Clinical Nutrition ESPEN 51 (2022) 97–103

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Randomized Controlled Trial

Effects of fructose restriction on blood pressure: Secondary analysis of a double-blind randomized controlled trial

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ARTICLE INFO

Article history:
Received 14 July 2022
Accepted 19 July 2022

Keywords:
Blood pressure
Fructose
Nutrition
Dietary intervention
Randomized controlled trial
Endothelial dysfunction

SUMMARY

Background: Despite convincing animal data, there is an ongoing debate on whether and how fructose affects blood pressure in humans. The aim of this study was to investigate the effects of fructose restriction on blood pressure, and the role of endothelial function herein.
Methods: forty-four overweight individuals were asked to follow a fructose-restricted diet (<7.5 g/meal and <10 g/day) for 6 weeks. They were randomly assigned to double-blind supplementation with glucose (=intervention group) or fructose (=control group) powder three times daily. Office blood pressure was measured with an automated device, and endothelial function was assessed by reactive hyperemia peripheral arterial tonometry, skin laser doppler flowmetry, and serum sE-selectin.
Results: Thirty-seven participants completed the study. Systolic blood pressure decreased significantly in the intervention group (change from baseline: −3.3 mmHg; 95%CI:-8.8,− 0.3), but this change was not statistically different from the control group. In contrast, diastolic blood pressure decreased significantly in the intervention group in comparison to controls (difference: −4.0 mmHg; 95%CI:-9.5,-0.5). Furthermore, the change in fructose intake was associated with the change in diastolic blood pressure (beta: 0.085 mmHg; 95% CI: 0.032;0.138). The endothelial markers were not affected by the intervention. Finally, the effects of the intervention on diastolic blood pressure appeared to be higher in individuals consuming high amounts of salt at baseline (difference: −9.0 mmHg; 95%CI:-14.5,-2.5).
Conclusions: Six-week fructose restriction per se results in a dose-dependent decrease in diastolic blood pressure. Further studies are warranted to elucidate the effects of fructose restriction on salt-sensitive hypertension in humans.
Trial registration: www.clinicaltrials.gov; NCT03067428.

1. Introduction

Despite the widespread consensus that added sugars — i.e. all sugars that are added during food manufacturing and preparation — are disadvantageous for cardiometabolic health [1–4], there is an ongoing discussion on whether the type of sugar matters [5].

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https://doi.org/10.1016/j.clnesp.2022.07.009

Although animal studies have convincingly shown that fructose raises blood pressure [6–8], the translation to humans is less straightforward. While acute fructose feeding trials have shown an effect on blood pressure in humans [9], meta-analyses of large cohort studies and randomized controlled trials have not shown an effect of fructose on blood pressure [10,11]. Besides acute versus chronic effects, the discrepancy between these animal and human studies may be explained by, amongst others, inaccurate assessment of both exposure and outcome (in cohort studies), and supplementation of fructose on top of a diet that is already rich in fructose (in randomized controlled trials).

The putative mechanisms by which fructose increases blood pressure have primarily been studied in animals. One of these includes an uric acid-mediated decrease in nitric oxide affecting endothelial function [12,13]. Another possible pathway is fructose-induced reabsorption of sodium in the enterocyte and proximal tubule, accounting for a synergetic action between fructose and sodium on blood pressure [14,15].

We recently conducted a double-blind randomized controlled trial in which the effects of fructose or glucose supplementation on intrahepatic lipid content were studied at a background of a complete fructose restricted diet, (Effects of fructose restriction on liver steatosis; FRUITLESS [16]). The aim of the current study was to investigate the effects of this dietary intervention on blood pressure and the potential role of endothelial function herein.

2. Research design and methods

2.1. Study population

Details of the FRUITLESS study have recently been described in detail elsewhere [16]. Since the FRUITLESS study was primarily designed to study the effects of fructose restriction on intrahepatic lipid content, participants were enrolled when they had a high a priori chance of an increased intrahepatic lipid content (i.e. BMI $\geq$28 kg/m^2 and a fatty liver index $\geq$60) and a daily fructose intake above the Dutch average [i.e. $\geq$ 45 g/d [17]]. Due to a slow recruitment rate, the latter inclusion criterion was abandoned during the recruitment phase. Exclusion criteria were (history of) liver disease, (history of) excessive alcohol consumption, major change in weight (i.e. >5%) and/or physical activity three months prior to the study, use of glucose-lowering drugs, recent illness, pregnancy and/or lactation, contraindications for MRI, and inability to give informed consent. All participants gave written informed consent prior to inclusion in the study. The study was performed according to the Declaration of Helsinki [18] and approved by the medical ethical committee of Maastricht University Medical Center.

2.2. Intervention

To study the role of fructose per se on cardiometabolic outcomes, independent of potential confounding effects of other macro/micronutrients, we asked all participants to consume a six-week fructose-restricted diet (i.e. <7.5 g/meal and <10 g/day). They were subsequently randomly assigned to supplementation with sachets of either glucose or fructose, three times daily. The dose of fructose or glucose supplementation equaled the amount of fructose that was restricted from the diet (amount of natural fructose reduced from diet [g/day] = amount of fructose or glucose supplemented [g/day]. As such, both groups followed an exactly similar diet with the only difference the amount of fructose, which was equal to the amount at baseline in the control group and less than 10 g/day in the intervention group. The glucose supplementation in the intervention group, which was similar in taste and appearance to fructose, allowed for an isocaloric comparison.

After the protocol amendment, individuals with a below average habitual fructose intake (<45 g/day) were also eligible to participate. To safeguard a substantial difference in fructose intake between the intervention and control group throughout the study – and hence, to have sufficient discriminative power – the fructose/glucose supplementation in these individuals was set at the average Dutch adult intake of 45 g/day. For example, if a participant consumed 10 g of fructose per day prior to the study, they received 45 g/day glucose or fructose during the intervention.

Dietary intake of fructose, macronutrients, total calories and sodium (at baseline and at completion was assessed by a 3-day food journal using a Dutch food composition table and fructose-specific food composition table [17]. All participants received instructions from one researcher (NSi) on how to use the journal. They were asked to prospectively record all consumed food items (brand and quantity) during two weekdays and one weekend day. Weight of the food product was provided by the participants or estimated using average quantities per portion. Recordings were always followed by a personal interview to clarify any obscurity [16].

2.3. Vascular measurements

Participants visited the research ward in the morning after an overnight fast. Fructose or glucose supplementation was not taken prior to the measurements. Systolic and diastolic blood pressure were measured four times in sitting position on the right arm after 10 min of rest with a 3-minute interval using an automated device (Omron, Hoofddorp, The Netherlands). The median of four measurements was used for further analyses.

The following endothelial function tests were included as secondary outcome measures in the original study protocol and have recently been described in detail elsewhere [19]: 1) reactive hyperemia peripheral arterial tonometry (RH-PAT; ENDOPAT Itamar Medical, Caesarea, Israel), which measures digital pulsatile arterial pressure changes accompanying pulse waves during reactive hyperemia after local ischemia, induced by inflating a cuff around the upper arm to suprasystolic values for 5 min. The reactive hyperemia index (RHI) was calculated as the ratio of the relative change in PAT signal amplitude in the test arm (= the average PAT signal amplitude during reactive hyperemia divided by the average PAT signal amplitude during baseline) over the control arm that was not exposed to ischemia. A low RHI is indicative of endothelial dysfunction of the small arteries [20]; 2) skin laser doppler flowmetry (LDF; Periflux 5000, Permid, Jarfalla, Sweden), which measures the changes in microcirculatory blood flow on the dorsal side of the lower arm during local heating (44 °C) using changes in reflected wavelength caused by moving blood cells to the probing light. A lower heat-induced skin hyperemia reflects microvascular endothelial dysfunction [21,22]. In addition skin microvascular flowmotion, i.e. the rhythmic changes in arteriolar diameter caused by vasomotion, was measured using LDF. It consists of a broad spectrum of oscillation frequencies with high-frequency oscillations originating from the cardiac and respiratory cycles, and low-frequency oscillations origination from the endothelial, neurogenic, and myogenic cycles. [23]; and 3) serum soluble E-selectin (sE-selectin), which was measured using a Diaclone ELISA kit (Diaclone SAS, Besancon Cedex, France).

2.4. Other measurements

Weight, height and waist circumference were determined at baseline and completion, as described previously [16]. Blood was drawn to determine serum uric acid (Enzymatic colorimetric assay, Cobas 8000 instrument, Roche Diagnostics, Mannheim, Germany), insulin, lipids and glucose, as described previously [16]. Insulin

resistance was estimated with the homeostasis model assessment of insulin resistance (HOMA2-IR) calculator (www.dtu.ox.ac.uk). A 24-hour urine sample was collected at baseline and at completion in pre-acidified plastic containers for determination of sodium (Indirect ISE-method, Cobas 8000 instrument, Roche Diagnostics, Mannheim, Germany), fructose (Ultra Performance Liquid Chromatography-tandem Mass Spectrometry [24], and uric acid levels (Enzymatic colorimetric assay, Cobas 8000 instrument, Roche Diagnostics, Mannheim, Germany).

2.5. Statistical analyses

Sample size calculation was based on the primary outcome measure of the FRUITLESS-study, i.e. intrahepatic lipid content. Taking into account a dropout rate of 15%, it was estimated that n = 22 individuals per treatment arm were required (alpha = 0.05, beta = 0.20) [16].

Dichotomous data are presented as frequencies. Continuous data are expressed as median (interquartile range). Changes from baseline within and between groups were analyzed with Wilcoxon's Signed Rank test and a Mann–Whitney U test, respectively. The 95% confidence interval (95% CI) for the difference within and between groups was calculated according to the Hodges-Lehmann method. In case of a statistically significant difference between the intervention and control group, the presence of a dose–response relationship was explored by linear regression analysis.

For reasons of statistical efficiency and to reduce the influence of biological variability on the endothelial function markers, a composite endothelial dysfunction score was calculated [25]. First, Z-scores for each marker were calculated (= individual value − population mean)/population standard deviation). Subsequently, the composite score was calculated as: ($Z_{sE\text{-}selectin} - Z_{RHI} - Z_{heat\text{-}induced\ skin\ hyperemia}$)/3, to align the directions of the effects of the individual markers. A high composite score reflects worse endothelial function. Flowmotion was not included in the composite score because both high and low values have been associated with adverse cardiometabolic traits [23].

A potential synergy between the intervention and dietary salt intake at baseline was explored by stratified analyses according to Dutch recommended intake (cut-off: 6 g per day), and formally tested by one-way ANCOVA with the introduction of an interaction term (intervention [yes/no]*dietary salt <6 g/day [yes/no]).

Finally, sensitivity analyses were conducted to assess 1) the impact of the protocol amendment, by performing stratified analyses according to dietary fructose intake at baseline (below and above 45 g/day), 2) the influence of any unbalanced randomization on the main outcome measure of this study (i.e. blood pressure). For this, one-way ANCOVA was conducted with the unbalanced variable as a covariate.

Results were considered statistically significant at $p < 0.05$, and at $p < 0.10$ for interaction. All analyses were carried out with IBM SPSS version 25 for Windows (SPSS Inc. Chicago, IL).

3. Results

3.1. Randomization and follow up

Forty-four participants were randomly allocated to the intervention group (fructose-restricted diet plus supplementation with glucose powder) or the control group (fructose-restricted diet plus supplementation with fructose powder). Six participants allocated to the intervention were not included in the final analyses for reasons that do not appear to be related to the intervention (discontinuation before receiving the allocated intervention [n = 2], discontinuation during the intervention because of personal reasons [n = 1], illness not related to the intervention [n = 1] and noncompliance [n = 1], and exclusion due to protocol violation [n = 1]). One participant in the control group discontinued because of illness not related to the intervention (Supplementary Figure 1) [16]. The baseline characteristics of the study population are displayed in Table 1 and Supplementary Table 1 (macronutrient composition). As previously described in detail [16], dietary fructose intake decreased substantially in both groups, without any difference between the groups (Supplementary Figure 2A). The median amount of glucose supplementation in the intervention group (50.0 g/day [46.0–70.8] did not differ from the amount of fructose supplementation in the control group (45 g/day [45.0–56.2]) (p = 0.40, Supplementary Figure 2B). When fructose supplementation was included, fructose intake in the control group increased significantly compared to baseline (Supplementary Figure 2C), which can be explained by the protocol amendment that allowed inclusion of individuals consuming fructose less than 45 g/day who were subsequently supplemented up to 45 g/day.

Twenty-four-hour urinary fructose levels, used as a biomarker of dietary fructose intake and, hence, adherence [24], showed a very similar pattern (Supplementary Figure 2D). Serum uric acid levels, but not 24 h urinary uric acid levels, showed a borderline significant reduction in the intervention group only (Supplementary Figure 3A-B).

Table 1
Baseline characteristics of the study population.

Characteristic	Control group (n = 21)	Intervention group (n = 16)
Age, years	52 (38–62)	55 (35–62)
Sex, male/female	6/15	6/10
BMI, kg/m^2	31.1 (30.2–35.6)	34.1 (28.8–37.3)
Waist circumference, cm	110 (104–114)	118 (107–128)
Smoking, n (% yes)	3 (14.3)	2 (12.5)
Alcohol intake, units/week	3 (0–5)	2 (1–5)
HOMA2-IR	0.86 (0.73–1.14)	0.84 (0.50–1.37)
Serum Total cholesterol, mmol/L	5.2 (4.2–6.0)	5.2 (4.3–5.6)
Serum HDL cholesterol, mmol/L	1.3 (1.0–1.5)	1.2 (1.1–1.3)
Serum LDL cholesterol, mmol/L	2.7 (2.3–3.8)	3.1 (2.3–3.8)
Serum triglycerides, mmol/L	1.3 (0.9–1.7)	1.6 (1.2–1.9)
Dietary fructose intake, g/day	37 (27–55)	42 (20–73)
Dietary salt intake, g/day	7 (4–8)	6 (4–7)
Systolic blood pressure, mmHg	128 (123–152)	138 (130–146)
Diastolic blood pressure, mmHg	84 (79–89)	85 (78–91)
Heart rate, beats per minute	63 (56–71)	67 (59–79)
Antihypertensive use, n (% yes)	2 (9.5)	2 (12.5)

Data are expressed as median (interquartile range).

There was a small decrease in BMI in both the intervention and control group (change from baseline: −0.2 kg/m^2; 95%CI: −0.5, 0.0; and −0.4 kg/m^2; 95%CI: −0.6, −0.1), which did not differ between both groups (difference in the change from baseline: −0.1 kg/m^2; 95%CI: −0.3, 0.5).

3.2. Effects of fructose restriction on blood pressure

Median systolic blood pressure showed a statistically significant decrease in the intervention group only (change from baseline: −3.3 mmHg; 95%CI: −8.8, −0.3 versus −1.5 mmHg; 95% CI: −4.5, 3.3 in the control group), but the change was not significantly different between both groups (difference in the changes from baseline: −2.0 mmHg; 95%CI: −8.0, 2.5, Fig. 1A). In contrast, diastolic blood pressure decreased significantly in the intervention group (change from baseline: −3.4 mmHg, 95%CI: −7.3, 0.0), which was statistically significantly different from the control group (difference in the changes from baseline: −4.0 mmHg; 95% CI: −9.5, −0.5; Fig. 1B). Furthermore, there was a linear relationship between the change in fructose intake and the change in diastolic blood pressure (regression coefficient [beta]: 0.085 mmHg; 95% CI: 0.032, 0.138; Fig. 1C). Similar strengths of associations, albeit not statistically significant, were observed when the two groups were analyzed separately (beta: 0.100 mmHg; 95%CI: −0.010, 0.210 in the intervention group and beta: 0.106 mmHg; 95%CI: −0.057, 0.268 in the control group).

3.3. Effects of fructose restriction on endothelial function

Although a small decrease in sE-selectin levels was detected in the intervention group, the change from baseline was not statistically significant (−8.1 ng/ml; 95% CI: −17.0, 1.3). The change between groups was not statistically significant either (difference in the changes from baseline: 0.07 ng/ml; 95% CI: −13.1; 12.1; Fig. 2A). Furthermore, no statistically significant differences in the change in the RHI and percentage heat-induced skin hyperemia were observed between both groups (differences in the changes from baseline: −0.05%; 95% CI: −0.4, 0.3 and −25.6%; 95% CI: −357.8; 441.5, respectively; Fig. 2B-C), nor there was an effect on the composite endothelial dysfunction score (Fig. 2D). Finally, no statistically significant effects were found for the flowmotion measurements (Supplementary figure 4A-D).

3.4. Effects of dietary sodium on fructose-induced decrease in diastolic blood pressure

Both dietary sodium intake and 24 h urinary sodium excretion did not change within and between the groups (difference in the changes from baseline: 0.2 g/day; 95% CI: −1.4, 1.6 and −13 mmol/24 h; 95% CI: −56.7, 29.3, respectively; Fig. 3A-B). Of interest, when the primary analysis for diastolic blood pressure was repeated after stratification for dietary salt intake at baseline (cut-off: 6 g/day), the treatment effect in those consuming higher amounts of salt at baseline appeared to be greater and was statistically significant (difference in the changes from baseline: −9.0 mmHg; 95% CI: −14.5, −2.5), than those consuming lower amounts (difference in the changes from baseline: −0.8 mmHg; 95% CI: −8.0, 5.5). Formal testing did, however, not reveal a statistically significant interaction term (p = 0.12; Fig. 3C).

3.5. Sensitivity analyses

To explore the effect of the protocol amendment on the observed outcomes, in particular on diastolic blood pressure, we repeated the analyses after stratification for dietary fructose intake at baseline (cut-off 45 g/day). No statistical interaction was observed (p = 0.22; Supplementary Figure 5).

Finally, since baseline systolic blood pressure tended to be higher in the intervention group (Table 1), one-way ANCOVA was conducted with inclusion of this variable as a covariate. This did not affect the primary results, nor did inclusion of baseline diastolic blood pressure, use of antihypertensive medication or BMI affect the results for the change in diastolic blood pressure upon intervention (data not shown).

4. Discussion

This double-blind, randomized controlled trial shows that a 6-week fructose-restricted diet resulted in a statistically significant decrease in diastolic blood pressure in comparison to an isocaloric comparator in overweight individuals. Although systolic blood pressure decreased significantly in the intervention group as well, the change was not different between both groups. The intervention was not associated with a favorable change in endothelial function.

4.1. Comparison with previous studies

The current study provides more clarity in the ongoing debate on the role of fructose in the development of hypertension. Although animal studies and, to a lesser extent, acute feeding studies in humans have shown that fructose raises blood pressure [9], previous meta-analyses of controlled feeding trials (median follow-up: 4 weeks) and observational studies did not observe an effect of fructose on blood pressure [10,11].

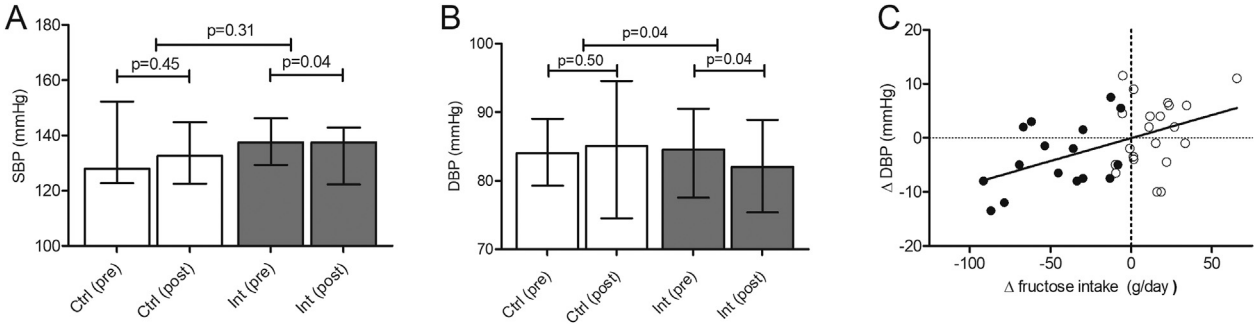

Fig. 1. Effects of fructose restriction on blood pressure. Median (± interquartile range) systolic blood pressure (SBP) (A) and diastolic blood pressure (DBP) (B), in the control group (Ctrl, white bars, n = 21) and intervention group (Int, grey bars, n = 16) at baseline (pre) and after completion of the study (post), and relationship between the change in fructose intake and the change in diastolic blood pressure in the control group (closed circles) and the intervention group (open circles) (C).

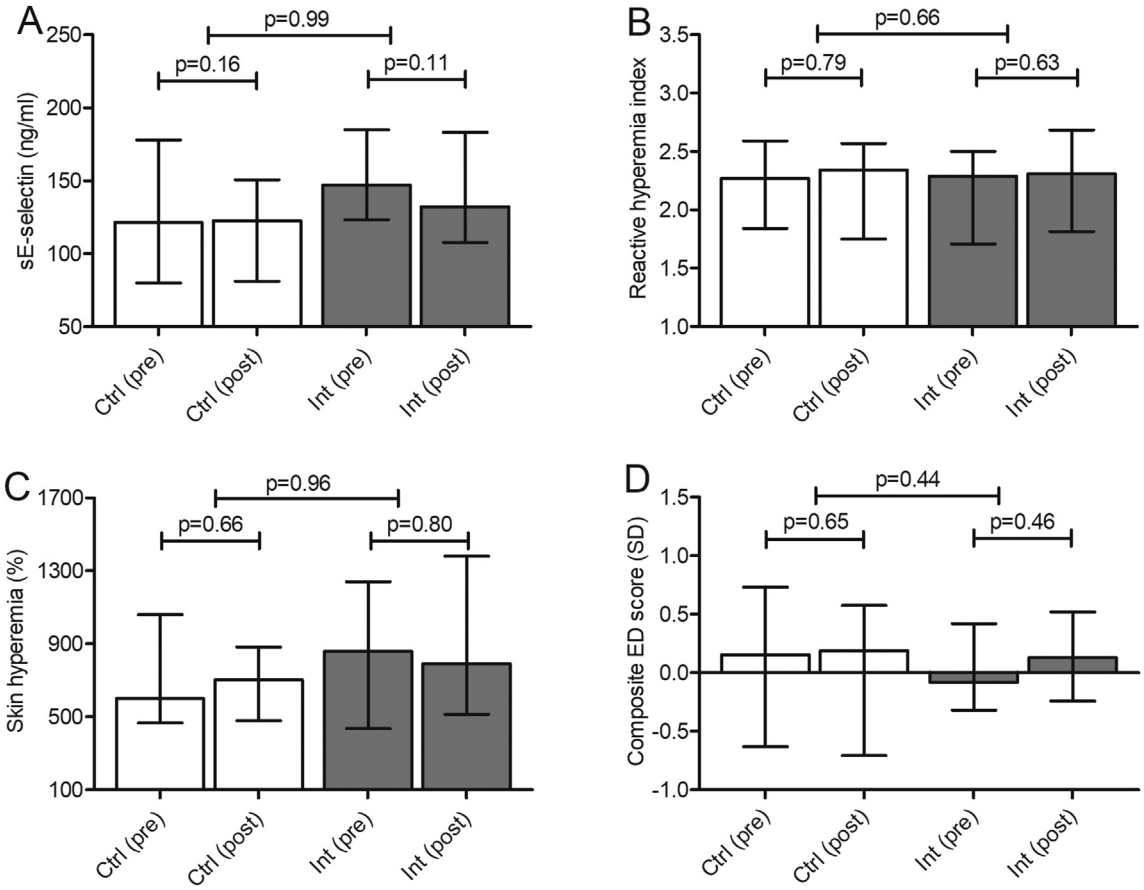

Fig. 2. Effects of fructose restriction on endothelial markers. sE-selectin (A), reactive hyperemia index (B), skin heat-induced hyperemia (C), and composite endothelial dysfunction (ED) score (D), in the control group (Ctrl, white bars, n = 21) and intervention group (Int, grey bars, n = 16) at baseline (pre) and after completion of the study (post). Data are expressed as median ± interquartile range.

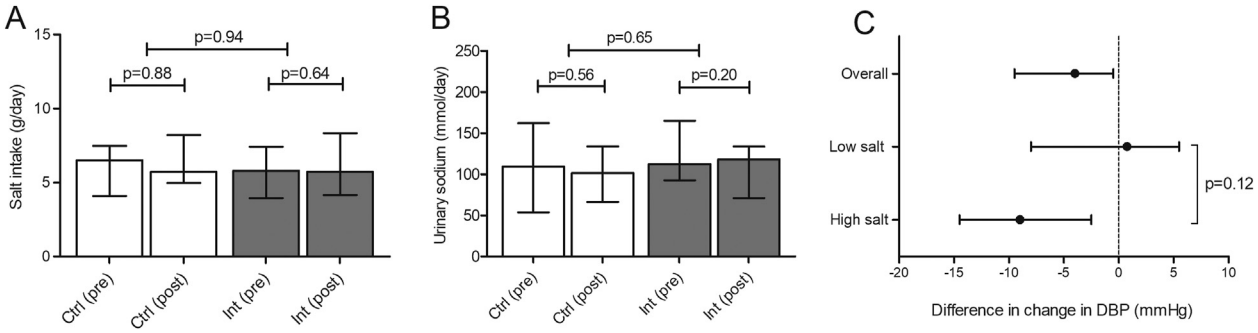

Fig. 3. Effects of dietary sodium on fructose-induced decrease in diastolic blood pressure. Salt intake (A) and urinary sodium concentration (B) in the control group (Ctrl, white bars, salt intake n = 21, urine sodium n = 19) and intervention group (Int, grey bars, salt intake n = 16, urine sodium n = 13) at baseline (pre) and after completion of the study (post), and subgroup analysis for the change in diastolic blood pressure (DBP) stratified by salt intake at baseline (cut-off 6: g/day) (C). Data are expressed as median ± interquartile range.

The present study, however, is unique by design, since the complete fructose-restricted diet combined with double-blind supplementation of either fructose or glucose allowed to examine the non-acute effects of fructose per se on blood pressure without the distorting effects of confounding factors, such as caloric intake or other lifestyle factors.

4.2. Putative mechanism by which fructose affects blood pressure

The mechanism by which fructose affects blood pressure in humans has remained unclear. Again, previous animal studies have provided several putative pathways, including fructose-mediated endothelial dysfunction [7]. In the present study, we were not able to translate these observations to humans. We used a panel of tests that assess endothelial function at different levels of the vascular bed, varying from small arteries to capillaries, but did not find any effect of fructose restriction.

An alternative pathway that has been revealed in animals is fructose-induced reabsorption of sodium in the proximal tubule mediated by the sodium–hydrogen exchanger 3, resulting in salt-sensitive hypertension [26]. Of interest, in the current study we observed a stronger effect of fructose restriction in individuals

consuming salt above the Dutch recommended intake of 6 g per day, although the interaction term failed to reach statistical significance. It should be noted that the number of individuals included in this study is probably too small for interaction analyses and, hence, further studies are warranted to address the effects of fructose on salt-sensitive hypertension in humans.

4.3. Clinical and societal implications

Notwithstanding the exact mechanism by which fructose affects blood pressure in humans, the current study shows that fructose restriction has a beneficial effect on diastolic blood pressure, which appeared to be dose-dependent *and* clinically relevant. Ten grams reduction in dietary fructose intake per day, corresponding with e.g. ~200 ml sugar sweetened beverage per day [27], was associated with ~1 mmHg decrease in diastolic blood pressure (Fig. 1C). Our findings, therefore, support current initiatives to reduce the intake of added sugars, e.g. by the reformulation of processed foods and the implementation of taxes on sugars, to improve population health [28–30].

4.4. Strengths and limitations

This study has several strengths and limitations. Strengths are, as aforementioned, the study design using an isocaloric comparator. Second, we used an objective, validated biomarker of fructose intake, i.e. urinary fructose levels [24], to demonstrate overall adherence. Finally, we used state-of-the-art markers of endothelial function. One of the major limitations of this study is that it was not primarily designed to assess the effects of fructose restriction on blood pressure and the role of the endothelium and salt intake herein. As a consequence, the inclusion criteria mainly focused on the a priori chance of high liver fat content at baseline, the primary outcome measure of the FRUITLESS study [16]. Second, automated blood pressure measurements were only conducted at the research ward, not in a 24-h ambulatory setting. Of note, as fructose is known to have acute effects on blood pressure [9], it is expected that the effects of fructose on 24-h ambulatory blood pressure would have been even more pronounced. Third, this study was not primarily powered for the current outcome measures. Given the high biological variability of endothelial function tests [31], it is anticipated that particularly this outcome measure is prone to type II statistical errors. We, therefore, also used a composite endothelial dysfunction score, which yielded similar results. Fourth, due to the relatively small number of participants, there is a risk of imbalanced randomization, which indeed appeared to be the case in this study, in particular for baseline BMI and systolic blood pressure (Table 1). We, therefore, performed additional sensitivity analyses to adjust for these baseline differences, which did not affect the primary outcomes. Fifth, discretionary salt intake, which has been estimated to account for 20% of the total salt intake in the Netherlands [32], was not assessed in the 3-day food journals and personal interviews, but is included in 24 h urinary sodium excretion. Finally, this study did not address the role of fructose in different food products, e.g. fruits and vegetables versus processed foods. This may be of importance, since there is evidence that the presence of other factors, such as vitamin C or flavonoids in fruits, can offset the detrimental effects of fructose [33,34] and, hence, could have mitigated the effects of fructose restriction per se on blood pressure in the current study.

5. Conclusions

This study shows that six-weeks fructose-restriction resulted in a statistically significant and clinically relevant decrease in diastolic blood pressure. Further studies are warranted to elucidate the underlying mechanisms, with special focus on the effects of fructose on salt-sensitive hypertension.

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on request.

Sources of funding

This study was supported by research grants from Nutricia Research Foundation (grant 2016-33) and the Netherlands Heart Foundation (grant 2015T042). The authors confirm independence from the sponsors; the content of the article has not been influenced by the sponsors. The authors have declared that no conflicts of interests exist.

Author contribution statement

L.E.F.J. conducted the analyses, researched the data, and wrote the manuscript. N.S. performed all the measurements. P.I.H.G. assisted N.S. during the measurements. M.C.G.J.B. and C.D.A.S. conceived the study, supervised the analyses, researched the data, reviewed the manuscript, and provided substantial revisions to the manuscript. A. J.H.M.H conducted the flowmotion/skin hyperemia response analyses, reviewed the manuscript, and provided substantial revisions to the manuscript.

M.D.G.E. performed the randomization procedure and preparation of the glucose/fructose supplementation. E.M.C.P. supervised the dietary counseling. E.J.M.F. and C.G.S. facilitated the measurements. All authors have read and approved the manuscript. M.C.G.J.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Declaration of competing interest

None.

Acknowledgements

We thank Petra M. Niessen (Department of Internal Medicine, Maastricht University Medical Center, Maastricht, The Netherlands) for their assistance during the execution of the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2022.07.009.

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