverse time points.

Quality assessment

Two reviewers independently appraised the studies using a the Cochrane scoring system (Moher et al., 2009). This standard quality assessment measures possible sources of bias in randomized trials, including the random sequence generation; the inhibition of awareness of the allocated intervention; the concealment of allocation to conditions; blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Three scores of high risk, low risk, and unknown risk could be given to each above-mentioned item.

Statistical analysis

Weighted mean difference (WMD) were calculated for each study and pooled using DerSimonnian and Laird random effect to take into account variability and heterogeneity between studies. If data were reported in a different format, standard calculations were executed to derive the mean and SD(Higgins, 2011, Hozo et al., 2005). Heterogeneity between studies was calculated using Higgins I2 and considered high if ≥50%. We conducted stratified analysis to examine possible sources of heterogeneity among the studies. The sensitivity analysis was accomplished using the leave-one-out technique, to determine the impact of each study on the combined effect size. Publication bias were assessed using funnel plots and symmetry using Egger's test, for which a p-value <0.1 were considered asymmetrical (Egger et al., 1997). If any publication bias was identified, it was tested via the 'trim and fill' method(Palmer et al., 2008). All statistical analyses were executed using Stata software (Stata Corp. College Station, Texas, USA).

Results

Study selection

The initial database search returned 22280 articles; after duplicates were removed, 14012 articles remained. After screening based on the title and abstract 491 articles were retained for full-text review. Finally, 19 articles (Hirsh et al., 2019, Trepanowski et al., 2018, Kessler et al., 2018, Izadi et al., 2018, Bowen et al., 2018, Astbury et al., 2018, Wei et al., 2017, Venchiarutti et al., 2017, Li et al., 2017, Lambert et al., 2017, Harder-Lauridsen et al., 2017, Zuo et al., 2016, Lee et al., 2016, Karimi et al., 2016, Ismail et al., 2015, Fernandes et al., 2015, Varady et al., 2013, Teng et al., 2013, Bhutani et al., 2013) with 23 studies were included in this meta-analysis (**Figure 1**).

Characteristics of the included studies

The characteristics of the included studies are provided in **Supplemental Table 2**. These studies were published between 2013 and 2019 and were conducted in the USA (Hirsh et al., 2019, Trepanowski et al., 2018, Wei et al., 2017, Zuo et al., 2016, Varady et al., 2013, Bhutani et al., 2013), UK (Astbury et al., 2018, Lee et al., 2016), Australia (Bowen et al., 2018, Venchiarutti et al., 2017, Lambert et al., 2017), Iran (Izadi et al., 2018, Karimi et al., 2016), Germany (Kessler et al., 2018, Lee et al., 2016), Malaysia (Ismail et al., 2015, Teng et al., 2013), Denmark (Harder-Lauridsen et al., 2017), Brazil (Fernandes et al., 2015). All studies were done on both genders except for two trial that included women only (Venchiarutti et al., 2017, Ismail et al., 2015), and three studies on men only (Venchiarutti et al., 2017, Harder-Lauridsen et al., 2017, Teng et al., 2013). The sample size in the included trials ranged from 11 (Lee et al., 2016) to 193 (Astbury et al., 2018). Participants in include studies were patients with Type-2 Diabetes Mellitus and Metabolic Syndrome (Li et al., 2017), obesity with obstrctive sleep apnoea (Fernandes et al., 2015), and overweight and obesity subjects. Methodological quality and risk of bias of included trials was detailed in **Supplemental Table 3.**

Meta-analysis results

Effect of fasting and energy restricting on SBP

23 studies including a total of 1397 participants (case=589 and control=808) reported SBP as an outcome measure. Overall results from the random-effects model indicated that fasting and energy restricting administration did result in significant change in SBP (Weight Mean Difference (WMD): -1.88 mmHg, 95% CI: -2.50, -1.25, p = 0.000) with significant heterogeneity among the studies (I^2 = 89%, p = 0.000) **(Figure2).** We subsequently stratified studies based on intervention type and intervention duration. These analyses displayed that intervention duration was source of heterogeneity which intervention duration ≤12 weeks (WMD: -3.26 ng/ml, 95% CI: -5.88, -0.69, I^2= 90%) more effectively reduced SBP than >12 weeks (WMD: -1.48 ng/ml, 95% CI: -2.37, -0.58, I^2= 86.6 %). In addition, these analyses showed that fasting regimens (WMD: -3.268 ng/ml, 95% CI: -5.204, -1.332, I^2= 85.0 %) more effectively reduced SBP than energy restricting diets (WMD: -1.09 ng/ml, 95% CI: -1.70, -0.47, I^2= 90.1 %) (**Supplemental figure 1.**).

Effect of fasting and energy restricting on DBP

23 studies including a total of 1397 participants (case=589 and control=808) reported DBP as an outcome measure. Combined results from the random-effects model indicated that DBP did change significantly following fasting and energy restricting administration (Weight Mean Difference (WMD): -1.32 mmHg, 95% CI: -1.81, -0.84, p = 0.000) with significant heterogeneity among the studies (I2 = 93.3 %, p = 0.000) (**Figure 3**). We subsequently stratified studies based on intervention type and intervention duration. These analyses displayed that intervention duration was source of heterogeneity which intervention duration ≤12 weeks (WMD: -3.02 ng/ml, 95% CI: -5.80, -0.25, I^2= 95%) more effectively reduced SBP than >12 weeks (WMD: -1.13 ng/ml, 95% CI: -1.83, -0.42, I^2= 92%). In addition, these analyses showed that fasting regimens (WMD: -1.63 ng/ml, 95% CI: -3.28, -0.03, I^2= 88.8 %) more effectively reduced SBP than energy restricting diets (WMD: -0.69 ng/ml, 95% CI: -1.20, -0.18, I^2= 94.6 %) (**Supplemental figure 2**).

Sensitivity analysis

To discover the impact of each single study on the combine effect size, we removed each trial from the analysis, step by step. For instance, we observed that rerunning the analysis without the one study (Izadi et al) changed the WMD for SBP from -1.88 mmHg (95% CI: -2.50, -1.26) to -2.50 mmHg (95% CI: -3.41, -1.58) (**Supplemental Figure 3,4**).

Publication bias

Evaluation of publication bias by visual inspection of funnel plot demonstrated no evidence of publication bias in the meta-analysis of fasting and energy restricting on DBP. However, there was a significant publication bias by visual inspection of funnel plot and egger tests for SBP. The trim and fill sensitivity method did not recognize any unpublished study. (**Figure 4)**.

Discussion

Hypertension represents a major, global, issue, and is associated with numerous injurious or life-limiting co-morbidities; thus, any viable mechanism to reduce or manage vascular indices, such as blood pressure, warrant detailed investigation. The efficacy of fasting or energy restriction to elicit acute or chronic alterations in vascular parameters is equivocal, and, to the author's knowledge, no systematic investigation has been conducted. Thus, in the current meta-analysis, we sought to investigate the effects of fasting and energy restriction on blood pressure in humans, by conducting a systematic review and meta-analysis and found, overall, that blood pressure was reduced following fasting and energy restriction.

Incumbent data suggests that increases in systemic oxidative stress and vascular inflammation are pivotal in the pathogenesis of hypertension(Harrison and Gongora, 2009, Kizhakekuttu and Widlansky, 2010); where excess vascular oxidative stress and inflammation, respectively, are key tenets of endothelial dysfunction, however, reductions of either have been shown to reverse endothelial dysfunction (Widlansky et al., 2003). The classic risk factors for atherosclerotic diseases, including vascular complications, include dyslipidemias, hypertension, diabetes mellitus, and smoking. In animal models, all of the aforementioned risk factors are demonstrably improved following calorie restriction, albeit aside from smoking. Clearly, rodent models do not provide a direct comparator to vascular issues that occur in humans (Rebrin et al., 2011), however, the positive effect of calorie restriction is also manifest in nonhuman primates(ZAINAL et al., 2000), where empirical data demonstrates that calorie restriction lowers both SBP and DBP(Lane et al., 1999). Hypertension is a major risk factor for atherosclerosis, stroke, and renal failure; whilst cardiovascular aging, which elicits a progressive increase in arterial stiffness, can lead to an inexorable rise in SBP (Burt et al., 1995). In humans, energy restriction positively effecting SBP and DBP has been demonstrated in previous work, such as in the Biosphere 2 experiment (Walford et al., 2002) where ~20%-unit reductions were evident. Indeed, in the present study, we found significant overall reductions in were in the magnitude of ~2 and ~1 mmHg for SBP and DBP, respectively.

Interestingly, long-term calorie restriction has been asserted to confer a protective effect against the risk of developing cardiovascular disease, evidenced by large decreases in SBP, DBP, cholesterol, triglycerides, IL-6, TNF-α levels and an increase in HDL cholesterol (Dolinsky and Dyck, 2011, Fontana et al., 2004). The incumbent reduction in cardiovascular disease risk is apparent through the carotid artery intima media remaining healthy and a total absence of atherosclerotic-related plaques (Fontana et al., 2004). This was contrary to the overall findings of this study; when sub-group analyses were conducted, it was evident that intervention periods of less than 12 weeks were more effective then longer durations. It is, therefore, worth considering whether extended intervention durations may confer a paradoxical effect, indeed, this was speculated to be true for the effect of fasting and calorie restriction on IGF-1 (Rahmani et al., 2019). Furthermore, in Fontana et al, where significant reductions were evident, the population studied were a homogenous group of older adult participants, whilst our summative assessment included data from a heterogenous range of ages, both which may have contributed to the resultant findings, but clearly warrants further investigation (Fontana et al., 2004).

Putative mechanism

Dharmashankar and Widlansky reported that hypertension can result in increased oxidative stress and inflammation, leading to decreased endothelium dependent vasomotor dysfunction, and although the precise mechanisms are not fully clear, reducing or ameliorating such oxidative stress clearly represents a viable mechanism (Dharmashankar and Widlansky, 2010). It has been asserted that, in response to fasting/energy restriction, fewer free radicals are produced in the mitochondria of cells, because energy restriction diets axiomatically limit energy utilization, which leads to less cellular oxidative damage (Klempel et al., 2013). Further prominent putative mechanisms include the stress resistance hypothesis and the induction of a scarcity program hypothesis (Klempel et al., 2013, Ryan and Nicklas, 2004, Jae et al., 2006). With regards to the former, following prolonged dietary restriction, increased resistance to various of biological stressors occurs, which subsequently permits cell resistance to injury induced by genotoxic, metabolic, or oxidative dysfunction (Schwingshackl and Hoffmann, 2013, Scagliusi et al., 2009, Nielsen et al., 2009). With regards to the latter, energy restriction is thought to induce cellular and organismal adaptation to scarcity, or the absence of nourishment, which leads metabolic processes slowing (Kris-Etherton et al., 2001). Moreover, related to why shorter-term interventions appeared to be more effective at reducing blood pressure, as compared to longer interventions, i.e. over 12-weeks; the acute hormonal response *in situ*, may conceivably be strongest in an initial period, with the bodily processes adapting over a longer period; indeed, for IGF, this was exemplified by Fontana and colleagues, as they demonstrated that a short-term 3-week calorie restriction, but not 1 and 6-year interventions conferred a significant decrease in circulating IGF-1 (Fontana et al., 2008), whilst three further studies also reported significantly reduced IGF-1 at study completion in the longest intervention-arms (Barnosky et al., 2017; Fontana et al., 2016; Tam et al., 2014). In addition, another probable contributor is participant fatigue, indeed, such longer-term studies are reliant on participant adherence to strict regimen, which, after a prolonged period of time, can decline. Nevertheless, despite the numerous putative mechanisms, a precise etiology is far from evident, and thus, the authors recommend detailed mechanistic work be carried out.

Strength and limitations

The primary strength of this study was that this meta-analysis provided a comprehensive overview of the effect of fasting and energy restriction on indices of blood pressure, far beyond evidence thus far, manifest in human-based RCTs; and given the potential influence on clinical treatment and management, this represents a major addition to the literature. The evidence base prior to this was lacking in summative, consensual, assessment, and thus necessitated a quantitative assessment, which we have provided. We demonstrated that there is sufficient evidence for fasting/energy restriction to elicit positive changes in SBP and DBP. Another strength of the present study is the amalgamation of participants, with a range of demographic statuses, ethnicities and ages. Notwithstanding, the current study has some limitations worth considering. The analyses were not restricted to include patients of only one type, where patients with Type-2 Diabetes Mellitus and Metabolic Syndrome (Li et al., 2017), obesity with obstructive sleep apnoea (Fernandes et al., 2015), and obesity, respectively, were included. Although this permitted a larger number of studies and participants to be included for analyses, this could conceivably impact mechanistic action and generalizability. Some included trials were small in sample size, as low as 11 participants, and it has been reported by Sterne *et al.* that it is conceivable for small sample sizes to yield bigger effect sizes in intervention arms than studies with larger participant pools, nonetheless, this was out of the operational control of the meta-analysis (Sterne and Egger, 2001). Correspondent to some previous work (Rahmani et al., 2019), although high levels of energy restriction were applied in the included studies, there were no serious adverse events reported. Tolerability of the fasting or energy restricting regimens was not investigated in the present study, however, in some previous studies, for example, Brandhorst et al (2015), evaluations of tolerability and perceptions of adverse events have been investigated; where only mild discomfort was reported, primarily manifest in the initial stages of the regimen, and was markedly reduced after the initial commencement (Brandhorst et al., 2015).

Conclusion

The principal finding of this study was that fasting and energy restricting diets elicited, overall, significant reductions in SBP and DBP. Subsequent subgroup analyses revealed that intervention duration ≤12 weeks and fasting regimens more effectively reduced SBP and DBP. To the authors' knowledge, this study is the first meta-analysis to investigate the effects of fasting and energy restriction on blood pressure and, thus, represents a milestone for future practice and research to build upon.

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