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Fructose restriction has beneficial effects on adipose tissue distribution but not on serum adipokine levels: Post-hoc analysis of a double-blind randomized controlled trial

Michelle A. J. van Oeteren[1,2] | Nynke Simons[1,2] | Pomme I. H. G. Simons[1,2] | Marjo P. H. van de Waarenburg[1,2] | M. Eline Kooi[2,3] | Edith J. M. Feskens[4] | E. M. C. (Liesbeth) van der Ploeg[5] | Mathias D. G. Van den Eynde[1,2] | Alfons J. H. M. Houben[1,2] | Casper G. Schalkwijk[1,2] | Martijn C. G. J. Brouwers[1,2,6]

[1]Laboratory for Metabolism and Vascular Medicine, Division of General Internal Medicine, Department of Internal Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

[2]Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, The Netherlands

[3]Department of Radiology and Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

[4]Division of Human Nutrition and Health, Wageningen University, Wageningen, The Netherlands

[5]Department of Dietetics, Maastricht University Medical Center, Maastricht, The Netherlands

[6]Division of Endocrinology and Metabolic Diseases, Department of Internal Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

Correspondence
Martijn C. G. J. Brouwers, Department of Internal Medicine, Division of Endocrinology and Metabolic Diseases, Maastricht University Medical Center, PO Box 5800, Maastricht 6202 AZ, The Netherlands.
Email: mcgj.brouwers@mumc.nl

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Summary

We aimed to examine the effects of isocaloric fructose restriction on adipose tissue distribution and serum adipokines. Individuals with BMI >28 kg/m^2 ($n = 44$) followed a 6-week fructose-restricted diet and were randomly allocated to (double-blind) oral supplementation with fructose (control) or glucose (intervention) powder three times daily. Visceral (VAT) and subcutaneous (SAT) adipose tissue was quantified with MRI. Serum interleukin 6 and 8, tumour necrosis factor alpha and adiponectin levels were measured with sandwich immunoassay. BMI decreased in both groups, but the change did not differ between groups (−0.1 kg/m^2, 95%CI: −0.3; 0.5). SAT decreased statistically significantly in the control group (−23.2 cm^3, 95%CI: −49.4; −4.1), but not in the intervention group. The change in SAT did not differ between groups (29.6 cm^3, 95%CI: −1.2; 61.8). No significant differences in VAT were observed within or between study arms. The VAT/SAT ratio decreased statistically significantly in the intervention group (−0.02, 95%CI: −0.04; −0.003) and the change was significantly different between groups (−0.03, 95%CI: −0.54; −0.003). Serum adipokine levels were not affected by the intervention. This study shows that a fructose-restricted diet resulted in a favourable change in adipose tissue distribution, but did

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not affect serum adipokines. Further studies are warranted to clarify the underlying mechanisms how fructose affects adipose tissue distribution.

KEYWORDS
adipokines, adipose tissue distribution, BMI, dietary intervention, fructose

What is already known about this subject?

- The high consumption of added sugars – including fructose – has paralleled the current obesity pandemic.
- Consumption of fructose-sweetened beverages in addition to an ad-libitum diet results in an increase in visceral fat mass.

What this study adds

- Isocaloric dietary fructose restriction results in a beneficial change in fat distribution, independent of BMI.
- Circulating adipokines are not altered after 6 weeks of dietary fructose restriction.

1 | INTRODUCTION

The high consumption of added sugars has paralleled the current obesity pandemic and its cardiometabolic sequelae.[1–3] Fructose and glucose are the principal added sugars. Despite serving as an energy substrate per se, there is an ongoing discussion on whether these two sugars exert differential effects on cardiometabolic factors.[4,5] For instance, a recent study has shown that fructose, more than glucose, stimulates de novo lipogenesis.[6]

Furthermore, Stanhope and colleagues have previously demonstrated that fructose- and glucose-sweetened beverages, provided alongside the usual diet, have differential effects on fat distribution, i.e. fructose causes a more pronounced increase in visceral adipose tissue deposition.[7] A recent meta-analysis showed that low-fructose diets improve BMI and waist circumference, along with beneficial effects on blood pressure, glucose regulation and serum triglycerides.[8] Whether the restriction of dietary fructose can also reverse visceral and subcutaneous adipose tissue volumes and, consequently, alter fat distribution and related adipokines, is unknown.[9–13]

We recently completed the 'Effects of fructose restriction on liver steatosis' (FRUITLESS) study, a double-blind, randomized controlled trial that investigated the effects of fructose versus glucose supplementation on a background of a fructose-restricted diet.[14] We found that isocaloric fructose restriction results in a decrease in intrahepatic lipid content and diastolic blood pressure.[14,15]

The aim of the current study was to examine the effects of isocaloric fructose restriction on fat distribution and circulating adipokines.

2 | METHODS

2.1 | Study population

This study is a post-hoc analysis of the FRUITLESS study, a double-blind randomized controlled trial. Details and the main results of the FRUITLESS study have recently been published elsewhere.[14,15] In short, adult participants were enrolled if they were at risk for increased intrahepatic lipid content (BMI ≥28 kg/m^2 and a fatty liver index of ≥60) and had a daily fructose intake above the Dutch average (i.e. >45 g/day).[16] The latter criterion was later abandoned due to slow recruitment. Participants were excluded in case of history of liver disease, history of excessive alcohol consumption, use of glucose-lowering medication, unstable weight (>5% change) 3 months prior to start of study, change in physical activity 3 months prior to start of study, recent illness, pregnancy and/or lactation, contraindications for MRI and inability to provide written informed consent. Forty-four participants were randomly assigned to the control group or the intervention group in a 1:1 ratio using block sizes of 4. Randomization was performed by an independent researcher. Moreover, the glucose and fructose powder were indistinguishable in terms of appearance and odour, and were prepacked in identical sachets by and independent researcher. Participants and assessors remained blinded to the allocation sequence upon completion of analyses. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the medical ethical committee of Maastricht University Medical Center (NL58360.068.16). Written informed consent was obtained from all subjects. The study was registered at ClinicalTrials.gov (NCT03067428).

2.2 | Intervention

All participants were asked to adhere to a 6-week fructose-restricted diet (i.e. fructose intake <7.5 g/meal and <10 g/day). The control group received fructose supplementation that equalled baseline fructose intake, i.e. the amount of fructose restricted from the diet. The intervention group received isoenergetic glucose supplementation. As such, the effects of isocaloric fructose restriction, without potential effects of other nutrients or differences in energy intake, could be

studied. Fructose and glucose powder for supplementation were identical in odour and colour and were distributed by an independent researcher.

To ensure sufficient power to discriminate between fructose intake of the control and intervention group, glucose and fructose supplementation in participants with a habitual fructose consumption of <45 g/day was set at 45 g/day. For example, if the habitual total fructose, i.e. free fructose and fructose from sucrose, intake was 10 g/day, the participant was supplemented with 45 g of either fructose or glucose. Participants received dietary guidance and information on how to use the food journal from one researcher (NSi) and were asked to record consumed foods and respective quantities. Dietary intake was assessed based on the 3-day food journal (2 week days and 1 weekend day) and ambiguities were clarified in personal interviews. Dietary fructose intake, energy content and micro/macronutrient composition were calculated using the Dutch food composition table.[17] The intra-individual coefficient of variation (CV) of daily fructose intake (based on 3-day food journal at baseline) was 42%. The inter-individual CV was 67%. Participants were asked to maintain their regular daily activity.

2.3 | Adipose tissue distribution

Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) volumes were quantified with MRI at baseline (T0) and at completion (T6). Measurements were performed on a 3 Tesla magnetic resonance (MR) scanner (Achieva 3 T-X, Philips Healthcare, Best, The Netherlands) with a 16-element torso coil (XL Torso Coil, Philips Healthcare). Five participants affected by morbid obesity were scanned on a wide-bore 1.5 Tesla MR scanner (Ingenia, Philips Healthcare). At the top of the L5 vertebral body, ten 5 mm thick transverse T1-weighted MR images with a slice gap of 10 mm were acquired. Scan parameters were as follows: field of view, 400 × 322 mm; acquired voxel size, 1.30 × 1.96 × 5.00 mm; reconstructed voxel size, 0.78 × 0.78 × 5.00 mm; repetition time/echo time, 400/10 ms; number of signal averages, 1; turbo spin echo factor, 4. The 3D image segmentation tool of the ITK-SNAP software application (http://www.itksnap.org) was used to calculate visceral and subcutaneous adipose tissue volumes.[18] For this purpose, three T1-weighted MR images caudal to the umbilicus were analysed. Using the 3D segmentation tool, the threshold was adjusted to optimize the separation between adipose and other tissue. Next, the cursor was placed at various locations within the visceral and subcutaneous adipose tissue. The bubble radius was adjusted to maximize the selection of adipose tissue while avoiding the inclusion of other tissues. The segmentation of adipose tissue was manually adjusted, if needed. The total volume of adipose tissue was calculated by multiplying the voxel count by the voxel volume of selected regions. Subsequently, VAT was manually excluded from the segmented regions, allowing for the calculation of SAT using the same calculation. VAT volume was then derived by subtracting SAT volume from total adipose tissue volume. We calculated the mean VAT and SAT volume based on these three image slices.

2.4 | Serum adipokines

Venous blood was drawn at T0 and T6 after an at least 8 h fast and 3 days abstinence from alcohol. Serum was stored at −80°C. Interleukin-6 (IL-6), interleukin-8 (IL-8), tumour necrosis factor-alpha (TNF-α) and adiponectin were measured with commercially available sandwich immunoassay kits (V-Plex Human Proinflammatory Panel II, #K15053D, Meso Scale Diagnostics LCC, Rockville, MD) and (U-Plex Human Adiponectin Assay, #K151BXC, Meso Scale Diagnostics LCC, Rockville, MD). The intra-assay CV for these assays was 7.8% for IL-6, 5.2% for IL-8, 6.0% for TNF-α and 2.7% for adiponectin.

2.5 | Other measurements

Height, weight, hip and waist circumference were measured at T0 and T6, as described previously.[14] Participants filled in a questionnaire regarding weekly alcohol consumption and smoking habits. Blood was drawn to determine serum insulin and plasma glucose.[14] Insulin resistance was estimated with the homeostasis model assessment of insulin resistance (HOMA2-IR) calculator (http://www.dtu.ox.ac.uk).[14]

2.6 | Statistical analyses

Sample size calculation was based on the primary outcome measure of the FRUITLESS study, i.e. intrahepatic lipid content.[14] To account for a 15% dropout rate, it was calculated that 22 participants per study arm were required ($\alpha = 0.05$, $\beta = 0.2$). Thirty-seven participants were included in the final analyses, 21 participants in the control group and 16 participants in the intervention group. Dropout was not related to the study procedure (Figure S1).

Dichotomous data are presented as frequencies. Continuous data are presented as median with interquartile range (IQR). Wilcoxon's Signed Rank test was used to analyse changes from baseline within groups. Differences between the control and intervention group were analysed with Mann–Whitney *U* test.

Sensitivity analyses were performed to (1) assess the effect of any unbalanced randomization on the main outcome measure of this study (i.e. adipose tissue distribution). For this, one-way ANCOVA was conducted with the unbalanced variable as a covariate and (2) evaluate the impact of the protocol amendment (i.e. abolition of the inclusion criterion 'baseline dietary fructose intake ≥45 g/day') on the primary outcome measure by analysing the interaction term (intervention [yes/no] * baseline dietary fructose ≥45 g/day [yes/no]) in a one-way ANCOVA. The main outcome measures were log-transformed for ANCOVA analyses. *P*-values <0.05 were considered statistically significant. Data were analysed with IBM SPSS Statistics v27 for Windows (SPSS Inc. Chicago, IL).

3 | RESULTS

3.1 | Adherence to the intervention

Baseline characteristics of the study participants are presented in Table 1. In both groups, the fructose-restricted diet resulted in a substantial decrease in median dietary fructose intake (from 36.9 to 2.2 g/day and from 42.1 to 1.4 g/day in the control and intervention group, respectively), which did not differ between the groups (difference between change from baseline [intervention versus control]: −6.7 g/d; 95%CI: −24.0; 13.0) (Figure S2A). The median amount of fructose supplementation in the control group (45 g/day [45.0–56.2]) was not different from the amount of glucose supplementation in the intervention group (50 g/day [46.0–70.8]) ($p = 0.40$) (Figure S2B). There was no statistically significant difference in total energy intake in both groups (−14 kcal/day, 95%CI: −236; 199, and −113 kcal/day, 95%CI: −395; 177, in the control and intervention group, respectively), nor a difference between groups (difference between change from baseline [intervention versus control]: −93 kcal/day, 95%CI: −480; 274) (Figure S2C).

As published previously,[14] HOMA2-IR did not differ in the intervention group (change from baseline 0.12, 95%CI: −0.17; 0.51), nor in the control group (change from baseline 0.06, 95%CI: −0.13;0.19). Moreover, there was no difference between groups (difference between change from baseline [intervention versus control]: 0.10, 95%CI: −0.21; 0.42).

3.2 | Effects of fructose restriction on adipose tissue distribution

BMI decreased in both groups upon intervention (change from baseline −0.4 kg/m^2, 95%CI: −0.6; −0.1 and −0.2 kg/m^2, 95%CI: −0.5; 0.03, in the control and intervention group, respectively), but the decrease was not significantly different between both groups (difference between change from baseline [intervention versus control]: −0.1 kg/m^2, 95%CI: −0.3; 0.5; Table 2, Figure S3). Hip and waist circumference did not statistically significantly change in the control group (change from baseline −1.1 cm, 95%CI: −4.6; 1.6, and: −1.5 cm, 95%CI: −3.9; 1.4, for hip and waist, respectively), nor in the intervention group (change from baseline −3.8 cm, 95%CI: −6.4; 0.1, and −0.1 cm, 95%CI: −2.5; 2.0, for hip and waist, respectively). Moreover, there was no difference between groups (difference between change from baseline [intervention versus control]: −2.5 cm, 95%CI: −6.0; 3.5, and 1.5 cm, 95%CI: −2.5; 4.5, for hip and waist, respectively).

SAT volume could not be quantified because of imaging artefacts in three and two participants in the control and intervention group, respectively. SAT volume decreased statistically significantly in the control group (change from baseline −23.2 cm^3, 95%CI: −49.4; −4.1), but not in the intervention group (4.2 cm^3, 95%CI: −16.7; 31.3) (Figure 1A). The change between groups was, however, not statistically significantly different (difference between change from baseline [intervention versus control]: 29.6 cm^3, 95%CI: −1.2; 61.8) (Table 2). VAT volume decreased non-statistically significantly in the

TABLE 1 Baseline characteristics of the study population.

	Control group ($n = 21$)		Intervention group ($n = 16$)	
	Median	IQR	Median	IQR
Age (years)	52	[38–62]	55	[35–62]
Sex (male/female)	6/15		6/10	
Smoking (*n*, %yes)	3, 14.3%		2, 12.5%	
Alcohol consumption (units/week)	3	[0–5]	2	[0–5]
Dietary fructose intake (g/day)	36.9	[27.1–54.6]	42.1	[20.3–73.4]
BMI (kg/m^2)	31.1	[30.2–35.6]	34.1	[28.8–37.3]
HOMA2-IR	0.86	[0.73–1.14]	0.84	[0.50–1.37]
Waist circumference (cm)	110.0	[104.3–113.6]	117.9	[106.5–128.4]
Hip circumference (cm)	112.0	[104.1–113.6]	108.0	[103.8–116.4]
Visceral adipose tissue (cm^3)	188	[144–247]	193	[168–250]
Subcutaneous adipose tissue (cm^3)	658	[429–844]	681	[468–855]
VAT/SAT ratio	0.3	[0.2–0.4]	0.3	[0.2–0.4]
Interleukin-6 (pg/mL)	0.66	[0.51–1.16]	0.70	[0.48–1.00]
Interleukin-8 (pg/mL)	9.75	[7.10–12.20]	9.30	[5.93–10.98]
Tumour necrosis factor α (pg/mL)	1.27	[1.03–1.55]	1.25	[1.02–1.46]
Adiponectin (μg/mL)	10.55	[8.75–12.13]	11.5	[7.90–16.75]

Abbreviations: BMI, body mass index; HOMA2-IR, homeostasis model assessment of insulin resistance; IQR, interquartile range; VAT/SAT ratio, ratio between visceral adipose tissue and subcutaneous adipose tissue.

TABLE 2 Effect of isocaloric fructose restriction on anthropometric outcomes.

	Control group ($n = 21$)		Intervention group ($n = 16$)			
	Treatment effect	95%CI	Treatment effect	95% CI	Difference	95%CI
BMI (kg/m^2)	−0.4	−0.6; −0.1	−0.2	−0.5; 0.03	−0.1	−0.3; 0.5
Visceral adipose tissue (cm^3)	−1.5	−11.0; 7.3	−9.7	−19.6; 5.0	−8.1	−20.8; 7.4
Subcutaneous adipose tissue (cm^3)	−23.3	−49.4; −4.1	4.2	−16.7; 31.3	29.6	−1.2; 61.8
VAT/SAT ratio	0.01	−0.01; 0.03	−0.02	−0.04; −0.003	−0.03	−0.54; −0.003

Abbreviations: BMI, body mass index; 95%CI, 95% confidence interval; VAT/SAT ratio, ratio between visceral adipose tissue and subcutaneous adipose tissue.

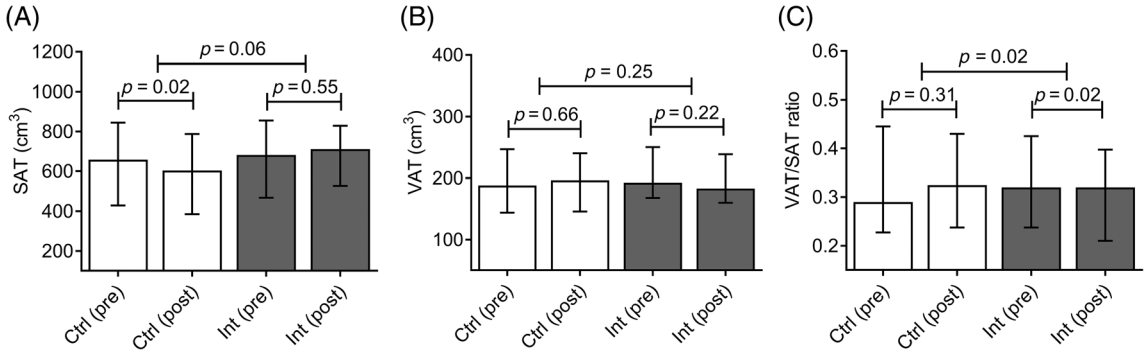

FIGURE 1 SAT (A), VAT (B) and VAT/SAT ratio (C) in Ctrl (white bars) and Int (grey bars) at baseline (pre) and end of study (post). Data are expressed as median ± IQR. Differences within groups are analysed with Wilcoxon's signed rank test; differences between groups are analysed with Mann–Whitney *U* test. Ctrl, control group; Int, intervention group; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; VAT/SAT ratio, ratio between visceral adipose tissue and subcutaneous adipose tissue.

intervention group (change from baseline: −9.7 cm^3, 95%CI: −19.6; 5.0) (Figure 1B). The change between groups was not statistically significantly different (difference between change from baseline [intervention versus control]: −8.1 cm^3, 95%CI: −20.8; 7.4) (Table 2). The VAT/SAT ratio decreased statistically significantly in the intervention group (change from baseline −0.02, 95%CI: −0.04; −0.003), but not in the control group (change from baseline 0.01, 95%CI: −0.01; 0.03) (Table 2, Figure 1C; individual data are shown in Figure S4). Furthermore, the change in VAT/SAT ratio was statistically significantly different between both groups (difference between change from baseline [intervention versus control]: −0.03, 95%CI: −0.54; −0.003) (Table 2).

3.3 | Effects of fructose restriction on serum adipokines

Serum adipokines could not be determined in two participants in the control group because of missing samples. Adipokines did not change statistically significantly in the control group (IL-6: change from baseline −0.03 pg/mL, 95%CI: −0.15; 0.09; IL-8: change from baseline 0.13 pg/mL, 95%CI: −1.30; 2.00; TNF- α: change from baseline 0.03 pg/mL, 95%CI: −0.07; 0.13 and adiponectin: change from baseline 0.30 μg/mL, 95%CI: −0.50; 1.30) (Figure 2A–D), nor did they change statistically significantly in the intervention group (IL-6: change from baseline 0.05 pg/mL, 95%CI: −0.15; 0.31; IL-8: change from baseline 0.45 pg/mL, 95%CI: −0.85; 1.70; TNF-α: change from baseline −0.10 pg/mL, 95%CI: −0.11; 0.18; and adiponectin: change from baseline 0.45 μg/mL, 95%CI: −0.75; 1.70) (Table 3). Furthermore, no statistically significant differences were observed between both groups (difference between change from baseline [intervention versus control] for IL-6: 0.05 pg/mL, 95%CI: −0.15; 0.37; IL-8: 0.20 pg/mL, 95%CI: −1.60; 2.10; TNF-α: −0.04 pg/mL, 95%CI: −0.19; 0.16 and adiponectin: 0.05 μg/mL, 95%CI: −1.40; 1.40).

3.4 | Sensitivity analyses

Stratification for baseline dietary fructose intake (cut-off 45 g/day) did not result in statistically significant interactions (VAT: $p = 0.77$, SAT: $p = 0.28$, VAT/SAT ratio: $p = 0.55$) (Figure S5). Moreover, one-way ANCOVA with baseline BMI, dietary fructose intake, SAT volume and VAT volume as a covariate did not affect the (log-transformed) primary outcome (Table S1).

4 | DISCUSSION

In this 6-week double-blind randomized controlled trial, we showed that dietary fructose restriction results in a statistically significant reduction of the VAT/SAT ratio in comparison to an isoenergetic

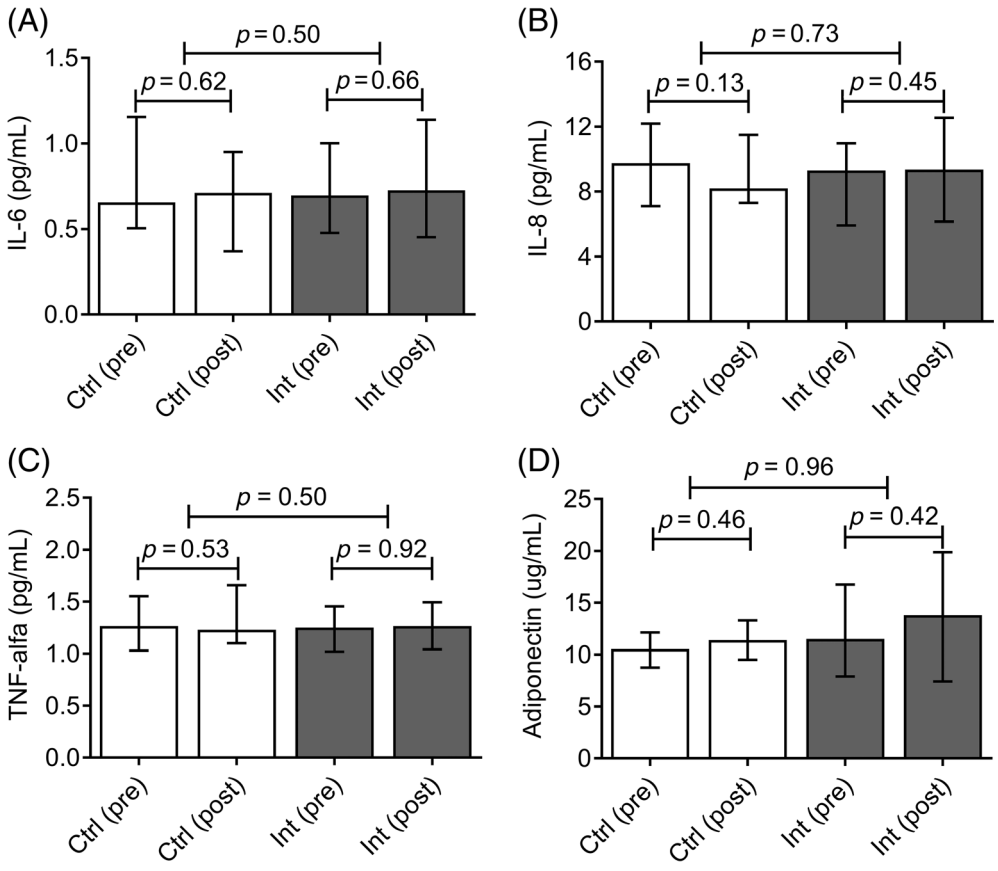

FIGURE 2 IL-6 (A), IL-8 (B), TNF-α (C) and adiponectin (D) in Ctrl (white bars) and Int (grey bars) at baseline (pre) and end of study (post). Data are expressed as median ± IQR. Differences within groups are analysed with Wilcoxon's signed rank test; differences between groups are analysed with Mann–Whitney *U* test. Ctrl, control group; Int, intervention group; IL-6, interleukin-6; IL-8, interleukin-8; TNF-α, tumour necrosis factor alpha.

TABLE 3 Effect of isocaloric fructose restriction on serum adipokines.

	Control group ($n = 19$)		Intervention group ($n = 16$)			
	Treatment effect	95%CI	Treatment effect	95% CI	Difference	95%CI
Interleukin-6 (pg/mL)	−0.03	−0.15; 0.09	0.05	−0.15; 0.31	0.05	−0.15; 0.37
Interleukin-8 (pg/mL)	0.13	−1.30; 2.00	0.45	−0.85; 1.70	0.20	−1.60; 2.10
Tumour necrosis factor α (pg/mL)	0.03	−0.07; 0.13	−0.10	−0.11; 0.18	−0.04	−0.19; 0.16
Adiponectin (μg/mL)	0.30	−0.50; 1.30	0.45	−0.75; 1.70	0.05	−1.40; 1.40

Abbreviation: 95%CI, 95% confidence interval.

comparator, i.e. glucose, in individuals with a BMI ≥28 kg/m^2. No statistically significant effects were observed for the circulating adipokines IL-6, IL-8, TNF-α and adiponectin.

Our findings are in line with the results from Stanhope and colleagues, who showed that the consumption of fructose-sweetened beverages resulted in an increased VAT volume.[7] Of interest, no differences in the change in BMI were observed between both groups in Stanhope's and our study, suggesting that fructose truly alters fat distribution. Previous studies have shown that visceral fat mass is allometrically related to total fat mass, i.e. any change in visceral fat mass – induced by either bariatric surgery, energy restriction or exercise – is explained by a change in total fat mass.[19] This does not appear to apply for fructose.

Several mechanisms have been proposed for the fructose-mediated change in fat distribution, including fructose-mediated secretion of very low-density lipoprotein particles and glucocorticoid activation.[20,21] Of interest, a recent population-based study showed that carriers of a common, functional variant in the gene encoding ketohexokinase (KHK), which catalyses the phosphorylation of fructose as the first step in fructose breakdown,[22] is associated with a lower VAT volume, but not with BMI.[23] These findings support the effects of fructose on fat distribution and suggest that fructose 1-phophate, or its downstream metabolites, are involved in fructose-mediated change in fat distribution.

In this post-hoc analysis of the FRUITLESS trial, no statistically significant differences were observed in circulating adipokines IL-6, IL-8, TNF-α and adiponectin. Adiponectin is of particular interest, because of its beneficial effects on insulin sensitivity and fatty acid oxidation.[24] Serum adiponectin levels have been shown to be inversely associated with VAT and intrahepatic lipid content.[25–27] In FRUITLESS, we

previously reported a reduction in intrahepatic lipid content upon isocaloric fructose restriction.[14] A previous epidemiological study reported an inverse relationship between the intake of fructose from sugar-sweetened beverages and fruit juice and serum adiponectin levels.[28] Furthermore, pharmacological inhibition of KHK resulted in an increase in adiponectin levels in humans.[29] It might be that the effect of a six-week intervention on adipose tissue volume was too small to detect statistically significant differences in circulating adiponectin (and other adipokines) in the current study.

Numerous studies have shown that visceral adiposity is a risk factor for cardiometabolic disease.[30] The current findings – together with the previously reported beneficial effects of fructose restriction on intrahepatic lipid accumulation and blood pressure[14,15] – support current societal initiatives, such as the implementation of a levy on sugar-sweetened beverages, to reduce the intake of fructose at the population level. Although the currently observed effects on VAT/SAT ratio were relatively small, which might be due to a relatively short follow-up period, it should be noted that small effects at the individual level could transform to relevant effects at the population level, the so-called prevention paradox.[31]

This study has several strengths and limitations. First, by the implementation of a fructose-restricted diet in both study arms and (double blind) supplementation of an isoenergetic comparator, the FRUITLESS study allowed to assess the effects of isocaloric fructose restriction. Second, we were able to quantify adipose tissue volume with multi-slice MRI, which is considered the gold standard.[32] The FRUITLESS study was, however, primarily designed and powered to study the effects of fructose restriction on intrahepatic lipid content. It can, therefore, not be excluded that type II errors may have occurred. We deliberately opted for a parallel design, even though a cross-over design has advantages, such as reducing variability. On the other hand, a cross-over design requires that all participants complete both six-week treatment arms, which we deemed too demanding as the diet is without all fructose containing food products, including fruits and vegetables. Furthermore, although we intended to provide isocaloric supplementation, BMI decreased in both study groups and caloric intake tended to be lower in the intervention group. Finally, some baseline characteristics such as BMI appeared to differ between both groups due to chance. To study the effects of any unbalanced randomization, we conducted additional sensitivity analyses, which did not appear to affect the outcomes.

In conclusion, we showed that a 6-week fructose restricted diet results in a statistically significant decrease in the VAT/SAT ratio, but not in serum adipokines. These findings support further studies to clarify the underlying mechanisms and societal measures to reduce the intake of fructose at the population level.

AUTHOR CONTRIBUTIONS

M.A.J.v.O. performed the laboratory measurements, conducted the analyses, researched the data, and wrote the manuscript. N.S. conceived the study and performed all the measurements. P.I.H.G. assisted N.S. during the measurements. M.P.H.v.d.W. performed the laboratory measurements. M.C.G.J.B. conceived the study, supervised the analyses, researched the data, reviewed the manuscript, and provided substantial revisions to the manuscript. M.D.G.V. d.E. performed the randomization procedure and preparation of the glucose/fructose supplementation. E.M.C.v.d.P. supervised the dietary counselling. 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.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

ORCID

Michelle A. J. van Oeteren https://orcid.org/0009-0000-2572-5305

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