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New Markers of Dietary Added Sugar Intake

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Abstract

Purpose of review—Added sugar (AS) consumption is associated with adverse health outcomes including weight gain and cardio-metabolic disease, yet the reliance on self-reported methods to determine AS intake continues to be a significant research limitation. The purpose of this review is to summarize recent advances in the development of two potential predictive biomarkers of added sugar intake: $\delta^{13}\text{C}$ and urinary sugar excretion.

Recent findings—The results of numerous cross-sectional investigations have indicated modest associations of the $\delta^{13}\text{C}$ sugar biomarker measured in a variety of sample types (e.g., fingerstick blood, serum, red blood cells, hair) with self-reported AS and sugar-sweetened beverage (SSB) intake, and $\delta^{13}\text{C}$ values have been reported to change over time with changes in reported SSB intake. Results from large-scale trials have suggested modest associations of urinary sugar excretion with reported sugar intake, and a dose-response relation has been demonstrated between urinary sugar excretion and actual sugar intake.

Summary—Valid markers of sugar intake are urgently needed to more definitively determine the health consequences of AS intake. Adequately-powered controlled feeding studies are needed to validate and compare these two biomarkers of sugar intake, and to determine what individual characteristics and conditions impact biomarker results.

Keywords

Sugar; biomarker; dietary assessment; isotope; sucrose; fructose

Introduction

A large body of evidence has associated added sugars (AS) consumption with adverse health outcomes, including metabolic and cardiovascular diseases [1–3], weight gain [4–5], and poor diet quality [6]. The World Health Organization recommends that “free” sugars (i.e., AS and sugars naturally present in honey, syrups, and fruit juices) be limited to less than 10% of total energy intake, and ideally to less than 5% [7], which is similar to the 10% or less AS intake recommendation in the United States[8]. Yet, current AS consumption

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Conflicts of interest

The authors have no conflicts of interest to disclose.

patterns typically exceed these levels. For example, mean AS intake in the United States is 13% of total energy intake [9], and ranges from 7 to 17% in European populations [7]. Intake levels among children tend to be even higher – representing 16% of total energy among children in the United States [10], and 12 to 25% in Europe [7].

Aside from intake recommendations, significant controversy exists surrounding the health effects of AS [2, 11, 12], due in part to the methodological limitation of utilizing self-reported dietary intake assessment techniques [12, 13]. Under-reporting is a particular problem for total energy intake and for socially undesirable foods, such as those containing AS (e.g., sweets, sugar-sweetened beverages [SSB]) [13, 14]. The availability of an objective marker of dietary AS intake could overcome this research limitation [13, 14], strengthen the evidence-base for intake recommendations, and significantly advance research addressing the health consequences of AS consumption.

This review will describe recent advances in the development of two biomarkers of AS intake: $\delta^{13}\text{C}$ in human tissues, which has been proposed as a predictive biomarker of corn and cane sugar intake, and urinary sugar excretion, which is a predictive biomarker of dietary sucrose and fructose intake.

Carbon Isotope Added Sugar Intake Biomarker: $\delta^{13}\text{C}$

Corn and cane plants utilize the PEP-carboxylase enzyme to pre-concentrate carbon dioxide prior to carbon fixation, a process known as “ C_4 photosynthesis”, and thus manufacture sugars naturally enriched in the heavy stable isotope of carbon (^{13}C) [15 **]. As digested food is absorbed from the intestines into the bloodstream, the carbon within food becomes carbon within tissues. Thus, a high ratio of $^{13}\text{C}:^{12}\text{C}$ (measured as “ $\delta^{13}\text{C}$ ”) in human blood may reflect a high ratio of $^{13}\text{C}:^{12}\text{C}$ in the diet, with corn and cane sugars as important contributors (Figure 1) [15**]. Because more than half of AS is consumed in the form of SSB, and the majority of the AS consumed in many countries is ultimately derived from corn and cane plants, the $\delta^{13}\text{C}$ value of human blood may be affected by SSB intake [15**, 18*]. Analysis of $\delta^{15}\text{N}$ is sometimes concurrently performed with $\delta^{13}\text{C}$ analysis; the resulting dual isotope model may be used to correct for the potential confounding effect of meat consumption, as much livestock is fed upon corn, a C_4 plant [19,20].

$\delta^{13}\text{C}$ values can be determined using a variety of biological specimens, including blood (i.e., whole blood, serum, red blood cells [RBC], blood glucose, RBC alanine), bone, hair, nails, saliva, and urine. Specimen types reflect different time periods of AS intake (e.g., blood glucose reflects acute AS consumption, whole blood reflects consumption over 2–3 weeks; hair reflects consumption over 2–4 months) [15**]. Prior to isotopic analysis, samples are quantitatively combusted to CO_2 (e.g., blood, nail and hair tissues) or separated from mixture using gas and/or liquid chromatography (e.g., blood lipids, blood glucose). Samples are then assessed for $^{13}/^{12}\text{C}^{16}\text{O}_2$ and $^{15}/^{14}\text{N}_2$ using natural abundance stable isotope mass spectrometry. This technique requires minimal staff training for sample collection and storage for most sample types, no special storage or shipping conditions after collection, and can be performed on minimally invasive specimens (e.g., fingerstick blood, hair, nails). The equipment currently used for isotopic analysis is costly. However, with the advent of cavity

ring-down spectroscopy technology, the future cost of high-precision $\delta^{13}\text{C}$ analysis could decline significantly within the next decade, as combustion modules are integrated into easy-use continuous flow systems. Thus, the ability to measure $\delta^{13}\text{C}$ value could become more widely available in the near future.

Recent Human Studies

Two recent reviews describe research investigating the $\delta^{13}\text{C}$ method as a potential AS intake biomarker in substantial detail [15**,21**]. Studies of this biomarker published within the past 1–2 years are presented in Table 1. These studies included individuals with a range of AS and SSB intake (e.g., both low and high consumers) and weight status. Study populations have been primarily either white or Yup'ik Alaskan natives, and studies of adult populations have included a wide age range. Only two investigations have focused on children [22,23], who generally have a higher AS intake than adults. Most two studies were cross-sectional. To date, controlled feeding studies longer than seven days [28] have not been performed in adults or children to validate this AS biomarker; most existing validation studies have utilized self-reported dietary intake assessment methods to evaluate comparative validity.

Results from the literature available are promising, in that significant associations have been reported between the $\delta^{13}\text{C}$ sugar biomarker and self-reported total sugar, AS and SSB intake. Associations have also been noted between biomarker values and overall diet quality [18*], and with objectively assessed health outcomes, including carious tooth surfaces [22], indicators of cardio-metabolic risk [25*], and diabetes [27]. Changes in $\delta^{13}\text{C}$ values also have been shown to change in response to reported changes in AS and SSB intake [24*]. Overall, the magnitude of associations are generally modest (i.e., $r=0.3\text{--}0.4$; $r^2=0.2\text{--}0.5$), possibly in part due to reliance on self-reported dietary assessment methods as the primary method of comparison which could underestimate actual AS intake.

Strengths and Limitations

Advantages of this approach include the ability to use a wide variety of sample types – some which are minimally invasive – and the ease of sample collection, processing and storage. Disadvantages include the potential confounding effects of non-sweetener corn and meat consumption which may or may not be an issue depending upon the study population [19,20], an inability to reflect all dietary sources of AS (e.g., beet sugar), the potential impact of additives or preservatives to samples such as blood or urine [15**,21**], and analytical equipment requirements. However, analytical challenges may be more feasible in the future with the availability of an easily operable instrument that will be within the financial reach of most hospitals. Approaches which may be less sensitive but more feasibly implemented in large-scale, community-based trials (e.g., fingerstick blood) may be more better suited to studies in which categorizing AS intake levels is of interest. Therefore, the $\delta^{13}\text{C}$ biomarker approach has the potential for widespread application – ranging from clinical- and field-based nutrition research to clinical practice.

Future Research Needs

The most pressing research need for this potential marker of sugar intake is a large-scale validation study, greater than 2–3 weeks in duration, using a controlled feeding design. A study with this design is also needed to evaluate the biomarker's sensitivity to detect changes in AS intake over time. Study samples should include more diverse populations in terms of geography, race/ethnicity, and age, as variations in non-sweetener corn/meat consumption patterns, regional agricultural practices, and tissue turnover times may differ according to stage of growth [15**,21**]. More investigation is needed to examine a variety of specimen types [26*], in order to more definitively determine the time frame of AS consumption reflected by marker values [15**,21**]. Although challenging from an analytical standpoint, research is also needed to investigate HbA1C as a potential substrate, which may reflect habitual AS intake over longer periods of time.

Urinary Sugar Excretion: Total Sugar Intake Biomarker

When the disaccharide sucrose is consumed, most is broken down to glucose and fructose and absorbed in the small intestine. However, small amounts (i.e., mg quantities, or ~0.05% of intake) of intact sucrose are also absorbed in the small intestine and, along with fructose, excreted in the urine [29**]. This observation suggested that urinary sucrose and fructose excretion could represent a biomarker of recent sugar intake, although both AS and naturally-occurring sources of sugar (i.e., fructose from fruit/fruit juices) are reflected by the urinary sugar excretion measurement.

To evaluate urinary sugar excretion, two or more 24-hour urine samples are collected per participant. A preservative (e.g., thymol, boric acid) should be added to the collection container to prevent degradation of the excreted urinary sugars. Sample processing is minimal. Several analytical approaches can be used, including a commercially available assay kit and a spectrophotometer. To verify the completeness of 24-hour urine collections, para-aminobenzoic acid (PABA) may be administered to participants prior to sample collection in tablet form or added into study foods. PABA excretion is assessed in urine samples using a colorimetric analysis [30], and urine samples with 85% PABA recovery are generally considered complete and acceptable for inclusion in biomarker analyses (30). Spot urine samples have also been evaluated for urinary sugar excretion [29**,31*].

Recent Human Studies

A recent review describes prior investigations of the urinary sugar excretion method as a potential sugar intake biomarker in detail [29**]. Studies published within the past 1–2 years are presented in Table 2. Both studies included large sample sizes of adults, and reported associations of biomarker values with self-reported sugar intake [31*,32]. Tasevska and colleagues [32] utilized a biomarker-based calibration equation to predict total sugar intake, and compared this to self-reported intake in a US sample. Kuhnle and colleagues [31*] collected spot urine samples from a UK sample. In general, associations appear low to modest (i.e., $r=0.2$).

Strengths and Limitations

Advantages of this technique include the use of a minimally invasive sample type, minimal sample processing requirements, the availability of a commercially available assay kit for urinary sugar analysis, the possibility of performing assessments in spot urine samples, and the ability to be used in populations which consume a greater variety of sugar sources (e.g., beet sugar). However, limitations include the short time period reflected by this sugar biomarker (e.g., several hours to one day), which is not ideal for determining diet/disease associations as intake can vary over time, and the assessment of total sugar intake rather than AS, the latter of which is primarily targeted by dietary intake recommendations. Two or more 24-hour urine collections per participant are needed at each assessment point, which is burdensome for participants. Therefore compliance can be problematic, and should be assessed to insure that samples are complete, although possibly selectively [33]. Dose-response associations between sugar intake and biomarker values have been reported, yet there is substantial within-subject variability in sugar excretion at the same level of sugar intake [29**]. Results can be impacted by numerous factor such as differences in intestinal permeability, which can vary with gastrointestinal disorders, infections, non-steroidal anti-inflammatory drugs, and alcohol usage [29**].

Future Research Needs

Literature dating back several decades is available on the urinary sugar excretion marker of sugar intake, much more than on the carbon isotope sugar biomarker method in modern populations. Data are also available from several large-scale epidemiological trials, and at least two controlled feeding studies [30-34]. Several studies had more of an emphasis on developing and utilizing calibration equations from biomarker values to predict sugar intake. Controlled feeding studies are needed to better understand what individual characteristics and conditions impact intestinal absorption and sugar excretion, and thus biomarker values. To date, almost all studies have focused on adults [29**].

Conclusions

An ideal dietary biomarker is minimally invasive with a low participant burden, feasibly implemented in clinical and field research settings, inexpensive, valid, reliable, and sensitive to reflect changes in dietary intake. Both markers of sugar intake discussed in this review have shown promise, although both techniques have limitations including expensive instrumentation. A panel of urinary metabolites has also recently been suggested as a potential biomarker of acute SSB intake [35*]. To advance this area of research, adequately-powered validation studies using a controlled feeding design, which would ideally compare the markers of sugar intake, are needed. Valid sugar intake biomarkers are urgently needed to more definitively determine the health impacts of AS intake on body weight and cardio-metabolic outcomes [2].

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Abbreviations

AS	added sugar
BMI	body mass index
BP	blood pressure
C	carbon
FFQ	food frequency questionnaire
HDL	high-density lipoprotein
HEI-2010	Healthy Eating Index – 2010
HR	hazard ratio
LDL	low-density lipoprotein
PA	physical activity
PEP	phosphoenolpyruvate
SSB	sugar-sweetened beverage
T2D	type 2 diabetes
UK	United Kingdom
US	United States

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Key Points

- Controversy exists surrounding the health effects of added sugar intake, due in part to the well-recognized limitations of self-reported dietary assessment methods.
- In recent years, two approaches to objectively assess added sugar intake have received the most attention – the carbon isotope biomarker $\delta^{13}\text{C}$, and the urinary sugars excretion biomarker.
- Most studies evaluating the $\delta^{13}\text{C}$ biomarker have been cross-sectional; only one short-term controlled feeding study has been conducted to date.
- Dose-response associations between actual sugar intake and urinary sugar excretion have been reported, although individual variability is substantial at the same level of sugar intake.
- Controlled feeding studies are needed to understand what individual characteristics and conditions impact biomarker values (e.g., age, disease states); the validity, reliability, and sensitivity of biomarker values using a variety of sample types and analytical approaches.

Figure 1.

Histogram of the carbon stable isotope composition of blood serum collected from 406 anonymous donors with unknown dietary history compared to values for low-added sugar menu items (A), fruit juice (B) and fruit sugar (C), as well as for high-added sugar menu items (D), corn and cane sugars (E) and sugared sodas (F). [Data from Bostic and Jahren (*unpublished results*), 16, 17]

Table 1

Summary: Recent research* investigating the $\delta^{13}\text{C}$ sugar intake biomarker

Study	Substrate Assessed	Population	Design	Results	Comments
Chi et al., [22]	Hair	US children aged 6–17 years, Yup'ik Alaska Natives, 50% female (n=51)	Cross-sectional	40g/d increase in AS intake (determined by hair $\delta^{13}\text{C}$ analysis) was associated with 6.4% absolute increase in the proportion of carious tooth surfaces ($p=0.02$). No associations of self-reported sugary foods/beverage intake with tooth decay.	49% of children reported consuming SSB 2–3 times/day. Weight status was not reported. Equation used to estimate AS intake from $\delta^{13}\text{C}$ hair analysis was developed using prior data from 14–79 year old Yup'ik.
Davy et al., [23]	Finger-stick blood	US children aged 6–18 years, 92% white, 46% female (n=140)	Cross-sectional	$\delta^{13}\text{C}$ test-retest reliability, $r=0.99$ ($p<0.0001$). $\delta^{13}\text{C}$ value was associated ($P<0.0001$) with self-reported SSB kcal, $r=0.35$.	Mean reported SSB intake was 116±11 kcal/d. 20% of sample was overweight/obese.
Fakhouri et al., [24]	Blood serum	US adults aged 25–79 years, 81% black, 66% female (n=144)	18-month trial, subset of PREMIER	A 12 fl oz/d reduction in self-reported SSB intake was associated with 0.17% reduction in serum $\delta^{13}\text{C}$ value ($p<0.0001$) over 18 months.	Results remained significant after controlling for multiple confounders, including corn consumption and $\delta^{15}\text{N}$. Mean BMI=34kg/m ²
Hedrick et al., [19]	Finger-stick blood	US adults aged 18 years, 91% white, 77% female (n=257)	Cross-sectional	$\delta^{13}\text{C}$ value was associated ($p=0.01$) with AS ($r=0.32$) and SSB ($r=0.39$). Including $\delta^{15}\text{N}$ resulted in minimal changes to the model's ability to predict AS/SSB intake.	74% of sample was overweight/obese. Mean reported SSB intake was 359±347 kcal/d. Non-sweetener corn intake was not associated with $\delta^{13}\text{C}$ value.
Hedrick et al., [18]	Finger-stick blood	US adults aged 18 years, 94% white, 83% female (n=216)	Cross-sectional	Regression models demonstrated that HEI-2010 (i.e., overall diet quality) ($R^2=0.16$), AS ($R^2=0.15$) and SSB ($R^2=0.14$) were all significant predictors of fingerstick $\delta^{13}\text{C}$ value. HEI-2010 was significantly different across $\delta^{13}\text{C}$ tertiles.	High habitual SSB consumers according to self-report (>200 kcal/d). Mean BMI=33kg/m ²
Nash et al., [25]	Red blood cells	US adults aged 19–94 years, 55% female, Yup'ik Alaska Natives (n=1076)	Cross-sectional	Total sugar intake was estimated via prediction equation using RBC $\delta^{13}\text{C}$ and $\delta^{15}\text{N}$ values; positive associations of sugar intake noted with BP and triglyceride concentrations; inverse associations noted with total-, HDL- and LDL-cholesterol concentrations.	68% were overweight or obese; BMI and waist circumference were not associated with estimated sugar intake.
Nash et al., [26]	Plasma, plasma glucose, RBC, hair	US adults aged 14–79 years, Yup'ik Alaska Natives Two sets of participants (n=52 with complete data; n=68 with partial data; ~50% female overall)	Cross-sectional	RBC and hair dual isotope ($\delta^{13}\text{C}$ and $\delta^{15}\text{N}$) models predicted self-reported total sugar ($R^2=0.52-0.53$), AS ($R^2=0.47-0.48$) and SSB intake ($R^2=0.34$). Plasma dual isotope models predicted SSB ($R^2=0.28$) but not total sugars or AS. Fasting plasma glucose was not associated with any of the self-reported sugar intake variables.	55–56% in each sample were overweight or obese; most were >21 years or older (84–90% of sample).
Patel et al., [27]	Blood serum	UK adults aged 40–79 years, 59% female (total n=1178; 476 T2D cases and 718 in subcohort)	Case-cohort study, longitudinal	$\delta^{13}\text{C}$ values were lower in cases than in the subcohort ($p=0.009$), and inversely associated with T2D (HR per tertile 0.74, $p<0.001$). No	European population with different primary sources of sugar intake than US samples. Mean BMI=26 kg/m ²

Study	Substrate Assessed	Population	Design	Results	Comments
				associations between $\delta^{13}\text{C}$ values and sugar intake determined by FFQ.	

* Published in 2014–2015.

Abbreviations used: US = United States; AS = Added Sugar; SSB = Sugar-sweetened Beverage; PA = physical activity; BMI = body mass index; HEI-2010 = Healthy Eating Index – 2010; BP = blood pressure; HDL = high-density lipoprotein; LDL=low-density lipoprotein; UK = United Kingdom; T2D = type 2 diabetes; HR = hazard ratio; FFQ = food frequency questionnaire.

Table 2

Summary: Recent research* investigating the urinary sugar excretion biomarker

Study	Sample type	Population	Design	Results	Comments
Kühnle et al., [31]	Spot urine sample	UK adults aged 39–77 years, 54% female (n=1734)	Longitudinal; 3-year follow up period	Baseline urinary sucrose concentration was associated with an increased risk of overweight/obesity and BMI at year 3, and with baseline self-reported sugar intake determined by 3 methods: 7 day diaries, 24-hr recall, and FFQ.	Self-reported sucrose intake was inversely associated with BMI. Mean baseline BMI =26kg/m ²
Tasevska et al., [32]	24-hour urine sample	US adults aged 60–91 years, 100% female, postmenopausal 64% white (n=450)	Cross-sectional	Associations between (log) biomarker-based total sugars intake and self-reported intake using three methods (FFQ, 4d diary, three 24-hr recalls) ranged r=0.13 – 0.16.	Using biomarker values, calibration equations were used to predict total sugar intake. 66% of sample was overweight/obese. A second follow-up sample (n=88) was included for reliability assessment at 6 mo.

* Published in 2014–2015.

Abbreviations used: UK = United Kingdom; BMI = body mass index; FFQ = food frequency questionnaire; US = United States.