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ARTICLE

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NAFLD-related SNPs are linked to changes in liver fat, measured by CAP score, and serum lipids in response to a 3-week sugar sweetened beverage intervention: A pilot study

Faustina Therase Jeyaraj,[1*] Sai Sravani Vennam,[1*] Kendra Nelson,[1] Katherine Watts,[2] Lydia R. Goss,[1] Brea C. Nance, [3]Baba B. Mass,[1] Venkata Saroja Voruganti[1,4]

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[1] Nutrition Research Institute, University of North Carolina at Chapel Hill, Kannapolis, NC
[2] University of North Carolina at Charlotte, Charlotte, NC
[3] Standard Process Inc., Kannapolis, NC
[4] Department of Nutrition, University of North Carolina at Chapel Hill, Kannapolis, NC
† *Both authors contributed equally to the work

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ABSTRACT

Studies show that increased consumption of sugar sweetened beverage (SSB) is linked to non-alcoholic fatty liver disease (NAFLD), a condition characterized by excess fat accumulation in hepatocytes. Genetic factors also influence NAFLD. We conducted a clinical trial (NCT03783195) to determine if SNPs related to NAFLD are associated with liver fat content and its changes in response to a 3-week SSB intervention in Caucasian adolescents and young adults. Fifteen participants (Males-5, Females–10, mean age 25.5 ± 9 yrs) consumed a beverage, daily for 3 weeks, consisting of fructose:glucose in 60:40 ratio. Liver fat content was measured by transient elastography through controlled attenuation parameter (CAP) score. At baseline, the CAP score was 212.5±10.1dB/m and was not significantly different between sexes. We genotyped ten NAFLD-related SNPs, of which rs1227756 in *COL13A1* (β=-22.4±7.5, $p<0.05$) was associated with baseline CAP score. Individuals carrying AA alleles had significantly higher CAP score than those carrying GG (234±34.7dB/m vs. 188 ± 25.3 dB/m). The CAP score decreased post SSB intervention, and the change was significantly associated with rs2228603 in *NCAN* (β=-20.1± 7.6, $p< 0.05$). The T allele carriers showed a greater reduction in CAP score as compared to CC carriers (Mean ± SE -23.3 ± 5.8 dB/m vs. -18.24 ± 43.2 dB/m). This change was, however, not observed when adjusted for age, sex and body composition. Significant associations were also observed between serum HDL and rs1260326 in *GCKR* and triglycerides and rs58542926 in *TMS6F2*. This pilot study shows a potential role for genetics in liver fat changes in response to SSB intervention that warrants a detailed investigation in a larger sample for a longer duration.

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INTRODUCTION

Non-communicable diseases like cancer, obesity, diabetes, cardiovascular diseases (CVD) and non-alcoholic fatty liver disease (NAFLD), have become a significant public health concern(1–7). NAFLD, representing a group of disorders including steatosis(2,8) and non-alcoholic steatohepatitis with fibrosis(9,10), has substantially risen in prevalence over the last two decades with the estimated prevalence being 20% among US adults and 25% in young adults(11–13). Over 64 million individuals are believed to have NAFLD with annual medical costs rising to more than $100 billion(14–16). NAFLD is more commonly observed in individuals who have obesity or diabetes and/or have metabolic syndrome, and has been associated with increased cirrhosis, liver-related mortality and hepatocellular carcinoma(17–19).

Unhealthy diet plays a major role in the development of NAFLD(20–22). Fructose, contained in soft drinks, fruit juices and energy drinks, affects many metabolic processes, foremost being an increase in fat accumulation in the liver(23–25) and contributing to the onset and progression of NAFLD(26–29). Fructose is almost entirely metabolized in liver and is rapidly phosphorylated to fructose 1 phosphate by ketohexokinase (KHK) with ATP depletion in parallel(30,31). The fructose 1-phosphate gets metabolized to dihydroxyacetone-phosphate and glyceraldehyde and finally to triglycerides[3-5] which get deposited in liver and leads to NAFLD(29,30,32–34). Although both glucose and fructose affect fat accumulation in the liver, fructose seems to be the more potent stimulator of *de novo* lipogenesis (DNL) than glucose(23,35,36). In population studies, it has been shown that fructose, and not glucose, is associated with increased visceral adiposity(37–40), insulin resistance(26,37,39,40) and hyperuricemia(41–43). Fructose is unique in its effects that it stimulates KHK and thus potentiates its own metabolism. Second, the rate of phosphorylation of fructose by KHK is 10 times higher than the phosphorylation of glucose by glucokinase(44,45). Third, fructose is directly absorbed into portal vein and delivered to the liver without entering the systemic circulation(30,44). Because of this pass through the liver, it is exposed to a much higher fructose load than other tissues. Fourth, fructose activates the lipogenic transcriptional factors, SREBP1c(46–48) and ChREBP(49–51) in the liver, promoting DNL. Finally, fructose tends to deplete liver ATP levels and one of the outcomes is generation of more AMP which get converted to uric acid(23,30,31). Uric acid has been shown to stimulate fat synthesis in the hepatocyte thus pointing to an additional pathway through which fructose can increase liver fat content(30,31).

In addition to diet, genetic factors contribute to the onset and progression of NAFLD(52,53). NAFLD is a complex and heritable phenotype. Family-based studies have reported heritability estimates for NAFLD to be between 20% and 70%(54–57) and genome-wide and candidate gene studies have identified several genes associated with NAFLD(58,59). Few studies have shown that fructose affects lipogenesis in liver in a genotype-specific manner. Davis and colleagues found that Hispanic children with GG genotypes of *PNPLA3* SNP rs738409 were more inclined to accumulate fat in the liver as compared to children with CC or CG genotypes(58). Similarly, another study investigating the effects of

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added sugars on liver fat found that individuals with TT of rs1260326 of *GCKR* increased their *de novo* lipogenesis by 44% during an oral fructose + glucose challenge(59). The aim of our study was to determine the role of key NAFLD-related single nucleotide polymorphisms (SNPs) in liver fat response to a 3-week sugar-sweetened beverage (SSB) intake in adolescents and young adults.

EXPERIMENTAL

Study design

This pilot open label trial was conducted at the University of North Carolina at Chapel Hill Nutrition Research Institute's (UNC-NRI). The review protocol is available at Clinical Trials.gov (# NCT03783195). A total of 72 participants aged 12 to 40 were screened. Inclusion criteria included ages between 12-40 years, no history of alcohol abuse (>7 drinks per week for a year), history of fructose intake of < 14 drinks per week and Caucasian ethnicity. Both ethnicity and race affect the deposition of fat in the liver(60). Studies have shown that the tendency to accumulate fat in the liver is higher in Asians and Hispanics as compared to While or Black Americans(61). To avoid differences in liver fat content changes that may be due to ethnic differences, we focused only on one ethnic group (Caucasians) in this pilot study. The exclusion criteria included ages < 12 and > 40 years, pregnant/lactating, known alcohol abuse or fructose intake > 14 drinks per week, not of Caucasian ethnicity, glucose levels > 100 mg/dl if fasting, > 140mg/dl if within 2 hours post meal and > 200 mg/dl if random sample, taking anti-hypertensive, anti-diabetic, uric acid and/or lipid-lowering medications, known diagnosis of diabetes, fructose intolerance, chronic kidney disease, NAFLD or any liver-related disease, hypertriglyceridemia, polycystic ovary syndrome, hypothyroidism, obstructive sleep apnea, hypopituitarism and hypogonadism, and liver fat fraction >5% as per baseline MRI scan. We excluded 54 participants after screening for being in the exclusion criteria, 2 participants dropped out due to taste issues, and 1 participant was excluded after baseline liver MRI scan due to their liver fat fraction being greater than 5%. The mean ages and BMI for the three participants who dropped out after visit 1 were 30 years and 27.5 kg/m^2, respectively. All participants gave written informed consent to the study and its procedures. The study was approved by the Institutional Review Board of the University of North Carolina at Chapel Hill (IRB # 17-3348).

15 participants completed the 3-week study. The study was divided into two visits. Both visits, spaced three weeks apart, followed the same procedure (**Figure 1**). Visit 1 and 2: Following a 12-hour overnight fast, participants arrived at UNC-NRI. They were given a standardized meal for dinner for the previous night and were asked to refrain from drinking. The participants collected their 24-hr urine the day prior to their visit and returned the samples at their visit. After signing the consent form, the participants had their anthropometrics measured. The weight measures of the subjects were taken standing while wearing shoes and light clothing. A stadiometer against the wall was used to measure height, in an upright standing position, to the closest 0.1cm. Their body mass index (BMI kg/m2) was calculated using the height and weight values. A stretch-resistant tape close to the umbilical region was

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measured for waist circumference (WC) to the nearest 0.1 inch. Bioelectric impedance analysis (BIA) using Tanita Dual Frequency Total Body Composition Analyzer (DC-430U, Tokyo, Japan) was used to record every subject's body composition. All anthropometric measurements were taken by the same staff member to minimize measurement variation and margin of error. Omron digital blood pressure monitor (HEM907XL, Omron Healthcare Inc., Lake Forest, IL, USA) was used on the right arm of the subjects to measure blood pressure. Two measurements of BP were taken with an interval of 1 min; the average was calculated and used in the statistical analysis. A detailed questionnaire on medical and dietary data was administered to the participants on the day of the visit. Participants were then provided individually packaged packets of powder containing 0.75g/kg body weight of fructose + 0.45g/kg body weight of glucose which approximates to the 60:40 ratio found in regular sodas(62). Participants were instructed to consume the packets of fructose dissolved in 24 oz of water and consume the drink daily for the three-week intervention period. They were also instructed to not consume any other SSBs during the 3-week period. All participants brought back empty packets for compliance checking.

Table 1: SNPs selected for genotyping

SNP	Gene	Risk allele	SNP position	Allele frequency in general population (ensembl)	Allele frequency in our study sample
rs12137855	*LYPLAL1*: Intergenic variant	C	1: 219275036	0.84	0.79
rs1227756	*COL13A1*: Intron variant	G	10: 69828748	0.61	0.43
rs738409	*PNPLA3*: Missense Variant	G	22: 43928847	0.26	0.27
rs887304	*EFCAB4B* : 3' UTR variant	T	12: 3648382	0.14	0.39
rs1260326	*GCKR* : Missense variant	T	2: 27508073	0.29	0.43
rs2854116	*APOC3* : Regulatory region variant	C	11: 116829453	0.55	0.47
rs2645424	*FDFT1* : Intron Variant	A	8: 11826954	0.52	0.30
rs58542926	*TMS6F2*: Stop gained Variant	C	19: 19268740	0.93	0.77
rs2228603	*NCAN* : Missense Variant	T	19: 19219115	0.04	0.13
rs4240624	*PPP1R3B* :Intron Variant	A	8: 9326721	0.89	0.87

SNP selection for genotyping

Ten single nucleotide polymorphisms (SNPs) were selected for genotyping based on their association with NAFLD or liver fat from previous published studies: rs12137855 in *LYPLAL1*, for its influence on

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triglyceride lipase in adipose tissue and depalmitoylating calcium-activated potassium channels(63), rs1227756 in *COL13A1,*for its association with connective tissue proliferation(64) and liver injury (65), missense variant rs738409 in *PNPLA3* for its role in energy usage/ storage in adipocytes(63,64), rs887304 in *EFCAB4B* gene for its role in calcium binding and regulation(65), *GCKR* rs1260326 for its involvement in hepatic fat accumulation along with large very low density lipoprotein (VLDL) and triglyceride levels(63,66), the missense variant in *APOC3* gene rs2854116 for its role in hypertriglyceridemia and impact of dietary fat intake and NAFLD(67,68), rs2645424 in *FDFT1* for its role in cholesterol biosynthesis(69), *TMS6F2* gene variant, rs58542926 for its role in post prandial lipemia(70,71), rs2228603 of the *NCAN* gene for its association with increased risk for liver inflammation and fibrosis(72), and rs4240624 of the *PPP1R3B* gene for its association with glycogen metabolism(73,74). The SNP positions and their frequencies are shown in **Table 1**.

Genotyping

DNA was extracted from saliva via an automated nucleic acid extraction platform (Anaprep 12, Biochain, Institute Inc. Newark, CA, USA) using the Anaprep Forensic DNA extraction kit (Biochain Institute Inc. Newark, CA, USA) Concentration and purity of genomic DNA was measured using NanoDrop Spectrophotometer. Genotyping was performed via Taqman® predesigned SNP genotyping assay (Applied Biosystems, Foster City, CA, USA) on Quant Studio 12k Flex Real-time PCR system (Thermo Fisher Scientific, USA).

Liver fat content and stiffness measurement

Transient elastography using Fibroscan® (Echosens, Netherlands) was used to assess fat content in the liver and liver stiffness(75,76). Fibroscan was done at both visits. This is a non-invasive measure that uses ultrasound technology to measure liver stiffness and adiposity. The CAP score, which is measured in decibels per meter (dB/m) is used to grade liver steatosis. A score below 238 dB/m is considered normal. A score between 238 dB/m to 260 dB/m indicates grade 1 (S1) steatosis. A score between 260 dB/m to 290 dB/m is S2 and 290 dB/m to 400 dB/m is S3. As for Emed values, a score between 2 kPa and 7 kPa (F0 -F1) is normal, a score of 7.5 kPa to 10 kPa (F2) is considered moderate scarring 10 kPa to 14 kPa (F3) is considered severe scarring and 14 kPa or higher (F4) is considered cirrhosis. In this study, CAP score was used to indicate the amount of fat in the liver[82,83].

Sample collection, processing and storage

At both visits, a fasting blood and a 24-hr urine sample were collected. A trained phlebotomist collected blood through venous puncture using 6-mL ethylenediaminetetraacetic acid (EDTA)-coated tubes and serum tubes (BD Vacutainer, Becton, Dickinson & Company, Franklin Lakes, NJ, USA). Immediately after collection, EDTA tubes were placed on wet ice and centrifuged at 3000 RPM for 15 min at 4^0C. Serum, plasma, buffy coat and urine samples were aliquoted and stored at -80^0C for further biochemical measurements.

Biomarker measurements

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At each visit, serum concentrations of lipids, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL) and triglycerides were measured using fluorometric assays (Abcam, Cambridge, MA, USA). Uric acid concentration in serum was measured using fluorometric assays, as per the manufacturer's instructions (Sigma-Aldrich, St. Louis, MO, USA) on BioTek Synergy 2 Multi-Mode plate reader (BioTek, Winooski, VT, USA). All measurements were conducted in duplicate, and their coefficient of variation was less than 10%.

Statistical Analysis

Statistical analyses were performed using STATA software version 19.5 (College Station, TX, USA). The primary outcomes for this study were CAP and Emed scores and the secondary outcomes were body composition measurements (BMI, waist circumference, waist-height ratio, percent body fat, fat mass and fat free mass), and serum concentrations of lipids (total, HDL, VLDL, LDL cholesterol and triglycerides) and uric acid. As a first step, paired t-tests were conducted to determine whether there were any significant changes in variables pre- and post-intervention. Linear regression analysis was performed to determine the association between the ten selected SNPs and baseline values and changes in body composition, liver fat content and serum concentrations of lipids and uric acid. Baseline or changes in liver fat content and other biomarkers were the outcome or dependent variables and SNPs were the predictor or independent variables. All analyses were adjusted for sex, age and baseline concentrations of the variables and waist-height ratio wherever applicable. All results were considered significant at $p < 0.05$.

RESULTS

The descriptive characteristics of participants are listed in **Table 2**. Fifteen males (n = 5) and females (n = 10) participated and completed the 3-week SSB intervention. Their mean BMI and age were 25.03 ± 1.1 Kg/m^2 and 25.53 ± 2.4 years, respectively. At baseline, significant differences were observed between females and males with respect to fat free mass (104.8 ± 3.8 vs 137.7±8 11.2g, $p < 0.05$), and percent body fat (31.5 ± 2.0 vs, 17.0 ± 3.0%, $p < 0.05$). Serum urate concentrations were significantly higher in males than females (7.35 ± 0.4 vs. 6.1 ± 0.3 mg/dl, $p < 0.05$). Baseline CAP score was significantly associated with fat mass ($\beta = 1.2 \pm 0.5$, $p < 0.05$), waist circumference ($\beta = 2.3 \pm 0.9$, $p < 0.05$), and systolic blood pressure ($\beta = 1.6 \pm 0.4$, $p < 0.005$).

Table 2: Descriptive characteristics of participants at baseline

	Female (N = 10)	Male (N = 5)	Total (N = 15)	
	Mean ± SE	Mean ± SE	Mean ± SE	P-value
BMI (kg/m^2)	25.54(1.24)	24(2.19)	25.03(1.07)	0.52
Age (years)	26.60(2.81)	23.40(4.66)	25.53(2.37)	0.54

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Percent body fat (%)	31.5 (2.0)	17.0 (3.0)	27.0 (26.0)	0.003
Fat Mass (lbs)	50.29(5.92)	31(8.31)	43.86(5.24)	0.08
Fat-free mass (lbs)	104.77(3.82)	137.68(11.20)	115.74(5.95)	0.003
Waist Circumference (Cm)	87.02(3.33)	89.36(6.33)	87.92(3.04)	0.73
Waist-height ratio	0.42(0.07)	0.50(0.03)	0.44(0.05)	0.43
SBP (mm Hg)	124.00(5.59)	126.00(8.50)	124.67(4.51)	0.84
DBP (mm Hg)	78.50(4.20)	81.40(5.49)	79.47(3.25)	0.69
Emed (kPa)	4.46(0.34)	4.59(0.38)	4.51(0.25)	0.82
CAP score (dB/m)	222.23(13.07)	192.00(12.66)	212.15(10.15)	0.17
Triglycerides (mg/dl)	65.7(17.18)	56(20.24)	62.47(12.92)	0.74
HDL (mg/dl)	34.19(8.29)	24.58(10.17)	30.98(6.39)	0.50
LDL (mg/dl)	126.06(13.30)	138.64(22.32)	130.25(11.21)	0.62
Total cholesterol (mg/dl)	172.38(15.58)	174.42(21.02)	173.73(12.09)	0.97
UA (mg/dl)	6.07(0.34)	7.35(0.41)	6.49(0.30)	0.04

A paired t-test was conducted to detect differences between pre and post intervention anthropometrics, liver fat content, and serum biomarker values (**Table 3**). Most of the biomarkers showed no changes post intervention. The CAP score, however, showed a decreasing, albeit statistically insignificant, trend ($p = 0.07$), contrary to our hypothesis. When data were analyzed with residuals after adjusting for age, sex and waist-height ratio, there was no difference in CAP score between pre and post intervention ($p = 1.00$). Similarly, we observed a decrease in serum urate concentrations after the 3-week intervention which was mitigated after adjusting for the covariates. The change in CAP score was significantly correlated with baseline waist circumference ($r2 = 0.53$, $p < 0.05$) and not with fat mass or systolic blood pressure as observed with baseline CAP score. Although baseline CAP score was not correlated with baseline waist-height ratio, the change in the two variables were significantly correlated ($r2 = 0.71$, $p < 0.005$). Change in Emed score, waist circumference and waist-height ratio were also associated with their baseline values ($p < 0.05$), respectively.

The ten genotyped SNPs were selected based on their links to NAFLD. Their minor allele frequencies ranged between 13 and 47%. Genotype-specific analysis showed that rs1227756, an intronic variant in *COL13A1* ($\beta = -22.4 \pm 7.5$, $p < 0.05$) was associated with baseline CAP score, with individuals carrying AA alleles having significantly higher CAP score (234 ± 34.7 dB/m) as compared to those with GG alleles (188 ± 25.3 dB/m).

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Table 3: Anthropometrics and biomarkers pre and post SSB intervention

Variable	Visit 1 (mean ± SE)	Visit 2 (mean ± SE)	P-value
BMI (kg/m^2)	25.03(1.07)	25.13(1.05)	0.27
PBF (%)	0.27(0.03)	0.27(0.03)	0.16
FM (lbs)	43.86(5.24)	44.71(5.24)	0.15
FFM (lbs)	115.74 (5.95)	115.77(6.15)	0.94
Waist circumference (cm)	87.92(3.04)	88.16(2.82)	0.88
Wc/Ht	0.45(0.05)	0.51(0.02)	0.16
SBP (mmHg)	124.67(4.51)	123.07(3.18)	0.75
DBP (mmHg)	79.47(3.25)	79(2.03)	0.88
E_med (kPa)	4.51(0.25)	5.01(0.49)	0.41
CAP score (dB/m)	212.15(10.15)	192.91(13.57)	0.07
Triglycerides (mg/dl)	62.47(12.92)	73.07(21.47)	0.41
HDL (mg/dl)	30.98(6.39)	29.72(5.66)	0.79
LDL (mg/dl)	130.25(11.21)	128.35(11.08)	0.79
Total cholesterol (mg/dl)	173.73(12.09)	172.68(12.95)	0.92
Uric acid (mg/dl)	6.50(0.30)	6.43(0.28)	0.04

At baseline, systolic blood pressure was associated with rs121137855, an intronic variant in *LYPLAL1* (β ± SE- -11.14 ± 4.3, $p < 0.05$). The same SNP was associated with changes in diastolic blood pressure (-9.91 (± 1.80), $p < 0.005$). The CAP score decreased post SSB intervention, and the change was significantly associated with rs2228603, a missense variant in *NCAN* (β=-20.1± 7.6, $p< 0.05$). The T allele carriers showed a greater reduction in CAP score as compared to CC carriers (Mean ± SE -23.3 ± 5.8 dB/m vs. 18.24 ± 43.2 dB/m). Significant associations were also observed between change in serum HDL and rs1260326, a missense variant in *GCKR,* (β ± SE 11.73 ± 4.6, $p < 0.05$), and triglycerides and rs58542926, a stop gained variant in *TMS6F2* (β ± SE 77.1 ± 26.2, $p < 0.05$).

Table 4: Regression analysis (change in variable as dependent variable and SNP as independent variable adjusted for baseline of the variable value, gender, age and waist circumference)

Primary outcome:

Change in variable	SNP Id	Beta coefficient ± SE	P value*	95% CI

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CAP_med dBm	rs58542926	22.26 (± 9.61)	0.05	-0.47	44.98
	rs2228603	-20.10 (± 7.59)	0.03	-38.05	-2.16

Secondary outcomes:

Change in variable	SNP Id	Beta coefficient (SE)	P value*	95% CI	
Systolic blood pressure	rs121137855	-11.14 (4.33)	0.04	-21.39	-0.9
	rs1227756	0.62 (4.60)	0.05	-1.44	0.01
Diastolic blood pressure	rs121137855	-9.91 (1.80)	0.001	-14.06	-5.56
HDL	rs1260326	11.73 (4.61)	0.04	0.82	22.63
TAG	rs58542926	77.07 (26.18)	0.02	15.16	138.97
VLDL	rs58542926	15.41 (5.24)	0.02	3.03	27.79

*results with p values < 0.06 shown here

DISCUSSION

The main aim of this study was to determine whether SNPs previously linked with NAFLD tend to associate with CAP score at baseline and CAP score's response to SSB intake. In this study we utilized transient elastography FibroScan, a non-invasive assessment of liver stiffness/fibrosis (Emed) and steatosis (CAP score). These measures have been increasingly used for NAFLD and NASH evaluation of patients over liver biopsy(77–80). The CAP scores present the total attenuation of sound waves, an indirect measure of steatosis(81–83),(84). However, in this study we used CAP scores as a surrogate measure of liver fat content as reported in some previous studies(85,86). We found that CAP score at baseline was positively associated with body composition and systolic blood pressure. Similar results have been shown by other studies(87,88),(89). In a study on NAFLD patients, CAP score was positively correlated with fat mass, waist circumference and waist-height ratio(87). In another study of patients with overweight and obesity, CAP values were positively associated with fat mass, BMI and homeostasis model assessment of insulin resistance (HOMA-IR) (88). Another study in youths, found that individuals with higher CAP score had higher BMI, waist circumference and other fat distribution measures(85).

A CAP score below 238dB/m is considered normal liver fat content (90). In our study, both males and females had a CAP score lower than 238dB/m. We hypothesized that the three-week SSB intervention will increase the liver fat content. In contrast, the CAP scores decreased slightly after the 3-week period. The non-alcohol related fat deposition in the liver is dependent on an individual's age, sex, dietary intake of simple sugars and saturated fats, physical activity and presence of other metabolic disorders such as obesity, insulin resistance and metabolic syndrome (91–93), (94). In our study, we think that the decrease in CAP score may be due to many reasons: participants' low CAP score at baseline, our stringent inclusion criteria with the exclusion of adverse metabolic conditions, young age of the participants, and the participants' activities and healthy lifestyle. This may also explain as to why there was no change in CAP score when the data were adjusted for age, sex and body composition.

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Although we had advised the participants to not alter any of their dietary habits, except reduction in SSBs, it is possible that the participants may have cut down their other sources of sugars. Studies under controlled or domicile conditions may reflect the true effect of simple sugars on liver fat content.

Emed score or the measure of fibrosis / liver stiffness where higher values indicate higher levels of liver stiffness or liver tissue scarring. In our study Emed scores were very similar between males and females, and we observed an increase in the mean scores after the fructose intervention which was negligible and non-significant. Like the liver physiological measures, anthropometrics and body composition measures such as percent body fat and fat mass showed no significant changes. There were significant differences in percent body fat and fat mass measures between males and females at baseline. Studies have shown that the response to fructose intervention is different in males and females (95,96). Males are usually reported to have adverse metabolic effects such as insulin resistance, high blood pressure and hyperlipidemia in response to increased fructose intake(96–98). Females, although higher in fat mass and percent body fat, tend not to have higher metabolic adversities compared to males(96,97). This may be due to the role of hormones such as estrogen in lipid metabolism and storage(99).

Fructose metabolism inherently generates uric acid (41), and hyperuricemia has been linked to the onset and progression of NAFLD(100–102). In a previous fructose response study in our lab, we found that fructose intervention caused serum uric acid level to spike and did not return to the baseline levels until 150 minutes after the intake of fructose(42,43). In this trial we wanted to understand the long-term effects of SSB on adiposity and uric acid. Examination of 3-week fructose exposure on serum urate levels in this study did not show any significant change in post intervention compared to baseline. However, we did find that males had a higher serum uric acid level than females at baseline which is consistent with other studies(42,43). This finding again highlights the difference in uric acid metabolism in males and females highlighting protective effects against hyperuricemia in pre-menopausal females (103,104).

In addition to sex-specific differences, interindividual variability - particularly genetic variation - affects hepatic lipid response to fructose intake(105). In this study we explored and found few potential links between NAFLD-related SNPs and liver fat content and serum lipids. The SNP rs121137855 of the *LYPLAL1* gene was related to systolic blood pressure especially the homozygous T genotype. This gene has been studied for metabolic traits such as fat distribution, obesity, and hypertension(63,106). Other SNPs rs2605100 and rs4846567 in the same gene, *LYPLAL1,* have been found to be associated with the above-mentioned phenotypes and appetite suppression in Japanese population(107,108). Another SNP rs2605100 in *LYPLAL1*was found to be associated with high blood pressure in a cohort of Chinese children(109). These findings suggest that *LYPLAL1* has several variants that could influence blood pressure and thereby cardiovascular function.

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SNP rs1227756 of the *COL13A1* gene was associated with increased systolic blood pressure (A/A genotype). This SNP has been studied in relation to lobular inflammation in Caucasian women(110). SNP rs2854116 in *APOC3* gene has been significantly associated with decreased diastolic blood pressure, especially in individuals with homozygous C genotype. Although this gene has been traditionally studied for its role in liver fat and dyslipidaemia(111–113), our results suggest a novel role in blood pressure regulation.

The other interesting link we found was between SNP rs58542926 and CAP values. Individuals with T allele of rs58542926 is in the *TM6SF2* gene has been observed to have lower CAP values. But in a previous study conducted in Hans Chinese population the same allele was associated with increased CAP scores and increased risk for NAFLD(114) . Although in another meta-analysis study of different populations including Chinese, the T allele of rs58542926 has been shown to be associated with lower lipid profile and protective against CVD risk(115). Combined with findings from our study which is 100% Caucasian, the SNP seems to take on a dual and opposite role depending on the ethnicity of the study population.

Individuals with homozygous C allele and homozygous T allele of rs2228603 has been observed to have lower CAP values. This SNP is in the *NCAN* gene and has shown a strong association with CAP score, with T alleles being linked to greater reduction in CAP score. In a previous study that consisted of European descent Caucasian and old order Amish population, the SNP's T allele was associated with increased risk of hepatic fat accumulation(116). In another study involving Chinese population, this same allele was associated with high level of HDL and also increased level of alkaline phosphatase showing opposite dual effects(117) . Interestingly in a study conducted in 80% female bariatric patient cohort, rs2228603 T was associated with increased risk of steatosis(72).

We also found relation between genetic variants and changes in serum HDL and triglycerides. The SNP rs1260326 in *GCKR* was associated with HDL in our study. In a children study, this SNP was associated with liver fat content as measured by MRI(118). Most studies reported T allele carriers to have lower levels of HDL which are in contrast to what we observed in our study(118–120). We found T allele carriers to have higher HDL levels than CC carriers. We found similar differences with respect to our association of rs58542926 in *TM6SF2* with serum triglycerides. Other studies reported T allele to be associated with lower triglycerides(121,122). Although we found higher concentrations in T carriers at baseline, their triglyceride levels decreased after the 3-week SSB intervention while CC carriers increased their triglycerides. This indicates that T allele may have a protective effect on serum triglycerides in our sample. The SNP rs738409 in *PNPLA3* has been linked to liver fat in many studies but we did not find its association either with the baseline levels or its changes.

There are a few limitations to the study which may need to be addressed in future studies. The sample of 15 is small for any type of clinical trial. Secondly, each genotype carriers were limited to 3-5 participants, and third, 3 weeks may be too short of a duration to observe significant changes in lipid

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profile such as LDL-C, HDL-C, total cholesterol etc. It is also possible that short-term fructose exposure might cause biochemical changes in hepatocytes without reaching the threshold for measurable fat accumulation. Also, anthropometrics such as weight gain and fat redistribution typically require more than 3 weeks to show significant changes. Underlying hormonal changes such as leptin, adiponectin, cortisol and other metabolic hormones do not significantly shift with the limited duration of SSB intervention. Also, the dosage of fructose might be too low to elicit measurable changes within this timeframe, as our dose is equivalent to two 12-ounce soda cans. The results may not be generalizable across all ethnic groups. And moreover, all participants had low or normal CAP scores at baseline (non-steatotic range) which may limit the sensitivity of CAP score. However, the key strengths of the study are its stringent inclusion criteria and homogenous sample, and that it is one of the very few that studied the association of genetic variants on changes in CAP score in response to a SSB ingestion in an ethnically homogenous population.

CONCLUSIONS

In summary, a 3-week SSB intervention did not affect the liver fat content or the liver fat markers in our young adult population. Genetic heterogeneity is another important puzzle piece in NAFLD to understand individual variability in disease susceptibility and progression. This study unlocks the possible role of SNPs that may influence the NAFLD onset and progression to better understand the role of genetics in this disease. It also provides pilot data for conducting larger studies where genetically susceptible groups could be identified and their response to nutrient intake can be measured. Together this could implement novel treatment, management and prevention strategies for NAFLD.

AUTHOR CONTRIBUTIONS

Conceptualization, VSV; methodology, FTJ, KN, KW, LRG, BCN, BBM; software, SSV, FTJ, VSV; formal analysis, SSV., FTJ, VSV; investigation, FTJ, SSV, VSV; resources, VSV; writing original draft preparation, FTJ, SSV, VSV; writing -review and editing, FTJ, SSV, LRG, VSV; project administration, VSV; funding acquisition, VSV. All authors have read and agreed to the published version of the manuscript.

CONFLICTS OF INTEREST

There are no conflicts to declare.

DATA AVAILABILITY

Data supporting the findings of this study are not publicly available due to privacy reasons, but are available from the corresponding author upon reasonable request with the corresponding author.

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FIGURE LEGEND

Figure 1: Consort diagram of the intervention study

Figure 2: Mechanism of dietary sugars and fat accumulation

ATP- Adenosine triphosphate; AMP- Adenosine monophosphate; *GCKR* – Glucokinase regulatory protein; ChREBP – Carbohydrate response element binding protein; SREBP- Sterol regulatory element binding protein; *PNPLA3* – Patatin-like phospholipase domain -containing protein 3; *TM6SF2* – Transmembrane 6 superfamily member 2; *APOC3* – Apolipoprotein C-III; *FDFT1* – Farnesyl-diphosphate farnesyltransferase 1; *LYPLAL1* - Lysophopholipase - like1 ; *PPP1R3B* – Protein phosphatase 1 regulatory subunit 3B; *EFCAB4B* – *EF* hand calcium binding domain containing protein 4B; *NCAN* – Neurocan; *COLI3A1* – Collagen type III alpha 1 chain

Abbreviations

ACC- acetyl coA carboxylase
ALP- alkaline phosphatase
ALT – alanine transaminase
AMP- Adenosine monophosphate
APOC3 – Apolipoprotein C-III
AST- Aspartate transaminase
ATP- Adenosine triphosphate
BMI – body mass index
CAP – controlled attenuation parameter
ChREBP – Carbohydrate response element binding protein
COLI3A1 – collagen type III alpha 1 chain
CVD – cardiovascular disease
DBP- diastolic blood pressure
DNL- de novo lipogenesis
EFCAB4B – EF hand calcium binding domain containing protein 4B
FAS – fatty acid synthase
FDFT1 – farnesyl-diphosphate farnesyltransferase 1
FLFS – fructose liver fat study
GCKR – Glucokinase regulatory protein
GGT – gamma glutamyl transferase
GLUT 2 – glucose transporter protein 2
GLUT 4 – glucose transporter protein 4
HDL- high-density lipoprotein

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LDL- low-density lipoprotein

LYPLAL1 - lysophopholipase - like1

NAFLD – Nonalcoholic fatty liver disease

NASH – non-alcoholic steatosis

NCAN – neurocan

PNPLA3 – patatin-like phospholipase domain -containing protein 3

PPP1R3B – protein phosphatase 1 regulatory subunit 3B

PWV – pulse wave velocity

SBP- systolic blood pressure

SNP- single nucleotide polymorphism

SREBP- Sterol regulatory element binding protein

TAG – triacylglycerols

TC – total cholesterol

TM6SF2 – transmembrane 6 superfamily member 2

UA – uric acid

VLDL – very low- density lipoprotein

WC – waist circumference

MAFLD - metabolic dysfunction-associated fatty liver disease

KHK – ketohexokinase

SSB- sugar sweetened beverage

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Figure 1: Consort diagram of the intervention study

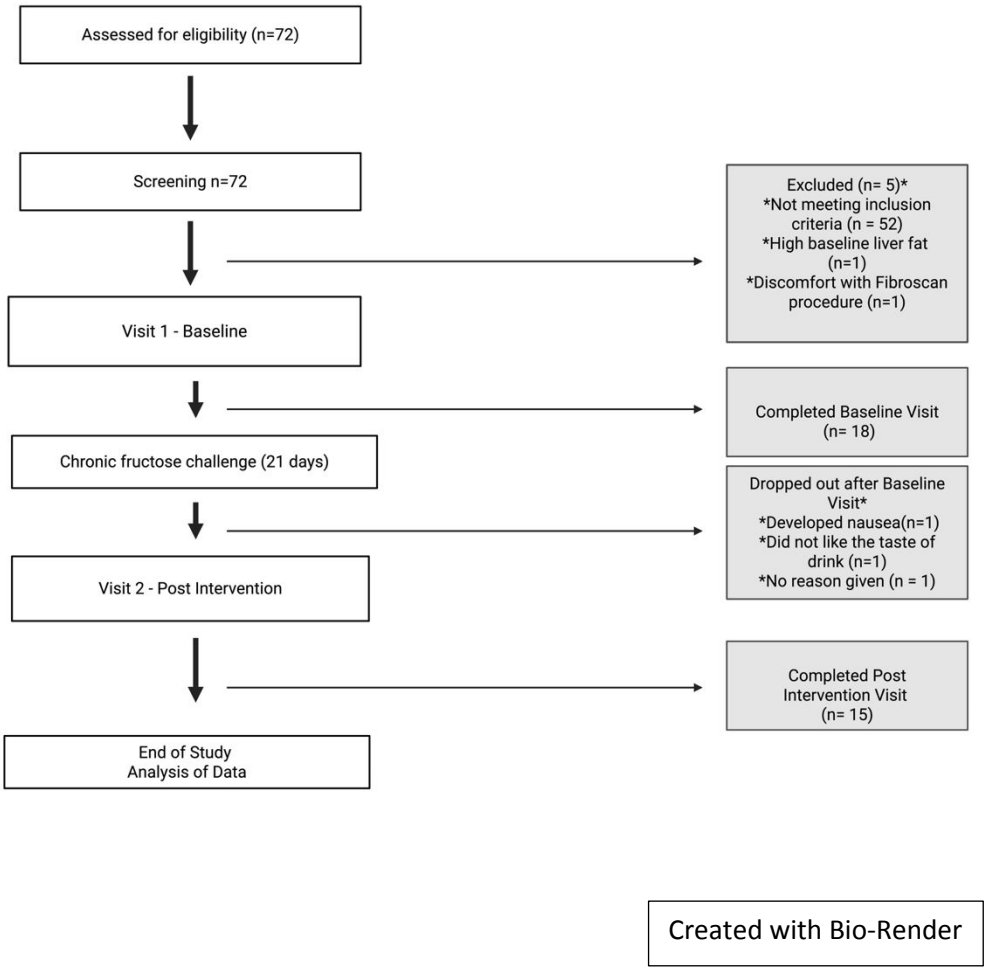

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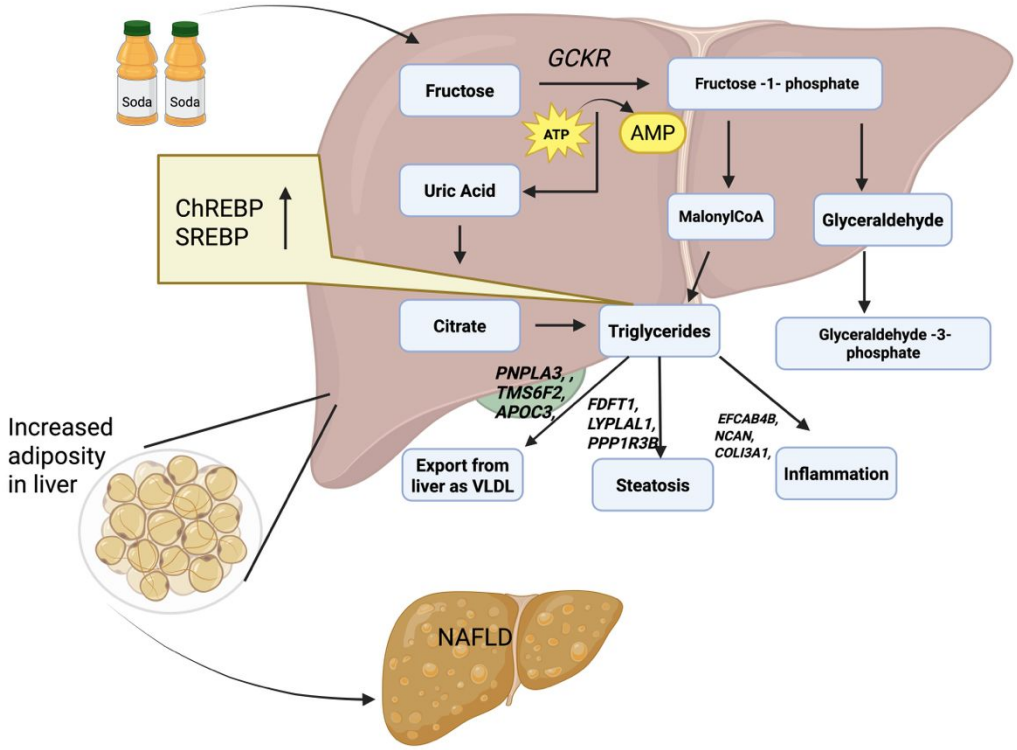
Figure 2: Mechanism of dietary sugars and fat accumulation



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DATA AVAILABILITY

Data supporting the findings of this study are not publicly available due to privacy reasons, but are available from the corresponding author upon reasonable request with the corresponding author.

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