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MAJOR ARTICLE

Aspartame Intake Relates to Coronary Plaque Burden and Inflammatory Indices in Human Immunodeficiency Virus

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Background. Dietary sweeteners may contribute to metabolic dysregulation and cardiovascular disease (CVD), but this has not been assessed in human immunodeficiency virus (HIV).

Methods. One hundred twenty-four HIV-infected and 56 non-HIV-infected participants, without history of known coronary artery disease were included. Dietary intake was assessed using a 4-day food record. Coronary plaque was determined using cardiac computed tomography angiography.

Results. Human immunodeficiency virus-infected participants had significantly greater intake of dietary sweeteners, including total sugar ($P = .03$) and added sugar ($P = .009$); intake of aspartame (artificial sweetener) was greater among aspartame consumers with HIV versus non-HIV consumers ($P = .03$). Among HIV-infected participants, aspartame intake was significantly associated with coronary plaque ($P = .002$) and noncalcified plaque ($P = .007$) segments, as well as markers of inflammation/immune activation (monocyte chemoattractant protein 1 and lipoprotein-associated phospholipase A_2), which may contribute to increased atherogenesis. In multivariable regression modeling, aspartame remained an independent predictor of plaque in HIV. In contrast, among non-HIV-infected participants, no sweetener type was shown to relate to plaque characteristics.

Conclusions. We demonstrate increased intake of dietary sweeteners and a potential novel association between aspartame intake, plaque burden, and inflammation in HIV. Our data suggest that aspartame may contribute to CVD risk in HIV. Further studies should address potential mechanisms by which aspartame may contribute to increased plaque burden and cardiovascular benefits of dietary strategies targeting aspartame intake in HIV.

Keywords. aspartame; atherosclerosis; dietary sweeteners; HIV; inflammation.

The number of acquired immune deficiency syndrome (AIDS)-related deaths continues to decline, and, simultaneously, the proportion of adults living with human immunodeficiency virus (HIV) over the age of 50 years is increasing globally [1]. As AIDS-related morbidity and mortality are declining, rates of non-AIDS complications such as cardiovascular disease (CVD) are increasing [2]. Large observational studies have demonstrated that individuals infected with HIV are at higher risk of developing CVD than individuals without HIV, even when controlling for traditional risk factors [3, 4]. Detailed studies using contrast-enhanced cardiac computed tomography (CT) angiography (CCTA) to measure coronary atherosclerosis have consistently demonstrated that noncalcified plaque lesions, a type of plaque more inflamed and prone to rupture, are increased in HIV-infected individuals compared with HIV-uninfected controls [5–7]. Heightened CVD risk in HIV is likely driven in part by nontraditional factors such as inflammation and immune activation, which potentiate atherogenesis in the setting of HIV [7]. To date, few studies have evaluated dietary factors in association with atherosclerosis and inflammation/immune activation in HIV.

In the general population, studies suggest that increased consumption of natural and/or artificial sweeteners may increase CVD risk factors including metabolic syndrome and type 2 diabetes [8–11]. Recent observational studies in the general population have also shown an increased risk of CVD events and/or CVD mortality among consumers of added sugar and diet soda that includes artificial sweeteners [12–15].

To our knowledge, no such studies to date have evaluated dietary sweetener consumption among individuals infected with HIV. In this study, we evaluate dietary sweetener consumption and assess relationships to immune and inflammatory markers and coronary plaque characteristics in HIV-infected individuals and matched controls.

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METHODS

Study Participants

Human immunodeficiency virus-infected individuals and non-HIV-infected controls were previously recruited. In this analysis, we include all participants, 124 HIV-infected and 56 non-HIV-infected participants, who returned a 4-day food record. Human immunodeficiency virus-infected patients were recruited from Boston area HIV clinics, community healthcare centers, and newspaper advertisements. Healthy controls were recruited from the same communities to ensure similar demographic characteristics. Data on coronary plaque characteristics and inflammation/immune activation markers have been previously reported in this cohort [5, 6, 16, 17]. In the current study, we assessed dietary sweetener consumption patterns for the first time in HIV. These data were not previously analyzed in this cohort, nor were they assessed in relationship to coronary plaque and inflammation/immune activation.

Inclusion and exclusion factors were identical for both groups with the exception of HIV serostatus and are detailed elsewhere [5, 6]. In brief, patients aged 18–60 were recruited based on absence of reported CVD. Patients with creatinine >1.5 mg/dL or creatinine clearance less than 60 mL/min were excluded to minimize risk of contrast nephropathy. Human immunodeficiency virus-infected patients were required to be on stable antiretroviral therapy (ART) for more than 3 months before participation.

The Institutional Review Boards of the Massachusetts General Hospital (Partners Human Research Committee) and Massachusetts Institute of Technology approved the study; written informed consent was provided by all study participants. In addition, the study was registered under Clinical Trial Registration number NCT00455793.

Study Procedures and Assessment of Cardiovascular Risk Factors

Medical and family histories, including CVD risk factors, were obtained from all participants. Among HIV-infected participants, duration of HIV diagnosis and detailed history of past and present ART were also elicited.

Assessment of Dietary Intake

Clinical research dietitians instructed participants on the proper completion of the 4-day food record. Participants recorded a detailed description of all foods and beverages consumed during a 4-day period, including 3 weekdays and 1 weekend day. The food record contained instructions for recording food and beverage consumption (including what to record and how to record each item), a sample food record for a single day's consumption, as well as methods to estimate serving sizes. Daily nutrient intake, inclusive of natural and artificial dietary sweeteners, was then assessed by clinical research dietitians using the completed food record and the Minnesota Nutrition Data System for Research (NDSR) software version 2006, developed by the Nutrition Coordinating Center (University of Minnesota Minneapolis, MN). Final calculations were completed using NDSR version 2012. The NDSR time-related database updates analytic data while maintaining nutrient profiles true to the version used for data collection. For this analysis, total sugar intake was broken down into added sugar intake, dietary sweetener intake (sucrose, fructose), and artificial sweetener intake (saccharin, aspartame).

Physical Activity Assessment

Physical activity was assessed using the Modifiable Activity Questionnaire to assess hours of leisure activity during the past year [18].

Cardiac Computed Tomography Angiography

Cardiac CT angiography imaging was performed using a 64-slice CT scanner (Siemens Medical Solutions). The CCTA protocol has been described previously [5, 6].

Metabolic, Biochemical, and Body Composition Parameters

All participants fasted before blood draws. Chemistries were determined using standard techniques. $CD4^+$ T-cell counts were determined by flow cytometry; HIV viral load was assessed by ultrasensitive assay (Roche Amplicor). Cross-sectional CT scan at the level of the L4 pedicle was performed to assess abdominal visceral adipose tissue (VAT) [19].

Immune Activation and Inflammatory Markers

Inflammatory and immune activation markers were measured as previously described [6, 16, 17] and included inflammatory markers: high-sensitivity C-reactive protein (hsCRP), oxidized low-density lipoprotein (oxLDL), and lipoprotein-associated phospholipase A_2 (Lp-PLA_2). Immune activation markers included soluble sCD163, sCD14, and monocyte chemoattractant protein 1 (MCP-1).

Statistical Analysis

Continuous measured outcomes are presented as mean (±standard deviation) values. Categorical measured outcomes are presented as numbers and percentages. Between-group comparisons were performed using the Student's *t* test for continuous measured outcomes and the χ^2 test for categorical variables.

To normalize aspartame for comparison to plaque in univariate regression and subsequent multivariable testing and nontraditional risk factors, log+1 aspartame values were used. Aspartame intake (yes/no) was also compared with plaque using Student's *t* test in a dichotomized analysis stratified by HIV status. In further sensitivity analyses, we compared demographic and clinical characteristics as well as dietary characteristics by aspartame intake (yes/no), stratified by HIV status.

In univariate analyses using Spearman's rho to account for the nonnormal distribution of aspartame intake, aspartame and intake of natural sweetener (total sugar, added sugar, fructose, and sucrose) were related to nontraditional risk factors, including inflammatory and immune activation parameters.

Potential factors mediating the relationship of aspartame to plaque parameters were explored. In the HIV cohort, known

traditional cardiovascular risk factors (race, age, smoking, sex, current diabetes mellitus, current hypertension, low-density lipoprotein [LDL] and high-density lipoprotein [HDL] cholesterol, triglycerides, and body mass index [BMI]) as well as candidate variables from univariate analysis using a P value <.10 to enter the model were included in a forward stepwise regression analysis to analyze factors contributing most significantly to coronary plaque, including total plaque segments and noncalcified plaque segments. Overall statistical significance was defined as $P < .05$. All statistical analyses were performed using SAS JMP (JMP Version 12.0; SAS Institute).

Results Demographics and Traditional Cardiometabolic Disease Risk Factors

Human immunodeficiency virus-infected and non-HIV-infected participants were well matched with respect to demographic and cardiometabolic disease risk factors including age, sex, hypertension, hypercholesterolemia, diabetes, smoking, physical activity, 10-year Framingham risk for coronary heart disease percentage, BMI, VAT, fasting glucose, total cholesterol as well as HDL and LDL. Fasting triglyceride levels were significantly greater among participants with HIV (Table 1).

Dietary Intake

Intake of total protein, dietary cholesterol, as well as dietary fat, did not differ between the HIV-infected and non-HIV-infected cohort. Energy consumption measured by kilocalories/day was similar between the 2 cohorts as was dietary fiber. Total sugar ($P = .03$), added sugar ($P = .009$), and sucrose consumption ($P = .004$) were significantly greater among the HIV-infected participants compared with non-HIV infected participants, whereas consumption of total carbohydrates ($P = .07$) and the artificial sweetener aspartame ($P = .07$) tended to be greater in the HIV cohort (Table 2). The proportions of participants who consumed aspartame between HIV and non-HIV groups were not different (29% and 27%, respectively, $P = .81$). Comparing aspartame consumers in each cohort, mean aspartame intake was increased in the HIV-infected cohort (164 vs 89 mg/day, HIV vs non-HIV, $P = .03$).

Demographic, Clinical, and Dietary Characteristics by Aspartame Intake (Yes/No)

In the HIV cohort, aspartame consumers were more likely to be white and had significantly increased VAT, BMI, total cholesterol, and LDL. Other parameters did not differ among aspartame consumers in the HIV cohort. These relationships were not observed among aspartame consumers in the non-HIV-infected cohort (Supplemental Table 1).

Dietary characteristics were also compared in an analysis of aspartame consumers vs nonconsumers, stratified by HIV status. Saccharin consumption was the only parameter that was significantly greater among HIV-infected aspartame consumers; all other dietary parameters were similar between HIV-infected aspartame consumers and nonconsumers. No differences in dietary intake were seen comparing aspartame consumers and nonconsumers among the non-HIV-infected group (Supplemental Table 2).

Table 1. Demographic and Clinical Characteristics[a]

Parameter	HIV-Infected Participants (n = 124)	Non-HIV-Infected Participants (n = 56)	*P* Value
Age, years	47 ± 7	46 ± 6	.26
Male sex, no. (%)	51 (41)	25 (45)	.66
White race, no. (%)	62 (50)	28 (50)	1.00
Current hypertension, no. (%)	28 (23)	9 (16)	.31
Current hypercholesterolemia, no. (%)	19 (16)	5 (9)	.23
Current diabetes mellitus, no. (%)	12 (10)	5 (9)	.86
Current smoker, no. (%)	56 (45)	21 (38)	.31
Physical activity, hours/weeks	9 ± 11	7 ± 7	.19
Framingham risk for CHD, 10-year risk %	4 ± 5	3 ± 4	.08
Body mass index, kg/m^2	27 ± 5	28 ± 5	.07
VAT, cm^2	137 ± 103	122 ± 90	.33
Fasting glucose, mg/dL	91 ± 30	87 ± 12	.31
Total cholesterol, mg/dL	184 ± 41	181 ± 31	.60
HDL cholesterol, mg/dL	54 ± 18	55 ± 16	.70
LDL cholesterol, mg/dL	103 ± 35	107 ± 28	.52
Triglycerides, mg/dL	136 ± 107	99 ± 56	.002
Systolic blood pressure, mmHg	119 ± 14	118 ± 14	.83
Diastolic blood pressure, mmHg	76 ± 9	77 ± 9	.70
Creatinine, mg/dL	0.94 ± 0.21	0.93 ± 0.23	.82
Duration since HIV diagnosis, years	14 ± 6	N/A	N/A
CD4$^+$ T lymphocytes, cells/μL	564 ± 301	N/A	N/A
Log HIV RNA viral load, copies/mL	1.8 ± 0.4	N/A	N/A
Undetectable HIV RNA <50 copies/mL, no. (%)[b]	94 (86)	N/A	N/A
Current antiretroviral therapy, no. (%)	123 (99)	N/A	N/A
Duration of antiretroviral therapy, years	8 ± 5	N/A	N/A
Current PI treatment, no. (%)	67 (54)	N/A	N/A
Current NRTI treatment, no. (%)	118 (95)	N/A	N/A
Current NNRTI treatment, no. (%)	46 (37)	N/A	N/A

Abbreviations: CHD, coronary heart disease; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; LDL, low-density lipoprotein; N/A, not applicable; NNRTI, non-nucleoside reverse-transcriptase inhibitors; NRTI, nucleoside/nucleotide reverse-transcriptase inhibitors; PI, protease inhibitor; RNA, ribonucleic acid; VAT, visceral adipose tissue.

[a]Data are presented as mean ± standard deviation unless otherwise indicated.

[b]HIV RNA available for 109 participants.

Coronary Plaque Characteristics and Relationships With Dietary Sweeteners

Coronary plaque characteristics were similar to those as previously published in this cohort [5, 6]. In linear regression analysis

Table 2. Dietary Characteristics of HIV-Infected and Non-HIV-Infected Participants[a]

Parameter	HIV-Infected Participants (n = 124)	Non-HIV-Infected Participants (n = 56)	*P* Value
Total energy, kcal/day	2179 ± 810	2018 ± 856	.24
Total carbohydrates, g/day	262 ± 109	229 ± 110	.07
Total protein, g/day	93 ± 38	91 ± 41	.83
Total cholesterol, mg/day	323 ± 175	292 ± 139	.20
Total fat, g/day	86 ± 37	82 ± 42	.47
Total fiber, g/day	19 ± 10	19 ± 12	.97
Total sugar, g/day	113 ± 59	92 ± 61	.03
Total added sugar, g/day	73 ± 52	53 ± 42	.009
Fructose, g/day	24 ± 17	21 ± 18	.23
Sucrose, g/day	48 ± 33	35 ± 25	.004
Aspartame, mg/day[b]	48 ± 115	24 ± 57	.07
Aspartame consumers, no. (%)	36 (29)	15 (27)	.81
Aspartame among consumers, mg/day	164 ± 163	89 ± 80	.03
Saccharin, mg/day	11 ± 40	8 ± 40	.59

Abbreviations: HIV, human immunodeficiency virus; Kcal, kilocalories.

[a]Data presented as mean ± standard deviation unless otherwise indicated.

[b]Data excluded for 1 participant with extreme value not included. This data point met criteria for exclusion using the Dixon criteria at alpha >0.99.

in the HIV cohort, aspartame was significantly and positively associated with number of coronary plaque segments (r = 0.28, *P* = .002), number of noncalcified plaque segments (r = 0.25, *P* = .007), as well as number of mixed segments (r = 0.18, *P* = .047) (Table 3). No other dietary sweetener was observed to be associated with coronary plaque characteristics in the HIV cohort. Among the non-HIV-infected participants, aspartame intake tended to be positively associated with number of calcified plaque segments (r = 0.26, *P* = .06); however, no significant relationships with dietary sweeteners including aspartame were observed with coronary plaque characteristics (Table 4).

To further explore the relationship with coronary plaque characteristics, we assessed plaque by aspartame consumption yes/no. In the HIV-cohort, number of coronary plaque segments were also significantly greater among aspartame consumers (2.8 ± 3.2 vs 1.4 ± 2.0, *P* = .02), whereas number of noncalcified plaque segments tended to be increased (1.4 ± 1.9 vs 0.7 ± 1.1, *P* = .07) among aspartame consumers (Supplemental Table 3). No relationships were observed between aspartame consumption and plaque characteristics in the non-HIV-infected cohort.

Relationship of Dietary Sweetener Intake to Immune Activation and Inflammatory Markers

Markers of monocyte/macrophage activation were significantly greater in the HIV-infected participants as previously published [6, 16, 17]. We related consumption of natural and artificial sweeteners to immune activation and inflammatory markers. Among the HIV cohort, significant and positive associations were observed for MCP-1 with total sugar (ρ = 0.23, *P* = .01), added sugar (ρ = 0.20, *P* = .04), sucrose (ρ = 0.20, *P* = .03), and aspartame intake (ρ = 0.25, *P* = .007). There was also a significant and positive association with Lp-PLA_2 and aspartame intake (ρ = 0.21, *P* = .02), whereas the association of oxLDL (ρ = 0.17, *P* = .07) and hsCRP (ρ = 0.17, *P* = .06) with aspartame was not as strong as the other variables (Table 5).

In the non-HIV cohort, significant and positive associations were observed for Lp-PLA_2 and total sugar (ρ = 0.31, *P* = .02), added sugar (ρ = 0.28, *P* = .05), and sucrose (ρ = 0.26, *P* = .05) intake, whereas significant and negative associations were observed for hsCRP and sucrose intake (ρ = −0.32, *P* = .02) and for sCD14 with total sugar (ρ = −0.42, *P* = .001), fructose (ρ = −0.42, *P* = .002), and sucrose (ρ = −0.30, *P* = .03) intake. No significant associations with markers of inflammation or immune activation were observed with aspartame intake (Table 6).

Factors Associated With Coronary Plaque Features in the Human Immunodeficiency Virus-Infected Cohort Determined by Multivariables Regression Models

To evaluate the independent association of aspartame and other factors to coronary plaque among the HIV-infected cohort, mutivariable regression modeling was performed. Both known traditional CVD risk factors and nontraditional risk factors associated with aspartame intake were included for assessment in the modeling. Race, age, aspartame intake, smoking status, and MCP-1 were shown to be significant predictors

Table 3. Univariate Relationship of Dietary Sweeteners and Coronary Plaque Characteristics Among HIV-Infected Participants

	Number of Plaque Segments		Number of Noncalcified Plaque Segments		Number of Mixed Plaque Segments		Number of Calcified Plaque Segments	
Parameter	r[a]	*P* Value	r[a]	*P* Value	r[a]	*P* Value	r[a]	*P* Value
Total sugars, g/day	−0.06	.56	−0.11	.22	0.02	.87	0.01	.95
Added sugars, g/day	−0.04	.68	−0.11	.28	0.07	.48	−0.05	.60
Fructose, g/day	−0.10	.29	−0.06	.51	−0.08	.42	−0.09	.31
Sucrose, g/day	−0.01	.91	−0.11	.26	0.07	.45	0.05	.63
Log aspartame, mg/day	0.28	.002	0.25	.007	0.18	.047	0.16	.08
Log saccharin, mg/day	0.09	.33	0.15	.10	−0.03	.77	0.06	.49

Abbreviation: HIV, human immunodeficiency virus.

[a]r is Pearson correlation coefficient.

Table 4. Univariate Relationship of Dietary Sweeteners and Coronary Plaque Characteristics Among Non-HIV-Infected Participants

	Number of Plaque Segments		Number of Noncalcified Plaque Segments		Number of Mixed Plaque Segments		Number of Calcified Plaque Segments	
Parameter	r[a]	*P* Value	r[a]	*P* Value	r[a]	*P* Value	r[a]	*P* Value
Total sugars, g/day	−0.10	.47	−0.11	0.43	0.01	.97	−0.14	.31
Added sugars, g/day	−0.10	.51	−0.05	0.73	−0.04	.78	−0.16	.29
Fructose, g/day	−0.02	.87	−0.03	0.85	0.08	.58	−0.16	.26
Sucrose, g/day	−0.19	.17	−0.21	0.12	−0.08	.57	−0.11	.41
Log aspartame, mg/day	0.05	.73	−0.14	0.34	0.11	.42	0.26	.06
Log saccharin, mg/day	0.08	.59	−0.01	0.97	0.11	.45	0.07	.62

Abbreviation: HIV, human immunodeficiency virus.

[a]r is Pearson correlation coefficient.

of total plaque segments; however, aspartame intake and age were significant predictors of noncalcified plaque segments in the models (Tables 7 and 8). In a sensitivity analysis, VAT was substituted for BMI, and aspartame intake remained an independent predictor of both total plaque and noncalcified plaque segments (data not shown).

DISCUSSION

This is the first study to evaluate the associations of natural and artificial dietary sweeteners with coronary plaque characteristics among a cohort of HIV-infected and non-HIV-infected participants. Participants in each group were well matched for overall CVD risk indices. Previous investigations exploring dietary intake among HIV-infected individuals have related saturated fat intake to elevated triglycerides [20] and alcohol intake to altered gut integrity and inflammation [21]. However, no studies to date have related dietary sweetener intake to measures of coronary plaque in an HIV-infected cohort. Our data demonstrate that consumption of dietary sweeteners was increased among the HIV-infected participants and that the artificial sweetener aspartame was associated with coronary plaque characteristics among individuals with HIV. The relationships with coronary plaque characteristics were not observed for other natural dietary sweeteners including total sugar, added sugar, sucrose, and fructose or saccharin, another artificial sweetener. Diet is well known to be related to CVD risk in the general population and is modifiable, unlike other CVD risk factors such as age and sex. Understanding dietary habits in relationship to measures of CVD risk among HIV-infected individuals, who are known to be at heighted risk for CVD, is critical for developing appropriate dietary counseling for this population.

Our data demonstrate that natural sweetener intake was significantly greater among the participants with HIV. In particular, added sugar intake was significantly greater in the HIV cohort, although added sugar intake for both the HIV and non-HIV cohorts exceeded the American Heart Association's recommendations of 36 grams/day for men and 24 grams/day for women [22]. However, in contrast to aspartame, no associations were observed between natural sweeteners and coronary plaque characteristics. Reasons for increased sweetener consumption among the HIV-cohort were not formally assessed in this study, but this observation could be due to a number of possible factors. Increased sweetener intake may be reflective of the general trend in the US population to exceed recommended limits, and guidance to limit added sugar is a more recent addition in the US Dietary Guidelines [23]. Moreover, dietary advice may be overlooked in the HIV population. It is also possible that there

Table 5. Univariate Relationship of Dietary Sweeteners and Immune Activation/Inflammation Markers Among HIV-Infected Participants

	Total Sugar, g/day		Added Sugar, g/day		Fructose, g/day		Sucrose, g/day		Aspartame, mg/day	
Parameter	rho[a]	*P* Value	rho[a]	*P* Value	rho[a]	*P* Value	rho[a]	*P* Value	rho[a]	*P* Value
Markers of Inflammation										
hsCRP, mg/L	0.06	.52	0.07	.49	0.05	.58	0.05	.61	0.17	.06
oxLDL, U/L	−0.01	.88	0.04	.69	−0.04	.66	−0.02	.80	0.17	.07
Lp-PLA$_2$ activity, nmol/(min × mL)	0.02	.79	0.10	.31	−0.16	.08	0.08	.38	0.21	.02
Markers of Monocyte/Macrophage Activation										
sCD163, ng/mL	−0.13	.16	−0.13	.19	−0.17	.06	−0.04	.67	−0.06	.52
sCD14, ng/mL	−0.12	.17	−0.04	.69	−0.05	.62	−0.13	.16	−0.14	.14
MCP-1, pg/mL	0.23	.01	0.20	.04	0.17	.06	0.20	.03	0.25	.007

Abbreviations: HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; Lp-PLA$_2$, lipoprotein-associated phospholipase A$_2$; MCP-1, monocyte chemoattractant protein 1; oxLDL, oxidized low-density lipoprotein; s, soluble.

[a]r is Spearman's rho.

Table 6. Univariate Relationship of Dietary Sweeteners and Immune Activation/Inflammation Markers Among Non-HIV-Infected Participants

	Total Sugar, g/day		Added Sugar, g/day		Fructose, g/day		Sucrose, g/day		Aspartame, mg/day	
Parameter	rho[a]	*P* Value	rho[a]	*P* Value	rho[a]	*P* Value	rho[a]	*P* Value	rho[a]	*P* Value
Markers of Inflammation										
hsCRP, mg/L	−0.25	.06	−0.15	.30	−0.22	.11	−0.32	.02	0.06	.67
oxLDL, U/L	−0.12	.40	−0.04	.77	−0.03	.85	−0.24	.07	0.14	.30
Lp-PLA_2 activity, nmol/(min × mL)	0.31	.02	0.28	.05	0.25	.07	0.26	.05	0.19	.16
Markers of Monocyte/Macrophage Activation										
sCD163, ng/mL	0.21	.12	0.17	.25	0.16	.26	0.21	.13	−0.10	.48
sCD14, ng/mL	−0.42	.001	−0.24	.10	−0.42	.002	−0.30	.03	0.03	.85
MCP-1, pg/mL	0.23	.10	0.35	.02	0.22	.22	0.14	.32	−0.12	.39

Abbreviations: HIV, human immunodeficiency virus; hsCRP, high-sensitivity C-reactive protein; Lp-PLA_2, lipoprotein-associated phospholipase A_2; MCP-1, monocyte chemoattractant protein 1; oxLDL, oxidized low-density lipoprotein; s, soluble.

[a]r is Spearman's rho.

may be a relationship between HIV, ART, and/or alterations in the microbiota to mediate taste receptors that may increase the affinity toward sweet taste.

Aspartame is metabolized in the circulation to aspartic acid, phenylalanine, and methanol. The sweetener provides 4 calories per gram and is the artificial sweetener most commonly found in diet sodas, cereals, yogurt, and chewing gum. Aspartame is known to be 200 times sweeter than regular sugar; therefore, the amount added to 1 diet soda is much less than the amount of sweetener added to 1 regular soda, resulting in its promotion as a "non-caloric alternative." The aspartame content of one 12-oz diet soda ranges from approximately 75 to 190 mg depending on the brand and type of soda, equaling approximately 0.02–0.05 kilocalories per diet soda, compared with approximately 150 kilocalories available from added sugar in a single soda. In the United States, the US Food and Drug Administration has assigned an acceptable daily intake (ADI) of aspartame of 50 mg/kg. The daily consumption of aspartame was increased among those consuming aspartame in the HIV cohort, but it fell well below the ADI, consistent with prior reports in the general population [24]. It is unknown whether elevated aspartame intake within the ADI contributes to coronary artery disease in the general population.

Several studies in the general population have explored the relationship of artificial sweetener intake, mostly in diet soda, to traditional CVD risk factors. Large observational studies such as the Multi-Ethnic Study of Atherosclerosis, the San Antonio Heart Study, and others have evaluated long-term consumption of artificial sweeteners and demonstrated that consumption of artificial sweeteners was positively associated with several

Table 7. Factors Associated With Coronary Plaque Features in the HIV-Infected Cohort Determined by Multivariables Regression Models[a]

		Total Plaque Segments		Noncalcified Plaque Segments		
Parameter	Order Parameter Entered in the Model	β-Estimate	*P* Value		β-Estimate	*P* Value
Race (white vs non-white)	1	0.561	.01			
Age	2	0.097	.001	2	0.031	.10
Smoking status (yes vs no)	4	0.413	.05			
Sex (male vs female)						
Current diabetes mellitus (yes vs no)						
Current hypertension (yes vs no)						
LDL, mg/dL						
HDL, mg/dL						
Triglycerides, mg/dL						
BMI, kg/m^2						
MCP-1, pg/mL	5	0.003	.06			
hsCRP, mg/L						
oxLDL, U/L						
Lp-PLA_2 activity, nmol/(min × mL)						
Log+1 aspartame, mg/day	3	0.512	.03	1	0.439	.002

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; Lp-PLA_2, lipoprotein-associated phospholipase A_2; MCP-1, monocyte chemoattractant protein 1.

[a]R^2 = 0.27 for total plaque segments, R^2 = 0.10 for noncalcified plaque segments. Covariates without data listed did not enter the model.

Table 8. Least Squares Multivariable Regression Model of Factors Entering Multivariables Regression Models to Predict Coronary Plaque in the HIV Cohort[a]

	Total Plaque Segments		Noncalcified Plaque Segments	
Parameter	β-Estimate	*P* Value	β-Estimate	*P* Value
Race (white vs non-white)	0.557	.01		
Age	0.099	.001	0.037	.04
Smoking status (yes vs no)	0.397	.06		
MCP-1, pg/mL	0.004	.04		
Log+1 aspartame, mg/day	0.477	.04	0.357	.007

Abbreviations: HIV, human immunodeficiency virus; MCP-1, monocyte chemoattractant protein 1.

[a]$R^2 = 0.26$, $P < .0001$ for total plaque segments and $R^2 = 0.10$, $P = .003$ for noncalcified plaque segments.

CVD risk factors including increased BMI, obesity, elevated fasting glucose, and type 2 diabetes [9, 25]. Our data extend these data by demonstrating possible effects of aspartame consumption specifically, rather than diet soda consumption in general, which includes any artificial sweetener. Traditional CVD risk factors including LDL, BMI, and VAT were significantly increased among HIV-infected, aspartame consumers, although fasting glucose was not different. These relationships were not observed in the non-HIV-infected cohort. Moreover, aspartame consumption was independently associated with coronary plaque and noncalcified coronary plaque segments in the HIV cohort when controlling for potential confounders such as traditional CVD risk factors and nontraditional CVD risk factors associated with coronary plaque formation. Our observation that VAT was significantly increased among HIV-infected, aspartame consumers might be via an effect of artificial sweeteners to regulate adipocyte lipid metabolism [26]. However, this needs further exploration because it is possible that HIV-infected patients with increased VAT opt to consume more aspartame.

Aspartame consumption is primarily related to total and noncalcified plaque in the HIV cohort. In the HIV population, nontraditional inflammatory markers more commonly relate to noncalcified, vulnerable plaque, whereas traditional risk factors more often relate to calcified plaque, as in the general population. Taken together, these data suggest that aspartame intake may contribute to plaque through nontraditional inflammatory pathways.

Markers of inflammation and immune activation were measured as part of previous studies [6, 16, 17]. Markers known to relate to coronary plaque in HIV, including MCP-1 [27] and Lp-PLA_2 [28], were found to be significantly and positively associated with aspartame consumption among the HIV-infected cohort. Monocyte chemoattractant protein-1 was also significantly and positively associated with sugar and sucrose intake in the HIV-infected cohort. In animal studies, administration of aspartame has been related to alterations in the structure and function of HDL [29, 30]; chronic inflammation is also known to alter HDL [31, 32]. Alterations in HDL may promote cell- mediated LDL oxidation and a subsequent increase in MCP-1 [30], all of which may have a downstream effect on atherogenesis. Although no relationships between aspartame and HDL were observed, the strong relationship between aspartame and MCP-1 might suggest a potential mechanism by which aspartame may affect plaque burden via immune activation.

Another potential mechanism of aspartame effects on plaque burden may relate to the enteric microbiome. Recent investigations in rodents suggest that artificial sweeteners, including aspartame and saccharin, have an effect on the enteric microbiota [33–35]. In a recent study, in vivo and in vitro administration of aspartame inhibited intestinal alkaline phosphatase (IAP) activity. Mice receiving aspartame and a high fat diet gained more weight, demonstrated glucose intolerance, and increased inflammation measured by tumor necrosis factor-α, compared with controls [34]. Phenylalanine, a major metabolite of aspartame, is known to inhibit IAP. Intestinal alkaline phosphatase is a protective, anti-inflammatory enzyme; its inhibition has been associated with increased intestinal inflammation, dysbiosis, and bacterial translocation resulting in systemic inflammation [36]. In human studies evaluating the effects of aspartame intake in healthy adults, aspartame consumers demonstrated a difference in overall bacterial diversity, although no differences in bacterial abundance or gene diversity were observed [37]. Human immunodeficiency virus infection is also known to alter the intestinal microbiota [38], and these alterations may also contribute to immune activation and inflammation in HIV. Indeed, there may be an additive effect of aspartame intake to further provoke the state of chronic immune activation and inflammation characterized by HIV infection, thereby enhancing atherosclerotic plaque formation. This may offer a potential explanation as to why similar effects of aspartame were not observed in the non-HIV-infected cohort.

Limitations

This study has some limitations as well as a number of strengths. This is the first study to date to investigate the relationship of dietary sweetener intake with detailed measures of coronary plaque and inflammation/immune activation in HIV. Aspartame is metabolized into amino acids in the circulation; therefore, the direct effect of aspartame may be different than determined from our findings. We cannot exclude the possibility that there may be confounding factors because the relationships observed were not present in the non-HIV cohort. Nevertheless, we continued to observe a signal for increased plaque burden in relationship to aspartame intake among HIV-infected patients despite controlling for several traditional and nontraditional

risk factors. There is also the potential of channeling bias, and the HIV-infected participants may have been receiving advice to substitute artificially sweetened "diet" foods for sugar. This appears less likely as total sugar intake was increased in the HIV group. Moreover, neither group approached recommendations with respect to fiber and fat, also suggesting the absence of any specific channeling of patients instructed to ingest more aspartame/artificial sweetener. Finally, the HIV and non-HIV groups were well matched in terms of overall CVD risk indices, and thus it would not be expected that the HIV group would be counseled to eat more artificial sweeteners. We used a standardized 4-day food record based on self-reported dietary intake, but this may not reflect chronic intake patterns. Finally, due to the cross-sectional nature of this study, definitive conclusions on causality cannot be made.

CONCLUSIONS

In summary, novel data from the current study suggests a unique, potential contribution of increased intake of the artificial sweetener aspartame to CVD risk, plaque burden, and inflammation in HIV infection. These findings should be considered as preliminary and hypothesis generating at the current time. Despite accumulating evidence suggesting that artificial sweeteners, including aspartame, may be associated with metabolic dysregulation resulting in CVD, we cannot determine causality between aspartame intake and coronary plaque formation because the possibility exists that there is confounding by other lifestyle/behavior and dietary factors not measured in this cross-sectional study. Further studies are critically important to explore the relationship of aspartame intake and coronary plaque burden, to identify mechanisms by which aspartame may exert its effects on plaque formation in the setting of HIV, and to assess whether dietary counseling on artificial sweetener intake may have cardiovascular benefit in HIV.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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