Sweetener associated with increased adiposity in young adults

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Many students experience weight gain during their first year of college, which has been attributed to environmental changes, including eating habits and activity patterns. A new study implicates the endogenous metabolite and sugar substitute, erythritol, as a novel physiological marker predictive of vulnerability to increased adiposity.


Upon entering college, many, but not all, young adults experience weight gain commonly called the ‘freshman 15’; such weight fluctuations might set the stage for the emergence of many future risk factors for chronic metabolic diseases including dyslipidaemia, hypertension and glucose intolerance. Generally attributed to poor eating habits, stress and reduced levels of physical activity, little is known about physiological markers that might predict which individuals are more or less vulnerable to weight gain. Now, Hootman and colleagues have conducted a prospective study (n = 264) designed to identify the presence of biomarkers that could predict changes in adiposity in this population.

Within the first 3 days of arrival at campus, students provided a baseline blood sample, and various measures of body composition were collected. A follow-up sample was obtained 9 months later, at the end of the academic year; 172 students (65%) provided data at both time points. In this relatively short period of time, weight gain >0.5 kg was experienced by 75% of the retained sample with an average increase in body mass of 3.6%. Although a small number of students had stable weight and adiposity measures (16 students), a larger subset (66 students) was classified as having increased central adiposity, with 4.0 kg gain in weight, 3.9 cm gain in waist circumference and 2.6% increase in dual-energy X-ray absorptiometry (DXA)-derived truncal adiposity on average.

To better understand factors and metabolic alterations that might predict levels of adiposity gain, the investigators used non-fasted plasma samples that were pooled into discrete categories defined by the investigators. These categories included the 16 weight-stable individuals and 66 central-adiposity gainers along with those segregated by HbA1c values (lowest 10%; 7 students; highest 25%; 21 students). Untargeted metabolomics analysis (that is, gas chromatography–mass spectrometry) revealed five metabolites that corresponded to differences in weight gain grouping: erythritol, fructose and three unknown metabolites. Of these, only erythritol retained significance for positive associations with adiposity gain and increased baseline HbA1c levels after false discovery rate correction. The origin of erythritol was not known, but the investigators proposed two possible sources: dietary consumption of the sweetener or its production through endogenous metabolism.

In the diet, erythritol occurs naturally in several foods, including wine, beer, watermelon, pear, grape and soy sauce. Erythritol is also a polyol, a sugar alcohol used as a sugar substitute in many food and drink items, including gums, yogurt and confectionary; in medications; and in combination with high-intensity sweeteners in products such as Truvia.

Current estimates indicate that 25% of children and 41% of adults in the USA consume foods or beverages manufactured with low-calorie or no-calorie sweeteners. Although the average daily consumption of erythritol has been estimated to be about 1 g per day, the highest consumers (90th percentile) consume far greater amounts (estimated at 4 g per day). In humans, the majority of the sweetener is excreted in the urine, with the remaining 5–10% oxidized to erythronate.

Unfortunately, dietary records analysing erythritol-containing foods and the consumption of no-calorie or low-calorie sweeteners by the students in the study were not obtained by Hootman and colleagues. Previous findings indicate that individuals with increased body
weight tend to consume more food and drink products containing low-calorie or no-calorie sweeteners—a possible explanation for the increased circulating levels of the metabolite in these individuals. Although controversial, increased adiposity, glucose intolerance and gut microbiota disturbances in response to consumption of low-calorie sweeteners have been well documented in both humans and animal models of diet-induced metabolic dysregulation. Of particular relevance to the study by Hootman et al., consumption of water sweetened with erythritol and aspartame has been shown to cause marked increases in adiposity and hyperinsulinaemia, along with other metabolic derangements in a mouse model of diet-induced obesity.

A second possibility that could account for the association between levels of erythritol and gain in central adiposity is endogenous production of erythritol. Although previous work has suggested that humans do not produce erythritol, Hootman et al. showed by in vivo and ex vivo blood incubation that humans do seem to be able to metabolize glucose to erythritol through the pentose phosphate pathway (PPP). The PPP pathway is a protective pathway aimed at reducing metabolic overload in the face of nutrient excess and is governed by the rate-limiting enzyme glucose-6-phosphate dehydrogenase (G6PD), which converts glucose into other metabolic by-products, including ribose for nucleotide biosynthesis and antioxidant factors. Excess flux through this pathway has a major effect on the pathogenesis of comorbidities related to hyperinsulinaemia and obesity. In animal models of obesity, G6PD expression is upregulated to facilitate flux through the PPP, and overexpression of the enzyme in adipocytes causes oxidative stress and macrophage recruitment that leads to insulin resistance. Given these findings, it is not unreasonable to suspect that increased PPP flux and G6PD upregulation could occur in response to excess glucose in humans. Whether this pathway accounts for the association between erythritol, glucose intolerance and central adiposity observed in the study by Hootman et al. requires further investigation.

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Limitations of the study by Hootman and colleagues included the use of pooled, rather than individual, samples, as well as segregation of data into finite categories, which resulted in a very small number of individuals in some categories. In addition, no consideration was paid to the sex of the participants despite apparent differences in the distribution of men and women across groups and known sex differences in metabolic profiles in humans. Although race and ethnicity of participants were also not reported, the next steps will include validation of erythritol as a biomarker for adiposity gain in other larger cohorts in which sex, race and ethnicity will be considered. Understanding the source of erythritol is also crucial. Data from three male individuals in the study suggested that erythritol might be produced from glucose, but the level of this production, its contribution to the entire erythritol pool and any metabolic effects have yet to be elucidated. Dietary contributions also need to be clarified as individuals in the present study were not fasted before sampling and the metabolite is known to persist 24–48 h after ingestion of meals. This aspect is especially important if those individuals with increased central adiposity consume more foods and beverages manufactured with non-nutritive sweeteners. If this is the case, the erythritol biomarker might merely be a reflection of differences in diet patterns rather than a physiological predictor of an adiposity gain phenotype.

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