Principles and Practice of Clinical Research
A Global Journal in Clinical Research
PPCR
ISSN: 2378-1890

HYP-FAST trial study protocol: a phase II, single-center, open-label RCT comparing the effect of early time-restricted feeding on blood pressure control versus standard of care in individuals with primary hypertension.

MA. Valentini[1], JE. Riceto Loyola Júnior[2], JC. Daltoe Inglez[3], R. Ferreira[4], J. Gordilho Souza[5], JL. Santana- Guerrero[6], D. Yucuma[7], V. Texeira Liutti[8], SBM. Abdelrahman[9], M. Pirazzoli[10], N. Kaegi-Braun[11], HA. Reyes[12], IMA. Ahmed[13], H. Elhiday[14], A. Gadelha Guimaraes[15], J. De La Cruz Oller[16], M. Louanne Friend[17], J. Sanches[18], A. Sierra Mencia[19], A. Kann[20], M. Quarti Machado da Rosa[21]

**Corresponding authors: Roseanne Ferreira, MD, Department of Health Research Methods, Evidence, and Impact, McMaster University, 1200 Main Street West, 2C, L8S 4K1, Hamilton Ontario, Canada. E-mail: roseanne.ferreira@gmail.com*

Rest of the author's affiliation at the end of the manuscript.

Received January 8, 2021; accepted March 23, 2021; published April 9, 2021.

Abstract:

***Background**: Primary arterial hypertension is the most prevalent chronic disease globally and significantly impacts public health. It is hypothesized that 16:8 early time-restricted feeding (eTRF) bolsters blood pressure management. To date, there are no randomized trials evaluating its benefits in the treatment of hypertension as a primary outcome.*

***Objective:** To determine if eTRF combined with lifestyle modifications is superior to the standard lifestyle modifications treatment of primary hypertension recommended by the 2018 European hypertension guidelines.*

***Methods:** This will be a superiority, parallel, open-label, randomized, phase II trial carried out in a single center in Zurich, Switzerland. Participants between 30 and 60 years of age, recently diagnosed with high normal and grade I hypertension will be randomly assigned to the eTRF 18:6 plus lifestyle modifications group or the standard lifestyle interventions group. The primary outcome will be the difference between the mean systolic blood pressure at eight weeks with the baseline measurement.*

***Discussion:** This will be the first trial to evaluate the effects of intermittent fasting in patients with primary hypertension. Potential limitations include patient compliance to the intervention. However, in a previous study, self-reported adherence was observed in 1128 of 1351 participants (83.50%). In addition, this study seeks strategies to improve adherence.*

***Conclusion:** We hope that this trial directs other authors to carry out future studies aiming for higher external validity and evaluation of long-term effects of intermittent fasting for the treatment of primary hypertension.*

***Keywords:** Hypertension; early time-restricted feeding; lifestyle modification*

DOI: http://dx.doi.org/10.21801/ppcrj.2021.71.2

Abbreviations:
eTRF: Early time-restricted feeding
BP: Blood Pressure
SBP: Systolic Blood Pressure
DBP: Diastolic Blood Pressure

INTRODUCTION

Primary arterial hypertension is the most prevalent chronic disease in the world. It is associated with several cardiovascular complications, playing a significant

impact on public health. According to the American Heart Association (AHA), there are 1.8 billion hypertensive individuals worldwide (Whelton et al., 2018). Despite several non-pharmacological and pharmacological treatments, half of the patients are unable to reach their treatment targets (Egan et al., 2010). Overweight, obesity and improper diet are some of the risk factors associated with the development of hypertension (Forman et al., 2009). Lifestyle modifications that address these risk factors have shown benefits in controlling blood pressure (BP) (Appel et al., 1997; He et al., 2013; Tuck et al., 1981). Hence, non-pharmacological treatments can potentially facilitate the management of primary hypertension.

The beneficial health effects of non-pharmacological interventions, such as early time-restricted feeding (eTRF), is a current topic of interest (Erdem et al., 2018; Kul et al., 2014; Nematy et al., 2012). eTRF is a type of intermittent fasting in which individuals eat their meals during the morning and early afternoon (eating window), followed by fasting throughout the rest of the day (fasting window) (Lazarou & Matalas, 2010). Previous studies suggest that intermittent fasting reduces markers of systemic inflammation and oxidative stress associated with cardiovascular diseases (Harvie et al., 2013; Moro et al., 2016; Wan et al., 2003). During fasting, triglycerides are broken down to glycerol and fatty acids, which are metabolized to ketone bodies in the liver. When ketone levels reach a threshold, they can activate specific metabolic pathways that result in enhanced DNA repair, mitochondrial autophagy and antioxidant defense while also inhibiting the mTOR pathway, reducing inflammation (de Cabo & Mattson, 2019).

Evidence suggests a positive effect of eTRF on BP control (Erdem et al., 2018). Ernsberger et al., (1994) reported a reduction in BP during fasting periods in an animal study. In humans, BP reduction becomes evident within two to four weeks after fasting initiation (Mager et al., 2006). Despite these findings, other studies have been controversial (Ural et al., 2008).

According to the 2018 European Guidelines, interventions on lifestyle modifications are the standard non-pharmacological interventions for hypertension. Since these measures are the available standard of care, it would be unethical to select a placebo as a comparison source (Williams et al., 2018).

We aim to determine if 16:8 eTRF combined with lifestyle modifications is superior to the standard lifestyle modifications treatment on systolic BP (SBP) control in patients recently diagnosed with high-normal BP or grade I primary hypertension.

MATERIALS AND METHODS

Trial Design

This study will be a phase II, single-center, superiority, parallel, open-label, randomized, controlled trial with a 1:1 allocation ratio. It will be registered at clinicaltrials.gov.

Study Setting

The trial will be conducted in a University Hospital of Zurich, Switzerland. Given the high incidence of hypertension (25% - 30%) in the Swiss population between 35 - 75 years (Fidalgo et al., 2019), a single-center will suffice for the recruitment.

Randomization

Participants will be randomized to either a 16:8 eTRF plus lifestyle modifications group or standard lifestyle interventions group, with a 1:1 allocation ratio. Randomization will be performed using a computer-generated sequence in random block sizes of 4, 6 and 8 to ensure allocation concealment. Research Electronic Data Capture (REDCap) will be used to distribute and maintain treatment allocation. An unblinded independent study personnel will have independent access to the randomization code.

Blinding

This will be an open-label trial. Given the nature of the intervention, blinding of participants and dietitians will not be feasible. Nevertheless, data collectors, outcome assessors, and data analysts will be blinded. No emergency unblinding will be required.

Eligibility Criteria

Inclusion criteria are age between 30 to 60 years old, body mass index (BMI) between 18 and 35 kg/m2, recent diagnosis (0-6 months) of hypertension (confirmed by 24h BP measurement with mean SBP between 130-159 mmHg and/or mean DBP 85-99mmHg) (Williams, 2018). Further inclusion criteria are the ability to use smartphone apps and provide informed consent.

Exclusion criteria are pregnancy, patients on antihypertensive drugs, severe hypertension (mean SBP above 160 mmHg or DBP above 100 mmHg) (Williams, 2018), any etiology of secondary

hypertension or any of the following diseases: coronary heart disease (angina, myocardial infarction), cerebrovascular disease (ischemic stroke, transient ischemic attack), peripheral artery disease (ankle/brachial index <0.9), diabetes mellitus, liver disease, chronic kidney disease with creatinine clearance (eGFR) <30 ml/min at screening, cancer within the past five years (other than non-melanoma skin cancer and cervical intraepithelial neoplasms), alcohol use disorder, drug abuse, eating disorders, unstable affective bipolar disorder or schizophrenia (diagnosed with DSM-V criteria) and co-enrolment in another trial.

Recruitment strategy

Recruitment will take place at primary care institutions in Zurich, using a healthcare-provider-based strategy. General practitioners will be asked to refer patients with newly diagnosed high-normal or hypertensive BP to the research coordinator. After evaluating inclusion and exclusion criteria, informed consent will be requested. Eligibility criteria will be reassessed by an investigator (resident in internal medicine under the PI's supervision) at the baseline appointment. All patients will undergo 24h BP measurement for confirmation of hypertension stage. A trained investigator (senior resident in internal medicine) will analyze results to confirm eligibility. Eligible and consented patients will then be randomized. Patients outside the scope of study eligibility criteria will be referred back to the general practitioner for treatment. An investigator (senior resident in internal medicine) will monitor side effects and report to the PI. (**Figure 1**)

Adherence

Psychosocial interventions are used to increase adherence to dietary interventions. In previous Mediterranean diet studies, nutrition education significantly improved the intention and consumption of fish, vegetables, and fruits ($p<0.05$) (Willis, 2019). Additionally, contact between subjects in group sessions and individual counselling can be associated with higher adherence. Dietary intervention studies, such as CALERIE (Dorling JL, et al., 2020), DPP (DDP Research Group, 2020), and Look AHEAD (Look AHEAD Research Group, 2006), successfully used similar strategies (Rickman et al., 2011). We chose three methods to increase adherence: a weekly session group, individual telephone sessions with subjects from both groups, and the use of a mobile application (see appendix for details).

The study design and randomization process will be explained to participants while also providing an e-mail and phone number for any additional questions. In case of SBP > 160 mmHg or diastolic BP > 110 mmHg, patients will be referred to the emergency department. These events will be reported as adverse events by the PI.

Interventions

Intervention and control groups will be instructed to carry on the standard non-pharmacological treatment for hypertension following the 2018 European Guidelines, which include:

- Sodium restriction < 2 g/day.
- Alcohol moderation < 14 units / week for men and < 8 units / week for women.
- Healthy diet: high consumption of vegetables, fruits, nuts, unsaturated fatty acids, low consumption of red meat and low-fat dairy products.
- Regular aerobic exercise: at least 30 minutes of moderate dynamic exercise on 5-7 days/week.
- Smoking cessation.

In the intervention group, a 16:8 fasting method will be applied. Subjects will be instructed to eat from 10 am - 6 pm daily and fast from 6 pm - 10 am daily. During the eight hours feeding window, subjects will be given the same recommendation as to the standard treatment group. The timing of food intake will also be recorded with the application.

Modification/discontinuation

Adverse events (AEs) related to fasting that will be screened for are headaches, dizziness, vomiting, diarrhea. Criteria for discontinuing fasting therapy are:

- Non-compliance
- Higher-grade cardiac arrhythmias
- Reflux symptoms
- Severe electrolyte disturbances: K+ <3.0 mmol/l or Na+ <125 mmol/l or Cl <90 mmol/l
- Circulatory depression (heart rate <45 or >120/min, systolic BP <70 mm Hg and/or diastolic BP <40)
- Symptomatic Hypoglycemia (<60 mg/dL)
- Uncomfortable hunger during the study

Patients with clinical emergencies or AEs will be instructed to visit the emergency department.

Outcomes

This study's primary outcome is to compare the difference between the mean systolic BP at eight weeks

of intervention and baseline, using a 24-hour validated BP monitor. During the baseline clinic visit, BP will be assessed in both arms, and, in case of discrepancies, the arm with higher pressure will be used for subsequent measurements. The result will be reported as the arithmetic average of successful systolic BP measurements (see appendix). BP measurements will be performed at baseline, at week four and week 8.

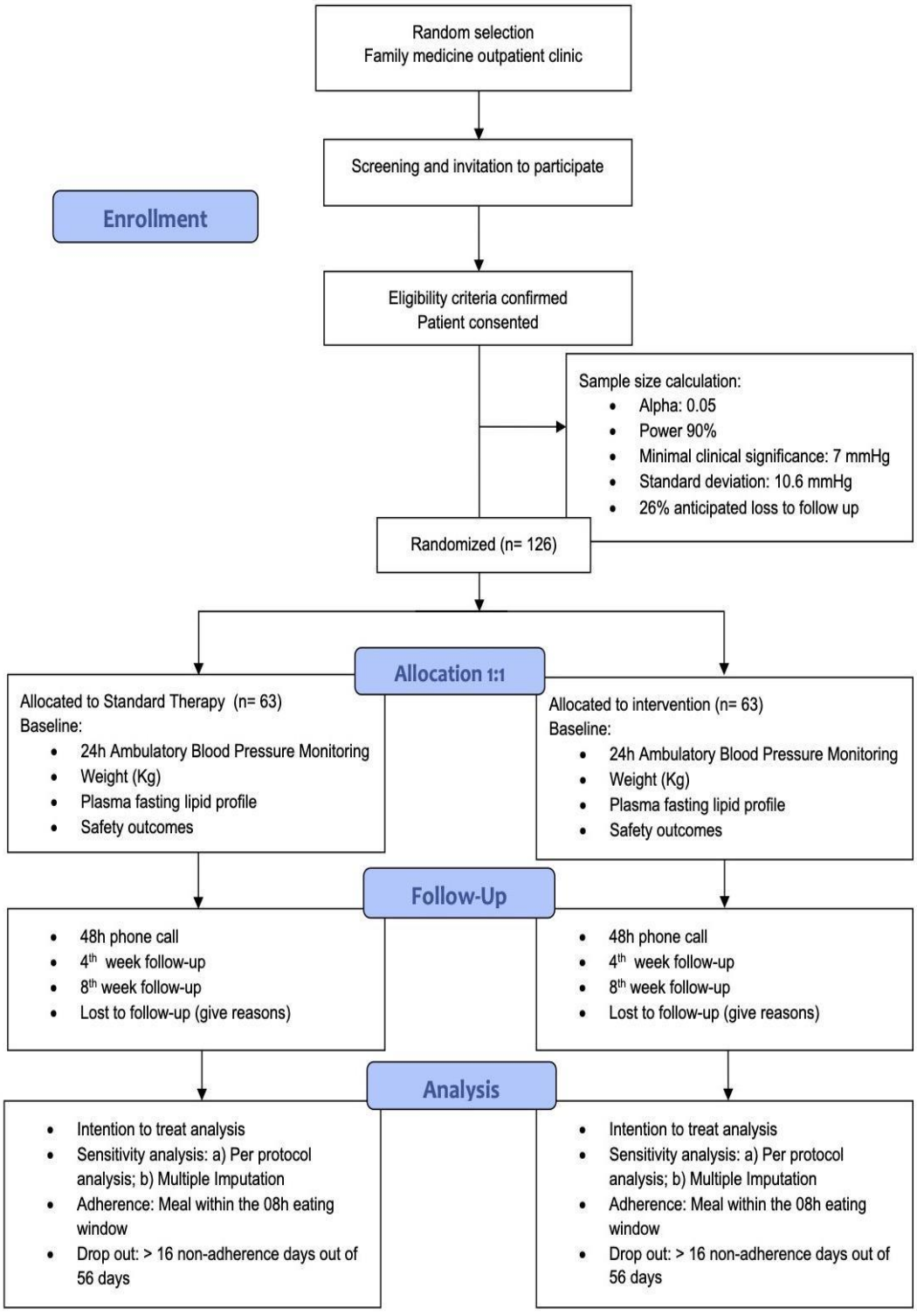

Figure 1. CONSORT flow diagram

Secondary outcomes of interest:

- Mean arterial BP and delta diastolic BP at eight weeks versus baseline. The mean arterial BP (MAP) will be calculated by dividing by 3 the sum of systolic BP and double the diastolic BP (continuous outcome).
- Weight loss (kg): bodyweight will be assessed at baseline, at week 4 and week 8. Measurement will be taken using a balance beam scale with participants without shoes and in light clothing (continuous outcome).
- Change in lipid profile: fasting plasma total cholesterol, direct LDL cholesterol, HDL-cholesterol, triglycerides concentrations will be measured (reported in mg/dL). Fasting blood samples will be collected between 5 am, and 9 am at baseline and week 8. (continuous outcome).
- Adherence to the early time-restricted feeding program: it will be measured using a mobile app. Participants will record the time they started and stopped eating daily. Adherence to the eTRF diet will be assessed as the number of adherent days per week. If the app indicates that the subject ate within the 8-hour window, that day will be labeled as "adherent"; if the app indicates that the subject consumed food outside of the 8-hour feeding window, that day will be labeled as "non-adherent". Subjects will be considered adherent to the intervention if they meet adherence criteria on 5 out of the 7 days of the week.
- Safety outcomes: hypoglycemia, electrolyte disturbances, headaches, migraine, acute back pain, muscle cramps, impaired vision (temporary), fluid retention (temporary) and changes in sleep patterns will be evaluated.

Data Management

Data will be entered electronically in the REDCap platform. The Institutional Review Board will approve the electronic form used for data entry.

The REDCap platform allows for the secure storing of the data. An additional copy of the data will be stored in a password-protected cloud drive that only the study staff will have access to.

Confidentiality of the subjects will be maintained. Each subject will be assigned a unique study ID number not related to their personally identifiable information. A subject log containing the list of personal identifiers and matched study IDs will be kept in a restricted password-protected file controlled by the PI and study coordinators.

Data will be uploaded to a secure REDCap database daily according to privacy regulations. Weekly reports evaluating the status of the data entry, missing, or pending data will be performed. Lastly, the database will be audited monthly to maintain data integrity.

Interim Analysis

An interim analysis will be performed once half of the total sample size has been recruited to evaluate the intervention's safety and the presence of proper documentation of adverse events. It will be performed by an independent statistician, blinded for the treatment allocation. The statistician will report to the independent committee, which will have access to all the data. They will report to the ethics committee and decide on the continuation of the trial.

Sample Size Calculation

This study was designed to achieve a power of 90% to allow for secondary analysis. The type I error was 0.05, and the allocation ratio 1:1. The effect size was conservatively determined at 7mmHg. The stated effect size in the literature is a mean of 11mmHg plus a standard deviation (SD) of +/- 4mmHg. Thus, the effect size for our trial was calculated by subtracting 1 SD from the mean. This effect size was also corroborated by a previous study on eTRF (Sutton et al., 2018). The SD for the present study population was considered to be 10.6mmHg (Appel et al., 1997). Assumptions were chosen based on Sutton and Appel's studies, considering the similarities of the sample population with the present study (including patients with SBP up to 160mmHg).

Based on the aforementioned variables, the sample size was calculated using the sample size calculator tool at Vanderbilt University: https://vbiostatps.app.vumc.org/ps/t-test/ind/2. The estimated total sample size of 100 patients is required to detect a difference of 7 mmHg. For this trial's purpose, we have considered the most conservative scenario of 26% loss to follow up according to a previous trial (Horne et al., 2020). The total sample size yield was 126 patients, 63 patients per trial arm.

Statistical Analysis

The primary analysis will follow the intention to treat principle. Due to the normal distribution of the primary endpoint variable, an independent sample t-test will be used to compare the outcomes. In case both groups are not balanced, linear regression and covariate

adjustment in the mean systolic BP will be performed to assess interference of sex, race, smoking status, BMI, hypertension severity and attendance in the group session between the groups.

For the secondary analysis, an independent sample t-test or the Mann-Whitney test for continuous outcomes will be used given the normality of distribution. Association between weight loss and systolic BP change in each group will be analyzed using Pearson Correlation. Incidence of adverse events will be reported as absolute values and proportions of patients who presented these symptoms. Adherence will be disclosed for the intervention group as a proportion and absolute value of patients who did not achieve the minimum criteria to be considered adherent.

A sensitivity analysis will be conducted using a per-protocol analysis to evaluate adherence to our treatment.

A two-sided p-value of less than 0.05 will be considered to indicate statistical significance for outcomes. Data will be analyzed using Stata 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

Missing Data

Patients in the intervention group will be instructed to eat during their 8-hour feeding window and record the times of fasting using the smartphone app. Patients who eat out of the allowed 8-hour window period will be considered "non-adherent". Two or more non-adherent days out of a week, with a total of 16 non-adherent days during the eight-week trial, will compute a "dropout" status to the participant. The reasons for dropout or withdrawals will be disclosed to inform on the difficulties of this intervention. We assume that most of the missing data mechanisms will be missing at random (MAR), i.e., related to the intervention, not the outcome.

An intention to treat analysis will be performed, and missing data will be addressed by a multiple imputation method to preserve randomization. It will provide a more conservative analysis of the treatment effect and a more precise estimation of this intervention's clinical challenges. Thus, reflecting the real-world aspect of lifestyle interventions.

DISCUSSION

This is a protocol for a phase II randomized controlled clinical trial that explores the potential beneficial effects of eTRF as an adjuvant strategy to classical lifestyle interventions in BP control.

It will be the first trial to evaluate the effects of eTRF in patients with primary hypertension, having 24h ambulatory BP measurement as the primary endpoint. Other studies that utilized BP as an outcome were non-randomized studies, presented poor methodological quality, or did not adjust outcomes for patient-important confounders (Erdem et al., 2018). Literature remains inconclusive, demonstrating the importance of this trial.

This trial's potential limitations include patient compliance to the intervention since eTRF may be challenging to adhere to. Nevertheless, in a previous study that evaluated the effects of eTRF on weight loss, the self-reported adherence observed was 83.50% (1128 out of 1351participants) (Lowe et al., 2020). A potential run-in phase was deliberated given the successful adherence reported by the Dietary Approaches to Stop Hypertension (DASH) trial (Appel et al., 1997). However, opting for the run-in phase would bring unnecessary complexity to the trial and possibly underestimate the effect size. Some individuals could have normalized BP levels before the study started. As a result, we chose to apply strategies such as weekly group sessions, motivational calls and the use of a mobile application that have shown promising results in increasing adherence (Rickman et al., 2011; Willis, 2019). For subjects missing their follow-up appointment, telephone calls will be made for rescheduling and determining the reason for not attending. Although the trial's short duration may help improve adherence to the intervention, it can also be a limitation in evaluating the long-term effects and feasibility of the therapy. Nevertheless, by demonstrating its effect on BP in the short-term intervention, it is expected that this study will encourage the development of future larger and longer follow-up clinical trials on this therapy.

Additionally, it is essential to point out that the present study has a potential risk for introducing performance bias since there is a risk of promoting health changes more emphatically in the intervention group than in the control one. Hence, outcome adjudicators will be blinded, in addition to the standardization of educational orientation sessions and scripted telephone calls to mitigate that.

Achieving changes in BP with non-pharmacological interventions is an excellent challenge for both patients and health care providers. The proposed study aims to add valuable insight to the body of evidence regarding non-pharmacological strategies to address hypertension. Results from this trial can

become a catalyst to advance new approaches for dietary intervention with secondary metabolic benefits of fasting. We hope that the results obtained in this trial will prompt researchers to consider other non-pharmacological approaches for the treatment of primary hypertension.

Acknowledgements

We thank Walid Omer for his invaluable help in designing the project. We also thank Professor Felipe Fregni and The Principles and Practice in Clinical Research faculty team for their critical comments for the improvement of our trial.

Author affiliations

1. Hospital de Pediatría S.A.M.I.C "Prof. Dr. Juan P. Garrahan". Buenos Aires, Argentina
2. Hospital Alemão Oswaldo Cruz. São Paulo, Brazil
3. Universidade Federal de Minas Gerais. Belo Horizonte, Brazil
4. Department of Health Research Methods, Evidence, and Impact. McMaster University, Hamilton, Canada
5. Faculdade de Medicina da Bahia Universidade Federal da Bahia, FMUFBA. Salvador, Brazil
6. Servicio Nacional de Salud. Santo Domingo, Dominican Republic
7. Department of Clinical Epidemiology and Biostatistics. Pontificia Universidad Javeriana, Bogota, Colombia
8. Hospital do Câncer de Londrina, Londrina, Brazil
9. Endocrinology, Medicine Department, Hamad General Hospital, DOHA, Qatar
10. Emergency Department, Clínica Alemana, Santiago, Chile
11. Department of Endocrinology, Diabetology and Metabolism, Cantonal Hospital Aarau, Aargau, Switzerland
12. Northern Light Eastern Maine Medical Center, Bangor Maine, USA
13. Hamad medical corporation, Doha, Qatar
14. DOH Amana Healthcare Medical and Rehabilitation Hospital, Mubadala Institution
15. A. C. Camargo Cancer Center, São Paulo, Brazil
16. Instituto Tecnológico de Santo Domingo, Santo Domingo, República Dominicana
17. Associate Professor. College of Community Health Science. Assistant Residency Director. University of Alabama Tuscaloosa Family Medicine Residency. Tuscaloosa, Alabama, USA
18. Instituto Brasileiro de Controle do Câncer - IBCC, São Paulo, Brazil
19. Hospital Clínico Universitario de Valladolid, España
20. Hospital Alemao Oswaldo Cruz, Sao Paulo, Brazil
21. Institute of Tropical Pathology and Public Health, Federal University of Goias. Goiânia, Goiás, Brazil

Conflicts of interest and financial disclosure

The authors have no financial or personal conflicts of interest. The final version of the manuscript has been approved by all authors. JLS is a member of the editorial team, therefore he excused himself from the editorial process.

REFERENCES

Appel, L. J., Moore, T. J., Obarzanek, E., Vollmer, W. M., Svetkey, L. P., Sacks, F. M., Bray, G. A., Vogt, T. M., Cutler, J. A., Windhauser, M. M., Lin, P. H., & Karanja, N. (1997). A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. The New England Journal of Medicine, 336(16), 1117–1124. https://doi.org/10.1056/NEJM199704173361601

de Cabo, R., & Mattson, M. P. (2019). Effects of Intermittent Fasting on Health, Aging, and Disease. The New England Journal of Medicine, 381(26), 2541–2551. https://doi.org/10.1056/NEJMra1905136

Diabetes Prevention Program (DPP) Research Group. (2002). The Diabetes Prevention Program (DPP): description of lifestyle intervention. Diabetes care, 25(12), 2165-2171. https://doi.org/10.2337/diacare.25.12.2165

Dorling, J. L., Das, S. K., Racette, S. B., Apolzan, J. W., Zhang, D., Pieper, C. F., & Martin, C. K. (2020). Changes in body weight, adherence, and appetite during 2 years of calorie restriction: the CALERIE 2 randomized clinical trial. European journal of clinical nutrition, 1-11. https://doi.org/10.1038/s41430-020-0593-8

Egan, B. M., Zhao, Y., & Axon, R. N. (2010). US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. JAMA, 303(20), 2043–2050. https://doi.org/10.1001/jama.2010.650

Erdem, Y., Özkan, G., Ulusoy, Ş., Arıcı, M., Derici, Ü., Şengül, Ş., Sindel, Ş., Ertürk, Ş., & Turkish Society of Hypertension and Renal Diseases. (2018). The effect of intermittent fasting on blood pressure variability in patients with newly diagnosed hypertension or prehypertension. Journal of the American Society of Hypertension: JASH, 12(1), 42–49. https://doi.org/10.1016/j.jash.2017.11.008

Ernsberger, P., Koletsky, R. J., Baskin, J. S., & Foley, M. (1994). Refeeding hypertension in obese spontaneously hypertensive rats. Hypertension (Dallas, Tex.: 1979), 24(6), 699–705. https://doi.org/10.1161/01.hyp.24.6.699

Fidalgo, A., Vollenweider, P., & Marques-Vidal, P. (2019). Ten-year incidence of hypertension in a Swiss population-based sample Incidence of hypertension in Switzerland. Journal of human hypertension, 33(2), 115–122. https://doi.org/10.1038/s41371-018-0116-4

Forman, J. P., Stampfer, M. J., & Curhan, G. C. (2009). Diet and lifestyle risk factors associated with incident hypertension in women. JAMA, 302(4), 401–411. https://doi.org/10.1001/jama.2009.1060

Gabel, K., Hoddy, K. K., Haggerty, N., Song, J., Kroeger, C. M., Trepanowski, J. F., Panda, S., & Varady, K. A. (2018). Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: A pilot study. Nutrition and healthy aging, 4(4), 345–353. https://doi.org/10.3233/NHA-170036

Harvie, M., Wright, C., Pegington, M., McMullan, D., Mitchell, E., Martin, B., Cutler, R. G., Evans, G., Whiteside, S., Maudsley, S., Camandola, S., Wang, R., Carlson, O. D., Egan, J. M., Mattson, M. P., & Howell, A. (2013). The effect of intermittent energy and carbohydrate restriction v. Daily energy restriction on weight loss and metabolic disease risk markers in overweight women. The British Journal of Nutrition, 110(8), 1534–1547. https://doi.org/10.1017/S0007114513000792

Horne, B. D., Grajower, M. M., & Anderson, J. L. Limited Evidence for the Health Effects and Safety of Intermittent Fasting Among Patients With Type 2 Diabetes. JAMA http://doi.org/10.1001/jama.2020.3908

Hsu, M. S. H., Harper, C., Gibson, A. A., Sweeting, A. N., McBride, J., Markovic, T. P., et al. (2018). Recruitment Strategies for a Randomised Controlled Trial Comparing Fast Versus Slow Weight Loss in Postmenopausal Women with Obesity-The TEMPO Diet Trial. Healthcare (Basel, Switzerland), 6(3). http://doi.org/10.3390/healthcare6030076

Kul, S., Savaş, E., Öztürk, Z. A., & Karadağ, G. (2014). Does Ramadan fasting alter body weight and blood lipids and fasting blood glucose in a healthy population? A meta-analysis. Journal of Religion and Health, 53(3), 929–942. https://doi.org/10.1007/s10943-013-9687-0

Lazarou, C., & Matalas, A.-L. (2010). A critical review of current evidence, perspectives and research implications of diet-related traditions of the Eastern Christian Orthodox Church on dietary intakes and health consequences. International Journal of Food Sciences and Nutrition, 61(7), 739–758. https://doi.org/10.3109/09637481003769782

LOOK AHEAD: Look AHEAD Research Group. (2006). The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. Obesity, 14(5), 737-752. https://doi.org/10.1038/oby.2006.84

Lowe, D. A., Wu, N., Rohdin-Bibby, L., Moore, A. H., Kelly, N., Liu, Y. E., Philip, E., Vittinghoff, E., Heymsfield, S. B., Olgin, J. E., Shepherd, J. A., & Weiss, E. J. (2020). Effects of Time-Restricted Eating on Weight Loss and Other Metabolic Parameters in Women and Men With Overweight and Obesity: The TREAT Randomized Clinical Trial. JAMA Internal Medicine. https://doi.org/10.1001/jamainternmed.2020.4153

Mager, D. E., Wan, R., Brown, M., Cheng, A., Wareski, P., Abernethy, D. R., & Mattson, M. P. (2006). Caloric restriction and intermittent fasting alter spectral measures of heart rate and blood pressure variability in rats. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology, 20(6), 631–637. https://doi.org/10.1096/fj.05-5263com

Moro, T., Tinsley, G., Bianco, A., Marcolin, G., Pacelli, Q. F., Battaglia, G., Palma, A., Gentil, P., Neri, M., & Paoli, A. (2016). Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength, body composition, inflammation, and cardiovascular risk factors in resistance-trained males. Journal of Translational Medicine, 14(1), 290. https://doi.org/10.1186/s12967-016-1044-0

Nematy, M., Alinezhad-Namaghi, M., Rashed, M. M., Mozhdehifard, M., Sajjadi, S. S., Akhlaghi, S., Sabery, M., Mohajeri, S. A. R., Shalaey, N., Moohebati, M., & Norouzy, A. (2012). Effects of Ramadan fasting on cardiovascular risk factors: A prospective observational study. Nutrition Journal, 11, 69. https://doi.org/10.1186/1475-2891-11-69

Rickman, A. D., Williamson, D. A., Martin, C. K., Gilhooly, C. H., Stein, R. I., Bales, C. W., et al. (2011). The CALERIE Study: design and methods of an innovative 25% caloric restriction intervention. Contemporary Clinical Trials, 32(6), 874–881. http://doi.org/10.1016/j.cct.2011.07.002

Sutton, E. F., Beyl, R., Early, K. S., Cefalu, W. T., Ravussin, E., & Peterson, C. M. (2018). Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. Cell metabolism, 27(6), 1212-1221

Tuck, M. L., Sowers, J., Dornfeld, L., Kledzik, G., & Maxwell, M. (1981). The effect of weight reduction on blood pressure, plasma renin activity, and plasma aldosterone levels in obese patients. The New England Journal of Medicine, 304(16), 930–933. https://doi.org/10.1056/NEJM198104163041602

Ural, E., Kozdag, G., Kilic, T., Ural, D., Sahin, T., Celebi, O., & Komsuoglu, B. (2008). The effect of Ramadan fasting on ambulatory blood pressure in hypertensive patients using combination drug therapy. Journal of Human Hypertension, 22(3), 208–210. https://doi.org/10.1038/sj.jhh.1002296

Wan, R., Camandola, S., & Mattson, M. P. (2003). Intermittent food deprivation improves cardiovascular and neuroendocrine responses to stress in rats. The Journal of Nutrition, 133(6), 1921–1929. https://doi.org/10.1093/jn/133.6.1921

Whelton, P. K., Carey, R. M., Aronow, W. S., Casey, D. E., Collins, K. J., Dennison Himmelfarb, C., DePalma, S. M., Gidding, S., Jamerson, K. A., Jones, D. W., MacLaughlin, E. J., Muntner, P., Ovbiagele, B., Smith, S. C., Spencer, C. C., Stafford, R. S., Taler, S. J., Thomas, R. J., Williams, K. A., … Wright, J. T. (2018). 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension (Dallas, Tex.: 1979), 71(6), e13–e115. https://doi.org/10.1161/HYP.0000000000000065

Wilkinson, M. J., Manoogian, E., Zadourian, A., Lo, H., Fakhouri, S., Shoghi, A., Wang, X., Fleischer, J. G., Navlakha, S., Panda, S., & Taub, P. R. (2020). Ten-Hour Time-Restricted Eating Reduces Weight, Blood Pressure, and Atherogenic Lipids in Patients with Metabolic Syndrome. Cell metabolism, 31(1), 92–104.e5. https://doi.org/10.1016/j.cmet.2019.11.004

Williams, B., Mancia, G., Spiering, W., Rosei, E. A., Azizi, M., Burnier, M., Clement, D. L., Coca, A., de Simone, G., Dominiczak, A., Kahan, T., Mahfoud, F., Redon, J., Ruilope, L., Zanchetti, A., Kerins, M., Kjeldsen, S. E., Kreutz, R., Laurent, S., … Desormais, I. (2018). [2018 ESC/ESH Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH)]. Giornale Italiano Di Cardiologia (2006), 19(11 Suppl 1), 3S-73S. https://doi.org/10.1714/3026.30245

Willis, A. W., Brown, O. N., & Greene, M. W. (2019). The use of psychological methodologies in cardiovascular disease interventions promoting a Mediterranean style diet: A systematic review. Nutrition, Metabolism, and Cardiovascular Diseases: NMCD, 29(4), 325–333. http://doi.org/10.1016/j.numecd.2018.12.011