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Lipoprotein(a) and diet: consuming sugar-sweetened beverages lowers lipoprotein(a) levels in obese and overweight adults

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Abstract **Lipoprotein(a) [Lp(a)] contributes to cardiovascular disease risk. A genetically determined size polymorphism in apolipoprotein(a) [apo(a)], determined by the number of Kringle (K) repeats, inversely regulates Lp(a) levels. Nongenetic factors including dietary saturated fat influence Lp(a) levels. However, less is known about the effects of carbohydrates including dietary sugars. In this double-blind, parallel arm study among 32 overweight/obese adults, we investigated the effect of consuming glucose- or fructose-sweetened beverages providing 25% of energy requirements for 10 weeks on Lp(a) level and assessed the role of the apo(a) size polymorphism. The mean (±SD) age of participants was 54 ± 8 years, 50% were women, and 75% were of European descent. Following the 10-week intervention, Lp(a) level was reduced by an average (±SEM) of −13.2% ± 4.3% in all participants (P = 0.005); −15.3% ± 7.8% in the 15 participants who consumed glucose (P = 0.07); and −11.3% ± 4.5% in the 17 participants who consumed fructose (P = 0.02), without any significant difference in the effect between the two sugar groups. Relative changes in Lp(a) levels were similar across subgroups of lower versus higher baseline Lp(a) level or carrier versus noncarrier of an atherogenic small (≤22K) apo(a) size. In contrast, LDL-C increased. In conclusion, in older, overweight/obese adults, consuming sugar-sweetened beverages reduced Lp(a) levels by ∼13% independently of apo(a) size variability and the type of sugar consumed. The Lp(a) response was opposite to that of LDL-C and triglyceride concentrations. These findings suggest that metabolic pathways might impact Lp(a) levels.**

Supplementary key words glucose • fructose • nutrition • Lp(a) metabolism • apolipoprotein

Despite its key independent role in CVD development, lipoprotein(a) [Lp(a)] remains an elusive trait with many unknowns. The critical role of elevated Lp(a) levels in CVD risk has been recognized in a number of clinical guidelines and scientific statements (1, 2). Moreover, the urgent need to better understand Lp(a)'s fundamental properties, genetic and nongenetic regulators of levels, and mechanisms impacting its metabolism and CVD risk has consistently been emphasized. Lp(a) is a type of circulating lipoprotein containing two apolipoproteins: apoB-100 and apo(a). Apo(a) is unique to Lp(a), with a repeated loop structure termed Kringles. The highly variable number of Kringle repeats, resulting in an extensive size polymorphism, is considered the major genetic regulator of Lp(a) plasma levels. There is a large interindividual and interpopulation variability in Lp(a) levels, which cannot be fully explained by genetic factors alone (3, 4).

Evidence suggests a role for other factors, including diet, in influencing Lp(a) levels (5). A notable example of diet's influence has been demonstrated by studies showing an increase of Lp(a) levels by up to 24% following a reduced intake of dietary saturated fats (6, 7). While carbohydrates are a common replacement for dietary saturated fats, the relationship between Lp(a) level and sugar consumption remains poorly understood. A large body of direct experimental evidence from both animal and human studies have shown that consumption of dietary sugar is associated with a wide range of detrimental metabolic changes and that fructose intake specifically increases de novo lipogenesis, promotes dyslipidemia, decreases insulin sensitivity, and increases visceral adiposity (8). However, it remains unknown how different types of dietary sugar impact Lp(a) levels. To address this evidence gap regarding the role of dietary sugar in modulating Lp(a) level, we investigated the biological effects of consuming the two major simple sugars in the diet,

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glucose, and fructose, providing 25% of energy requirements for 10 weeks on Lp(a) levels in older, overweight/obese adults enrolled in a double-blind, parallel arm metabolic study. We tested whether the effects on Lp(a) levels would vary by sugar types (glucose vs. fructose) as well as by genetically determined apo(a) sizes. The relationships between changes in Lp(a) and changes in other metabolic parameters have also been examined.

MATERIALS AND METHODS

Study design

The study design has been previously described (8, 9). Briefly, this was a double-blind, parallel arm study that enrolled matched participants and consisted of three phases: (1) a 2-week inpatient baseline period during which participants consumed an energy-balanced diet; (2) an 8-week outpatient intervention period during which participants consumed either fructose- or glucose-sweetened beverages providing 25% of daily energy requirements along with their usual ad libitum diet; and (3) a 2-week inpatient intervention period during which participants consumed fructose- or glucose-sweetened beverages providing 25% of daily energy requirements with an energy-balanced diet. The inpatient periods were designed to enable comparisons of the high fructose and glucose diets under well-controlled metabolic conditions (8, 9).

Study participants

Inclusion criteria in the original study were age from 40 to 72 years and a BMI of 25–35 kg/m^2 with a self-reported stable body weight during the prior six months (8, 9). Exclusion criteria included evidence of diabetes mellitus, renal and/or hepatic disease, fasting serum triglyceride (TG) concentration ≥400 mg/dl, hypertension, history of bariatric surgery, current smoking, exercise >3.5 h/week, and use of thyroid, lipid-lowering, glucose-lowering, antihypertensive, antidepressant, or weight-loss medications. Diet-related exclusion criteria included habitual ingestion of more than one sugar-sweetened beverage (SSB) per day or more than two alcoholic beverages per day. The study follows the Declaration of Helsinki principles, was approved by the UC Davis institutional review board and each participant provided written informed consent. Thirty-nine participants enrolled in the study, and experimental groups were matched for sex, BMI, and fasting TG and insulin concentrations (8). Seven participants (n = 3 from the glucose group and n = 4 from the fructose group) did not complete the study due to inability/unwillingness to comply with the study protocol or personal/work-related conflicts, as described previously (8). The present study is based on data of 32 participants who completed the study.

Diets—inpatient baseline and intervention

During the 2-week baseline and 2-week intervention inpatient metabolic phases of the study, participants resided in the UC Davis Clinical and Translational Science Center's Clinical Research Center (CCRC) and consumed energy-balanced diets providing 15% of energy as protein, 30% as fat, and 55% as carbohydrate as previously detailed (8) (Supplemental Table S1). The diet was designed as a 4-day rotating menu composed of conventional foods served in three meals, with 25% of the energy provided at breakfast, 35% at lunch, and 40% at dinner. During the inpatient periods, the participants were limited to only the food provided and were required to consume all of the food given. During the inpatient intervention period, the only difference between the two diets was that 25% of the overall carbohydrate content (in total 55%) of the intervention diet was provided by fructose- or glucose-sweetened beverages. The baseline (0 weeks) and final (10 weeks) intervention blood collections were performed after the subjects had consumed energy-balanced, weight-maintaining diets in the CCRC for 10 days per study protocol (8). Specifically, during a scheduled 24-h serial blood collection that occurred on day 11 of each of the 2-week inpatient baseline and 2-week inpatient intervention periods, three fasting blood samples were collected in EDTA at 0800, 0830, and 0900 h. These samples were pooled and stored at −80°C in multiple aliquots.

Diets—outpatient intervention

Participants were instructed to consume their usual diets. Sugars were provided to the participants as three daily servings of glucose- or fructose-sweetened beverages flavored with an unsweetened drink mix (Kool-Aid; Kraft). Participants were instructed to drink three servings per day, one with each meal, and to not consume other sugar containing beverages, including fruit juice, during the study protocol (8). The participants, CCRC personnel, and investigators were blinded to the sugar assignments. Compliance was monitored by measuring riboflavin in urine samples (fluorescein counts) collected at the time of beverage pickup. Urinary riboflavin levels were 14.6 ± 1.3 times higher in participants consuming glucose and 12.4 ± 0.8 times higher in participants consuming fructose during the intervention weeks than during baseline, which suggested the two groups were comparably compliant (8). Estimates of food intake during the outpatient phase of the study were collected by 24-h recall using the USDA 5-step multiple pass method (10) on six random days and were averaged.

Measurements of body weight, blood pressure, and laboratory variables

During the inpatient periods, participants were weighed daily in the morning before breakfast. Blood pressure was measured with an automatic blood pressure cuff (Welch Allyn) twice daily during inpatient periods. Glucose concentrations were measured with an automated glucose analyzer (YSI) and insulin by radioimmunoassay (Millipore). Other lipid and lipoprotein concentrations, including total cholesterol, HDL, TGs, apoB, and apoA-1 were determined using a Polychem Chemistry Analyzer (Polymedco Inc.). Free fatty acid concentrations were measured with an enzymatic colorimetric assay (Wako) adapted to a microtiter plate. Oxidized LDL was measured with an ELISA (Mercodia). Plasma LDL concentration was determined by direct homogenous assay using detergents (LDL-EX; Denka Seiken Co.) (11). The accuracy of this homogenous method has been described (12, 13). All data in the present analysis are from measurements in fasting samples collected during the 2-week inpatient baseline (0 weeks) and final intervention periods (10 weeks).

Determinations of Lp(a) plasma levels, apo(a) sizes, and dominance patterns

Plasma Lp(a) concentrations were measured in fasting samples collected at baseline (0 week) and 10 weeks with an apo(a) size insensitive immunoassay (Mercodia ELISA) as previously described (14–16). Apo(a) isoform sizes were determined once by Western blotting with sodium dodecyl sulfate-agarose gel electrophoresis of plasma samples, followed by immunoblotting using a modified protocol of Kamboh *et al.* (17). Briefly, apo(a) bands were visualized with the colorimetric substrates nitro blue tetrazolium chloride/5-bromo-4-chloro-3-indolyl-phosphate (Roche Diagnostics GmbH, Mannheim, Germany) using alkaline phosphatase–conjugated rabbit anti-goat IgG (Fc) antibody (Thermo Fisher Scientific, Rockford, IL). The results were related to human apo(a) isoform standard with known apo(a) isoforms (Technoclone GmbH, Vienna, Austria) taking the inverse relation between the number of K4 repeats (i.e., apparent molecular mass) and isoform mobility during agarose gel electrophoresis into account. The protein isoform expression pattern was assessed by optical analyses of the apo(a) protein bands on the Western blots, followed by a computerized analysis of scans as described previously (14, 18–20). If a single apo(a) band was detected, it was considered as the smaller size apo(a). Apo(a) isoform dominance patterns were defined as larger dominating, smaller dominating, and codominating as previously described (18).

Statistical analyses

We used standard descriptive statistics to summarize variables, including participants' characteristics, with mean ± SD or median (interquartile range) if skewness was high for continuous variables and frequency and percentage for categorical variables. When we made inferences about the mean, we reported SEM. For variable changes from baseline to the end of the study, we derived changes in absolute values ("delta") as well as percent changes per the following calculation: (end of the study value – baseline value)/baseline value × 100%. When we tested the effect of sugar on outcomes, for example, Lp(a) levels, we used ANCOVA, analyzing the follow-up value as outcome with sugar group as an indicator and baseline value as covariates. As our study represented an exploratory/secondary analysis conducted after the primary hypothesis testing in the original trial (8), no adjustments were made for multiplicity in statistical comparisons. To identify potential determinants of Lp(a) response to SSB intake, we conducted a multiple linear regression analysis for changes in Lp(a) levels with changes in other laboratory variables, adjusting for potential covariates such as age, sex, metabolic syndrome (MS) risk factors, and baseline Lp(a) level. MS risk factors included hypertension, obesity, high TG, low HDL-C, and high glucose concentrations. Data analyses were conducted using SAS version 9.4.

RESULTS

Participant characteristics

The mean (±SD) age of all participants was 53.7 ± 7.9 years (range: 43–70 years), 50% were women, and 75% were of European descent (Table 1). The mean BMI was 29.3 ± 2.9 kg/m^2 and 28% of participants had ≥3 MS risk factors. In all participants, the mean (±SD) fasting concentrations were 119 ± 29 mg/dl for directly measured LDL-C, 40 ± 10 mg/dl for HDL-C, 145 ± 69 mg/dl for TGs, 88 ± 5 mg/dl for glucose, and 14.5 ± 6.8 μU/ml for insulin. The two groups consuming either glucose or fructose did not differ significantly for baseline anthropomorphic and metabolic characteristics per study design (8).

TABLE 1. Baseline characteristics of the study participants[a]

Variables	All (n = 32)
Age (years)	53.7 ± 7.9
Men, n (%)	16 (50%)
Race/ethnicity, n (%)	
White	24 (75%)
Hispanic	5 (16%)
African American	3 (9%)
Body weight (kg)	85.8 ± 10.5
Body mass index (kg/m^2)	29.3 ± 2.9
Systolic blood pressure (mmHg)	121 ± 7
Diastolic blood pressure (mmHg)	77 ± 6
Metabolic syndrome risk factors, n (%)	
≤1 risk factor	13 (41%)
2 risk factors	10 (31%)
≥3 risk factors	9 (28%)
Total cholesterol (mg/dl)	187 ± 32
LDL cholesterol (mg/dl)[b]	119 ± 29
HDL cholesterol (mg/dl)	40 ± 10
Triglycerides (mg/dl)	145 ± 69
Glucose (mg/dl)	88 ± 5
Insulin (μU/ml)	14.5 ± 6.8
Free fatty acid (mEq/L)	0.383 ± 0.129

Data represent mean ± SD or number (%).
[a]We previously reported no significant differences among groups for the type of sugars and sexual phenotypes (8).
[b]Directly measured fasting concentration.

Diets

The macronutrient composition of the inpatient diets is shown in Supplemental Table S1. As previously reported, during the 8-week outpatient period, when participants consumed their usual ad libitum diet along with the SSB, no significant sugar- or sex-group differences in fat, sugar, or alcohol intake as a percentage of energy intake or in the amount of energy consumed relative to calculated energy requirements were observed and both groups of participants gained comparable amounts of weight (~1.4 kg) (8, 9).

Effect of consuming SSB on Lp(a) levels in all participants and separately by sugar types

We determined Lp(a) levels at baseline and at week 10 of intervention in fasting plasma samples. We tested the effect of consuming SSB via changes (percent and absolute) in Lp(a) levels from baseline in all participants first and then separately by sugar types (Table 2). In all participants, Lp(a) level decreased from 10.3 (4; 28) mg/dl at baseline to 7.8 (4; 27) mg/dl at week 10, resulting in a significant relative change of −13.2% ± 4.3% (P = 0.005). Among the 15 participants who consumed glucose, Lp(a) level decreased by −15.3% ± 7.8% (P = 0.07), corresponding to an average absolute reduction of −3.7 mg/dl ± 1.4 mg/dl (P = 0.02), from baseline to the end of the study. Similarly, among the 17

TABLE 2. Baseline Lp(a) and triglycerides levels and changes from baseline to week 10 in all participants and separately by glucose and fructose groups

Variable	All Participants n = 32	Glucose Group n = 15	Fructose Group n = 17
Lp(a) level:			
Baseline (mg/dl)	10.3 (4; 28)	12.6 (4; 33)	7.1 (4; 27)
Unit change (mg/dl)	−4.3 ± 2.1	−3.7 ± 1.4[a]	−4.9 ± 3.9
Percent change (%)	−13.2 ± 4.3[b]	−15.3 ± 7.8	−11.3 ± 4.5[a]
TG level:			
Baseline (mg/dl)	145 (101; 166)	146 (98; 168)	144 (104; 164)
Unit change (mg/dl)	5.7 ± 4.0	10.6 ± 3.5	1.4 ± 6.7
Percent change (%)	6.8 ± 3.3	9.7 ± 3.2[a]	3.9 ± 5.5

Data are shown as median (IQR) for baseline levels and mean ± SEM for unit and percent changes from baseline to week 10.
IQR, interquartile range; Lp(a), lipoprotein(a).
[a]$P < 0.05$.
[b]$P < 0.01$.

participants who consumed fructose, Lp(a) level decreased by −11.3% ± 4.5% ($P = 0.02$), corresponding to an absolute reduction of −4.9 mg/dl ± 3.9 mg/dl ($P = 0.22$). The effects of consuming glucose- versus fructose-sweetened beverages on Lp(a) levels after adjusting for baseline Lp(a) levels was not significant with a difference of 0.95 mg/dl ± 3.3 mg/dl ($P = 0.77$). Additionally, results for fasting TG concentrations are given in Table 2.

Exploratory analysis of variability in Lp(a) response by baseline Lp(a) levels in all participants

Next, we explored whether Lp(a) response would differ by baseline lower versus higher Lp(a) levels based on a cut-off level of 30 mg/dl. Among the 25 participants with a lower baseline Lp(a) level (<30 mg/dl), Lp(a) was reduced by an average of −1.4 mg/dl ± 0.5 mg/dl ($P = 0.01$), while the reduction was −14.8 mg/dl ± 8.9 mg/dl ($P = 0.15$) in the seven participants with a higher (≥30 mg/dl) baseline Lp(a) level. When assessed with percent changes, the average reductions in Lp(a) levels were −12.9% ± 5.3% ($P = 0.02$) and −14.1% ± 6.0% ($P = 0.06$), respectively, in the lower versus higher Lp(a) groups. Although we provide P values, we recognize the limitations associated with statistical power due to the exploratory nature of the analysis. In a middle-aged African American male participant with a very high baseline Lp(a) level (153 mg/dl), we observed a large (~43%) reduction from baseline to week 10 following the fructose intervention. A substantial reduction in the expression intensity of apo(a) protein bands on a Western blot supported the observed change in circulating Lp(a) level. This participant had a low baseline LDL-C level (directly measured, fasting: 74 mg/dl) which increased to 90 mg/dl at week 10.

The role of apo(a) isoform sizes

Apo(a) isoform sizes were detected in all participants excluding only one participant with a very low Lp(a) level. The prevalence of a double apo(a) isoform phenotype was 64% (n = 19). Among these 19 double isoform carriers, 10 (53%) had smaller-dominating, 7 (37%) had codominating, and 2 (10%) had larger-dominating patterns. The distribution of apo(a) sizes across the two sugar groups were similar, with an average of 26 K versus 26 K repeats for the smaller and 29 K versus 31 K repeats for the larger apo(a) sizes in the glucose versus fructose groups, respectively. The prevalence of a small size apo(a) defined as ≤22 K was 26% (n = 8). As expected, the carriers of a small size of apo(a) had substantially higher baseline median (interquartile range) Lp(a) levels compared with the noncarriers [22 (9; 77) mg/dl versus 9 (4; 20) mg/dl, respectively]. However, the responses in Lp(a) levels following the SSB consumption in all participants did not significantly differ by the carrier status. Thus, Lp(a) level was reduced on average by −14.7% ± 3.4% versus −12.7% ± 5.7% in carriers versus noncarriers of a small size apo(a), respectively ($P = 0.76$). The corresponding absolute reductions were −5.1 mg/dl ± 4.4 mg/dl versus −4.1 mg/dl ± 2.8 mg/dl, respectively. These findings indicate that the Lp(a)-reducing effect of SSB may not be influenced by apo(a) size variability.

The relationship between changes in Lp(a) and changes in other variables including LDL-C in all participants

We previously reported that directly measured fasting LDL-C concentration was significantly increased in participants who consumed fructose (+13.9% ± 2.3%, $P < 0.01$) (8). The LDL-C concentration was also increased in those who consumed glucose, but the increase was not significant (+3.6% ± 3.0%, $P > 0.05$). **Figure 1** depicts the contrasting effect of consuming SSB on Lp(a) and LDL-C concentrations. Individual responses of LDL-C and Lp(a) concentrations in all participants and by sugar types are shown in **Figure 2**. We also used regression analysis to explore potential determinants of Lp(a) response to SSB intake in all participants. After adjusting for age, sex, MS risk factors, and baseline Lp(a) level, changes (absolute and percent) in Lp(a) levels were not significantly associated with changes in fasting LDL-C, HDL-C, TGs, ApoB-100, ApoA-I, free

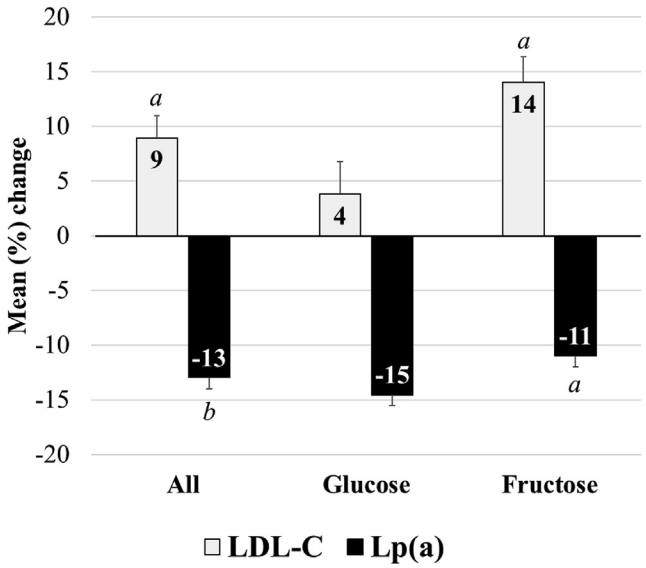

Fig. 1. Opposite effects of consuming sugar-sweetened beverages on directly measured fasting LDL-C versus Lp(a) concentrations in all participants and by sugar types. Data are shown as mean (SEM) percent change in Lp(a) and directly measured LDL-C concentrations from baseline to week 10. Graphs are based on data from 32 participants for all, 15 participants for the glucose, and 17 participants for the fructose groups. a: $P < 0.05$; b: $P < 0.01$. Lp(a), lipoprotein(a).

fatty acid, insulin, or oxidized LDL (Supplemental Table S2).

DISCUSSION

The critical role of elevated Lp(a) levels in CVD risk is well established by clinical guidelines and scientific statements (1, 2). Consumption of SSB has also been shown to be positively associated with CVD (21). To the best of our knowledge, this is the first study examining the effect of consuming sugar, specifically fructose- and glucose-sweetened beverages, on plasma Lp(a) levels in relation to apo(a) size polymorphism. In this double-blind, parallel arm study among older, overweight/obese adults, consumption of SSBs providing 25% of energy requirements for 10 weeks resulted in a significant 13% reduction in Lp(a) level, without any significant difference in the effect by sugar types. Moreover, there was no evidence for a potential modulation of Lp(a) response to SSB consumption by genetically determined apo(a) sizes. These findings suggest a role for dietary simple sugars in modulating Lp(a) levels independently of the apo(a) size polymorphism.

While Lp(a) levels are mainly genetically determined (22), evidence also suggests a role for other factors, including dietary (5). Most available evidence from well-designed dietary studies suggests that replacement of saturated fats with other macronutrients—such as monounsaturated fats or complex carbohydrates—increases Lp(a) levels, while consistently decreasing LDL-C concentration (5, 7, 23). The findings in the present study lend support to the notion that specific diet components can impact Lp(a). The reduction in Lp(a) level in response to consuming simple sugars is in contrast to the effect of consuming complex carbohydrates. Studies have shown that replacement of dietary saturated fats with complex carbohydrates increased Lp(a) levels by 11–24% and this Lp(a)-increasing effect was observed in diverse cohorts, including healthy, metabolically challenged, and/or African American participants (6, 24–26). In the present study of simple sugars, however, Lp(a) was significantly reduced by an average of −13%. It is noteworthy that in both cases (replacing saturated fats with complex carbohydrates or consuming simple sugars), LDL-C responded in the opposite direction to what was observed for Lp(a). Thus, LDL-C concentration increased in response to SSB consumption, and in particular to fructose-sweetened beverage consumption (~14%) (8), while it was reduced by 7–11% in studies that replaced saturated fats with complex carbohydrates (6, 25, 26). The latter LDL-C reduction, as described (6, 25), can be translated to a 10% relative risk reduction for major CVD events (24), while the increase of up to 24% in Lp(a) level due to saturated fat replacement may generate ~7% increase in CVD outcomes (27). Therefore, the opposing changes in Lp(a) and LDL-C concentrations induced by SSB consumption in the present study may have implications on CVD risk and require further investigations.

The Health Professionals Follow-Up Study of 42,883 men showed that participants in the top quartile of SSB intake had a 20% higher relative risk of coronary heart disease than those in the bottom quartile (relative risk = 1.20; 95% confidence interval, 1.09–1.33; P for trend <0.01) (28). This analysis also showed that intake of SSB (e.g., sodas) was significantly associated with decreased Lp(a) levels. Specifically, the mean reduction in Lp(a) per 1 SSB per day was −2.8 mg/dl. This is in line with our findings as we observed a decrease of up to −5 mg/dl in Lp(a) level with three servings of SSB per day. As we discussed (8), the amount of sugar consumed by the participants in our study, 25% of energy requirements, is higher than the estimates for the average consumption of added sugars by U.S. adults; although self-reported intake data suggested that ~13% of the U.S. population consumes >25% of energy from added sugars (29). In 2010, around the time the original study was conducted, the Report of the Dietary Guidelines Advisory Committee on the Dietary Guidelines for Americans 2010 suggested a maximal intake level of 25% or less of total energy from added sugars. Several systematic reviews also concluded that a 25–50% daily energy from sugar was safe and one review specified that fructose consumption up to 140 g/day does not result in biologically relevant increases of fasting or postprandial TG in healthy, normal-weight individuals (30).

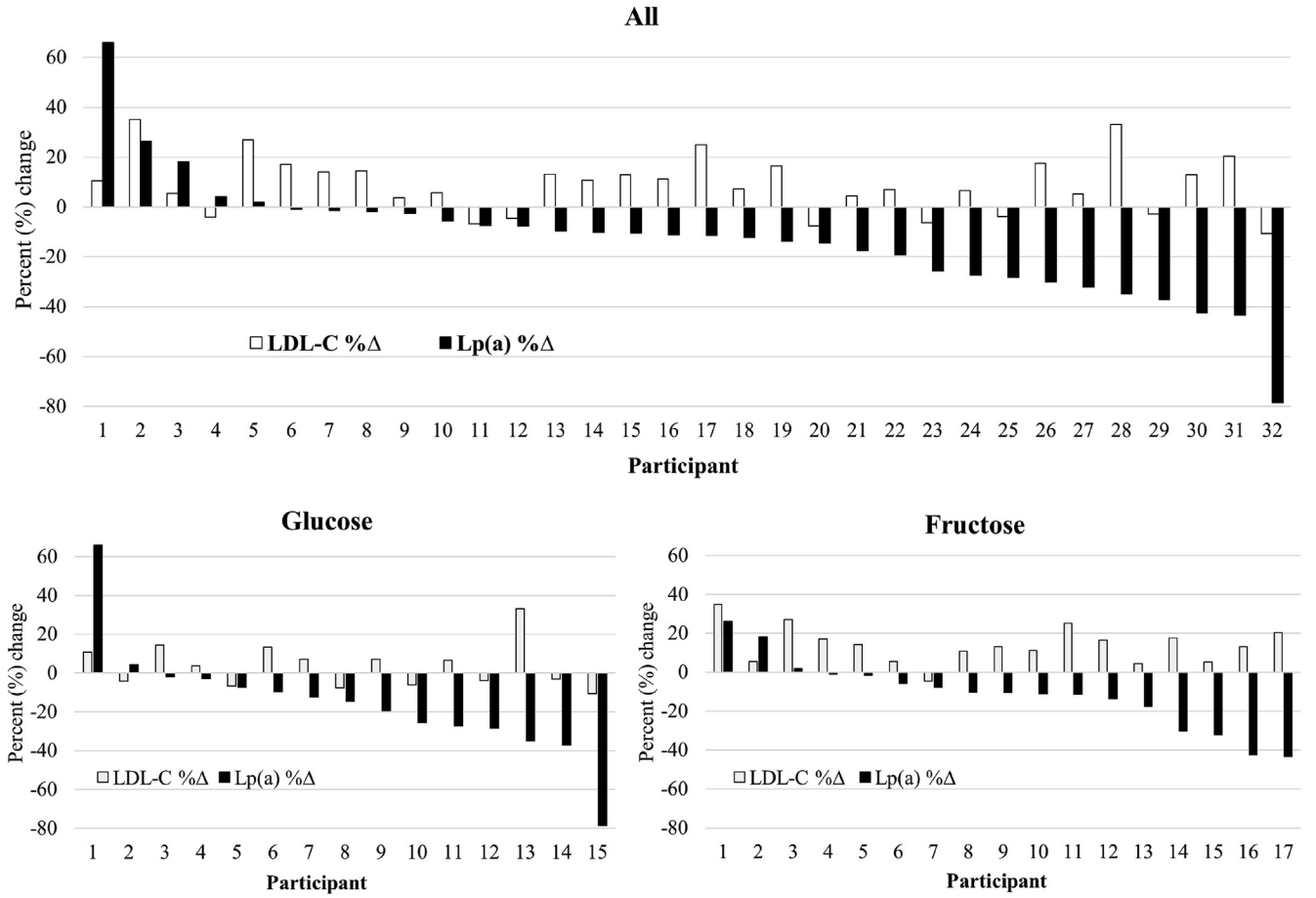

Fig. 2. Individual responses of Lp(a) and directly measured LDL-C concentrations to sugar-sweetened beverages consumption in all participants and by sugar types. Data are shown as percent change in Lp(a) and directly measured LDL-C concentrations from baseline to week 10. Graphs are based on data from 32 participants for all (top panel), 15 participants for the glucose (bottom left panel), and 17 participants for the fructose (bottom right panel) groups. Lp(a), lipoprotein(a).

Our result showing that both fructose- and glucose-sweetened beverages induced decreases in Lp(a) levels was surprising as the metabolism of these two simple sugars are governed by vastly different mechanisms. Unlike glucose metabolism, fructose metabolism is independent of phosphofructokinase regulation. Therefore, its hepatic uptake and metabolism to de novo lipogenesis substrate is not controlled by energy status (31). The increased fructose-induced hepatic de novo lipogenesis generates fatty acids for TG production while also limiting fatty acid oxidation in the liver (32). Thus, fructose-induced de novo lipogenesis may increase hepatic lipids via both supplying endogenous fatty acids and by increasing the intrahepatic availability of fatty acids derived from the circulation (32). This results in an increased VLDL synthesis and secretion (33). Glucose, on the other hand, is mainly metabolized in the peripheral circulation. Previously we reported that fasting TG levels increased in response to consuming both glucose- and fructose-sweetened beverages, reaching a statistical significance in the glucose group (8). The lack of a significant increase in TG levels in the fructose group was explained by the high variability in baseline values in this group. Nevertheless, despite their very different effects on lipid metabolism, consumption of both glucose and fructose exerted the same Lp(a)-decreasing effect. This highlights the need for more studies to elucidate potential mechanism(s) by which these two simple sugars impact Lp(a), especially since Lp(a) level is mostly determined by its synthesis rather than its clearance (34). In this context, it is interesting to note the lack of impact by apo(a) isoforms on Lp(a) response to SSB consumption. Apo(a) is exclusively synthesized in hepatocytes, where its endothelial reticulum residence time is proportional to the number of Kringle repeats (35). As a result, large apo(a) isoforms are more susceptible to proteasomal degradation (34, 35), explaining why circulating Lp(a) levels are on average higher in carriers of small apo(a) isoforms as observed in the present study. Additionally, our attempts to identify potential determinants of Lp(a) response to SSB intake did not reveal any significant results. Changes in Lp(a) levels were not significantly correlated with changes in other lipids and lipoproteins, including fasting TG and free fatty acid concentrations. While current data do not fully support an association

between Lp(a) and metabolic pathways based on other previously assessed lipid/lipoprotein parameters, the results nevertheless suggest that this might be a possibility. Future studies are needed to confirm or refute this hypothesis.

Future investigations should aim to apply LDL-C measurements not confounded by cholesterol contained in Lp(a). As most clinical measurements of LDL-C concentration include the cholesterol contained in Lp(a), it can lead to an inaccurate estimation of the actual LDL-C response to dietary interventions in the presence of elevated Lp(a) (25). Such precision-guided assessments will be key to correctly estimate the actual change in LDL-C, in particular, in a setting where these two atherogenic lipoproteins change in an opposite direction as in the present study of simple sugars as well as dietary studies of saturated fats (7, 25, 26). Despite using a direct homogenous assay for LDL-C measurement, we cannot rule out the potential impact of cholesterol contained in Lp(a) on LDL-C concentration, as evidence suggests that contribution of Lp(a)-cholesterol to LDL-C is independent of whether direct LDL-C assays are used or whether formulas are applied (36). Although Lp(a) level in the present study was expressed as mg/dl, the preferred method for expressing Lp(a) is the nmol/l particle concentration (37). Nevertheless, we did not observe any significant association between changes in Lp(a) and LDL-C in response to SSB consumption. Studies have shown that for every 39 mg/dl (1 mmol/l) increase, the observational hazard ratio was 1.6 for Lp(a) and 1.3 for LDL-C, and the causal risk ratio in corresponding genetic analyses was 2.0 for Lp(a) and 2.1 for LDL-C (38). A recent study reported that the odds ratio for coronary heart disease for a 50 nmol/L higher Lp(a)-apoB was 1.28 than 1.04 for the same increment in LDL-apoB, suggesting that the atherogenicity of Lp(a) based on this approach is 6-fold higher than that of LDL (39). However, it is unknown how relative risk is affected when dietary components such as fructose and saturated fat induce concurrent and opposite changes in LDL-C and Lp(a) concentrations.

Lifestyle modifications, including diet, remain a cornerstone of improving cardiovascular health. Beyond generalized dietary guidelines recommended at the population level, a more informed and individualized dietary advice in the context of precision nutrition would be required for optimal health and disease prevention (40). Given the high prevalence of elevated Lp(a), affecting ~1.4 B people worldwide (37), and the growing evidence that diet impacts Lp(a) level (6, 7, 25), there is a need to better understand the biological effects of various dietary macronutrients on Lp(a) levels. Focus areas of future research may include: (1) taking a comprehensive approach in the context of overall balance between key risk factors, (2) studying specific subgroups, for example, individuals with high/very high Lp(a) levels, and (3) assessing how Lp(a) atherogenic properties, beyond plasma levels, are impacted by dietary interventions. The latter may include detailed analyses of Lp(a)-cholesterol (41), Lp(a) carried oxidized phospholipids (42), Lp(a) endogenous enzymes (43), inflammatory response elements (44, 45), and thrombotic factors (46).

This study has some strengths and limitations. We studied both men and women recruited in a single geographical location. This study was of adequate duration to detect changes in both LDL-C and Lp(a) concentrations; however, studies with extended durations are required to fully delineate the long-term effect on Lp(a) level and its relevance to overall CVD risk. Another limitation may be the less diverse ethnic/racial makeup of the participants, which prevented further analyses. The analyses by higher and lower baseline Lp(a) levels using the cut-off of 30 mg/dl were exploratory in nature because this study was not statistically powered to address this issue. Moreover, due to the eligibility criteria for the original study to recruit individuals with a BMI of 25–35 kg/m^2, the findings may not be directly translated to individuals with a BMI outside this range regardless of the lack of impact by body weight on Lp(a) levels. Therefore, well-powered investigations in individuals with elevated Lp(a) levels of >50 mg/dl (a well-recognized cut-off for risk assessment) (1, 2) and/or in those with normal body weight are needed to extend and confirm these observations. Finally, more studies are needed to elucidate the role of genetic factors, beyond apo(a) sizes, in Lp(a) response to dietary changes and associated cardiovascular outcomes. Nevertheless, the present findings contribute to a better understanding of the metabolic regulation of Lp(a) levels based on a well-designed dietary study in a cohort of men and women at risk of CVD.

In conclusion, consuming SSB providing 25% of energy requirements for 10 weeks reduced Lp(a) level by ~13% in older, overweight/obese adults. This effect on Lp(a) level was independent of apo(a) size variability or the type of sugar (glucose vs. fructose) consumed. The Lp(a)-decreasing effect of consuming fructose-sweetened beverage contrasts with its risk-enhancing, detrimental effects on other CVD risk factors, including LDL-C and TG concentrations. These findings underscore the impact by metabolic regulation of Lp(a) levels and further studies are warranted to elucidate specific mechanism(s) underlying the effect of SSB consumption to reduce circulating Lp(a) levels as well as how Lp(a) atherogenic properties such as its cholesterol and/or oxidized phospholipids contents respond to dietary changes.

Data Availability

The datasets generated and analyzed during the present study are available from the corresponding

author Byambaa Enkhmaa (ebyambaa@ucdavis.edu) on request.

Supplemental data

This article contains supplemental data (8).

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Conflict of interest

The authors declare that they have no conflicts of interest with the contents of this article.

Abbreviations

CCRC, Clinical and Translational Science Center's Clinical Research Center; Lp(a), lipoprotein(a); MS, metabolic syndrome; SSB, sugar-sweetened beverage; TG, triglyceride.

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