

Effect of Acute Consumption of Artificially Sweetened Beverages on Blood Glucose and Insulin in Healthy Subjects

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Abstract

Introduction: Non-caloric artificial sweeteners (NAS) consumption may not be safe for health. Several cohort studies have found a positive association between consumption of artificially sweetened beverages (ASB) with weight gain chronic non-communicable diseases. Therefore, it is of interest to study the effect of the consumption of NAS on glucose and insulin response in different conditions.

Aim: To determine the effect of acute NAS consumption on blood glucose and insulin curves in healthy people.

Methods: A randomized double-blind clinical trial was conducted in 9 apparently healthy subjects who were randomly assigned to drink one can of ASB and one can of sugar sweetened beverages (SSB) and repeated under identical conditions for 3 times each beverage. Blood glucose and insulin levels were measured in the fasted state and during 180 min after the ingestion of the beverage. Areas Under the Curve (AUC) for glucose and insulin were calculated for the values above baseline for the 3 hour period following the drink intake. Within and between coefficients of variation were calculated.

Results: The ASB beverage induced a significantly lower area under the curve (AUC) for plasma glucose ($87 \pm 182 \text{ mg} \cdot \text{min}/\text{dl}$) and plasma insulin ($36 \pm 50 \mu \text{ UI} \cdot \text{min}/\text{ml}$) compared with the SSB drink (glucose $954 \pm 669 \text{ mg} \cdot \text{min}/\text{dl}$ and insulin $1738 \pm 887 \mu \text{ UI} \cdot \text{min}/\text{ml}$) $p < 0.05$.

Conclusion: The acute consumption of NAS in carbonated beverages, under fasting conditions, does not produce change in blood glucose or insulin in healthy subjects.

Keywords: High-Intensity sweeteners; Non-Nutritive sweeteners; Artificial sweeteners; Glucose intolerance; Insulin

Highlight

- A positive association between consumption of artificially sweetened beverages (ASB) with weight gain has been found.
- A positive association between consumption of non-caloric artificial sweeteners (NAS) and glucose intolerance has been described.
- The consumption of NAS in carbonated beverages, under fasting conditions, does not produce effects on glycaemia or insulinemia in healthy subjects.

Introduction

During the last decades, the prevalence of overweight and obesity has increased in different regions of the world [1], as well as in the Chilean population. In 2003, 61% of the Chilean population suffered from overweight or obesity, increasing to 74% in 2017, according to the last results of the National Health Survey 2016-2017 [2]. The increase of overweight and obesity is accompanied by the rise in non-communicable chronic diseases (NCDs) [2]. In order to treat these diseases many interventions have been suggested, among them losing weight through physical exercise and low calories diets (LCD). One way to consume LCD is by replacing sugar with Non-Caloric Artificial Sweeteners (NAS), which has led to an increase in their consumption since 1965 [3].

Although the Food and Drug Administration established Acceptable Daily Intakes (ADIs) for different NAS, there is concern about the effects of these compounds on health [4]. There is an association between the use of NAS and weight gain and increased risk of developing T2D or Metabolic Syndrome (MetS) [5-7]. Epidemiological studies reported that the consumption of artificially sweetened beverages (ASB) is

associated with an increased risk of weight gain and, therefore, a greater risk of developing overweight or obesity in a dose-dependent manner [8], as well as being positively associated with the incidence of MetS and T2D, higher fasting blood glucose and greater waist circumference [9]. However, other cohort studies found opposite results, where only sugar sweetened beverages (SSB) were associated with increased risk of T2D in men [10] and increased risk of weight gain [11].

It is postulated that NAS are not inert and could affect the biological processes related to glucose homeostasis and energy [6,7]. Three mechanisms related to metabolic dysregulation have been studied, which are not necessarily exclusive. In animal studies with saccharin and aspartame, NAS can interfere with learned responses that contribute to glucose control and energy homeostasis, including appetite control and adequate weight gain [5,7,12-14]. However, in human studies this mechanism has not been demonstrated [15-20]. NAS can interfere with the intestinal microbiota in animal and human models [16,21,22]. Saccharin [21] or aspartame NAS [22] produce glucose intolerance mediated by gut dysbiosis. Finally, NAS can interact with sweet taste receptors expressed in the gut, modulating glucose metabolism by

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producing increased glucose uptake and triggering insulin secretion secondary to an increase in the secretion of Glucagon-Like Peptide-1 (GLP-1) [9]. GLP-1 stimulation and insulin secretion were greater in healthy subjects who were provided beverages or solutions containing NAS, followed by an oral glucose tolerance test (OGTT) of 75 grams of glucose, compared with beverages containing sucrose [9,23-27]; Similar results are described in Type 1 Diabetes (T1D), but not in T2D [23,24]. However, we do not know if stimulating the cephalic phase by perceiving a sweet taste during the oral intake of a sweetened drink stimulates the secretion of insulin and increases the glycaemia.

With the hypothesis that NAS reduce insulin sensitivity, the aim of this study was to determine the effect of an acute consumption of non-caloric artificial sweeteners after an overnight fast, on glucose and insulin responses.

Methods

A double-blind RCT with cross-over design study was carried out within the facilities of the Institute of Nutrition and Food Technology (INTA) of the University of Chile.

Healthy volunteers of both sexes aged between 26 and 56 years were invited to participate in the study. Exclusion criteria were pregnancy, a fasting blood glucose >110 mg/dl, or a family history of type 1 or 2 diabetes, body mass index <20 and >28 kg/m², being on a special diet, or under any medication.

After subjects signed an informed and written consent, they were cited to INTA for a fasting blood glucose testing and recording of personal data [28].

Glucose and insulin response to a SSB or an ASB were measured in each subject and repeated under identical conditions six times, at intervals of at least 1 week. In a randomized way, the volunteers ingested 350cc (1 can) of an ASB sweetened with 84 mg of aspartame and 56 mg of Potassium Acesulfame (AceK) (0.7 kcal), or 350cc (1 can) of a SSB sweetened with 38.7 g of sucrose (154 kcal) on three occasions for each beverage. The two drinks had the same flavour and composition, except by the sweetener and were blinded to the researchers and participants (the cans were completely covered). The procedure was performed according to Wolever & Jenkins [29] recommendations and our previous experience [30,31].

On each test day, subjects attended to INTA between 07:30 h and 08:30 h, after an overnight fast of 12 hours. Thirty minutes after installation of a catheter in a peripheral arm vein, two blood samples (3 ml) were taken at 15 min. intervals to obtain the baseline glucose and insulin values. Just after the second sampling (time 0), one of the drinks was ingested within 10 minutes. Subsequently, blood samples (3 ml) were obtained at 15, 45, 60, 90, 120, 150 and 180 minutes, to measure glucose and insulin. The subjects were sitting comfortably in a quiet room and they did not ingest foods before the end of the test.

Blood samples were centrifuged at 3000 rpm for 15 minutes at 4°C. Glucose was measured using the glucose oxidase method (GOD PAP) and insulin was measured with radioimmunoassay (RIA) using commercial kits (DPC, Los Angeles, CA, USA) [30].

AUC for glucose and insulin (gAUC and iAUC) were calculated, according to the procedure of Wolever & Jenkins [29], using serum glucose and insulin concentrations obtained before and during the 3 hours period following the drink ingestion as shown in Figure 1.

Sample size was calculated using the data obtained in a previous related study [30]. We expected to find a gAUC and iAUC of the ASB 20% greater than the gAUC and iAUC of the SSB and considering an alpha error of 0.05 (95% confidence level), a beta error of 0.2 and. We also considered 15% loss rate, rendering a sample size of 10 volunteers.

Statistical analyses were performed using the Stata MP 13 program. Descriptive data are expressed as mean ± standard deviation. Wilcoxon test was performed for non-parametric variables to assess differences between AUC. One-way ANOVA was performed to assess variations in plasma glucose and insulin per type of product. Differences were considered significant at p<0.05. Finally, an analysis of the variability of the AUC for glucose and insulin was made according to the coefficient of variation results.

The individual variability of gAUC and iAUC were calculated using the coefficient of variation (CV = 100 x SD/mean) for each subject. The mean value obtained for each subject was used to calculate the inter-individual coefficient of variation.

Results

Ten healthy volunteers, 5 men and 5 women who met the inclusion criteria, were enrolled in the study as shown in Table 1. Nine individuals completed the study, since one did not finish the study due to poor tolerance to prolonged fasting.

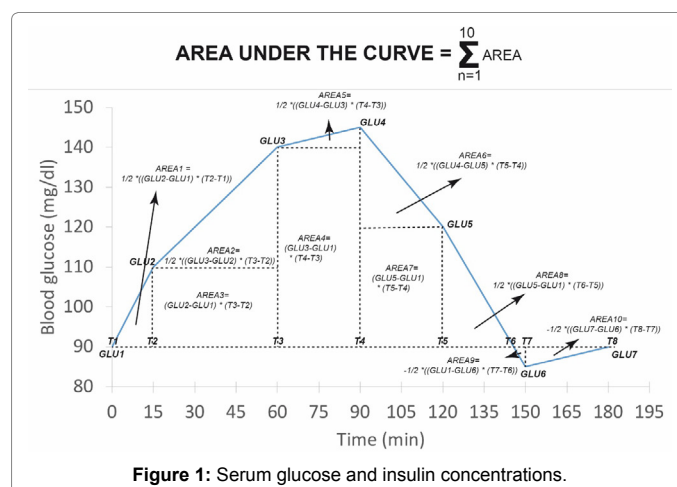


Figure 1: Serum glucose and insulin concentrations.

Volunteer	Age (years)	Weight (kg)	Height (m)	BMI (kg/m ²)	Glycemia (mg/dl)	Pulse (x')	SBP (mm Hg)	DBP (mm Hg)
1	27	60.9	1.61	23.6	82.3	60	101	66
2	26	51.3	1.57	20.8	91.3	72	109	67
3	36	65.5	1.60	25.6	90.7	68	113	60
4	26	81.8	1.77	26.1	90.3	82	122	70
5	25	55.6	1.53	23.8	73.9	79	100	53
6	27	60.9	1.70	21.1	82.9	77	105	64
7	31	62.4	1.67	22.4	92.3	70	114	73
8	25	80.5	1.72	27.2	81.6	64	130	79
9	26	73.5	1.70	25.4	94.8	54	123	71
10	25	54.5	1.69	19.1	85.3	82	117	73
Average	27.4	64.7	1.66	23.5	86.5	70.8	113.4	67.6
SD	3.5	10.7	0.08	2.6	6.4	9.5	9.9	7.4

Note: *P-value <0.05. SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; SD: Standard Deviation' Minutes.

Table 1: General characteristics of volunteers.

The AUCs of glucose and insulin of each volunteer and their coefficients of variation, after ingesting the SSB or the ASB, are shown in Tables 2 and 3. Plasma glucose levels did not change after ingesting the ASB. After ingesting the SSB, the glucose peaked at 15 min ($p > 0.05$). At 90 and 120 minutes blood glucose dropped below the basal levels (>0.05). At 180 minutes, blood glucose levels were similar for both drinks. The insulin curve only changed with the SSB, with the maximum insulin peak at 15 minutes. At 180 minutes with both drinks, the insulin levels were similar.

Intra-individual variability of the glucose AUC was 58% (0- 173%) for ASB and 63% (28- 122%) for SSB. The inter-individual variability was 208% for ASB and 70% for SSB. Intra-individual variability of the insulin AUC was 128% (71- 173%) for ASB and 32% (8-63%) for SSB. The inter-individual variability was 139% for ASB and 51% for SSB.

Glucose and insulin curves are depicted in Figures 1 and 2. The AUC for glycaemia and insulinemia are significantly higher for SSB than for ASB Figure 3.

Discussion

According to these results, in healthy adults who regularly consume sweeteners and sugar, the acute intake of artificially sweetened

beverages after an overnight fast does not produce significant changes in blood glucose or insulin. As expected sugar-sweetened beverages increase blood glucose and insulin 15 min after ingestion and at 90 minutes blood glucose drops below the baseline.

We must be very careful with the interpretation of the results due to the great intra and inter variability observed in this study as in others performed by our group [31]. Intra-individual variability for the same beverage means that several factors could influence insulin and glucose homeostasis, such as the health status of the subject, the previous day's diet, the level of stress, which can cause changes in gut motility and glucose uptake, or lack of sleep that may decrease insulin sensitivity in healthy subjects [31]. To diminish the effects of these factors, each individual performed three tests with both drinks. However, we observed a greater inter-individual variability for glucose and insulin, for ASB compared to SSB, suggesting that glucose and insulin respond differently to SSB and ASB in healthy subjects, therefore, it could be that response to ASB is more dependent on the individual conditions previously mentioned.

Our results are comparable to those of other randomized clinical trials, despite differences in their methodology. Although *in vitro* studies

Beverage Volunteer	Artificially sweetened			Sugar sweetened		
	Blood glucose AUC (x ± SD)			Blood glucose AUC (x ± SD)		
1	15	±	25	2116	±	937
2	32	±	50	606	±	537
3	0	±	0	1726	±	1482
4	0	±	0	290	±	84
5	200	±	306	1245	±	674
6	0	±	0	338	±	124
7	0	±	0	574	±	290
8	540	±	192	1315	±	710
9	0	±	0	366	±	446
Average	87*	±	182	954*	±	669
Median	0			606		537

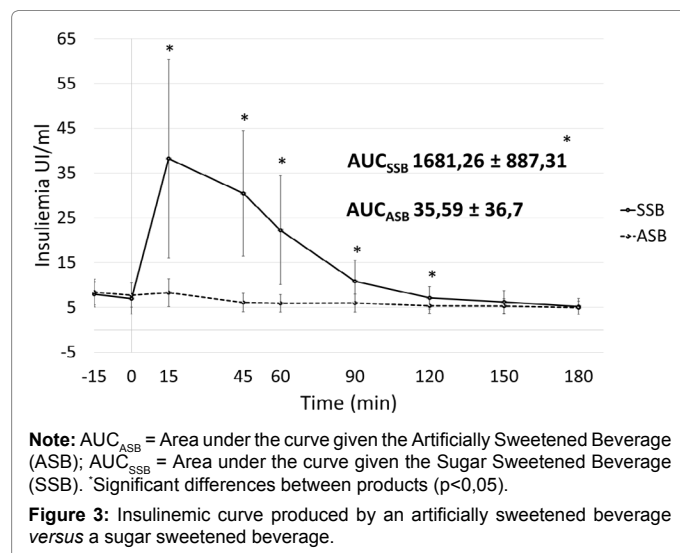
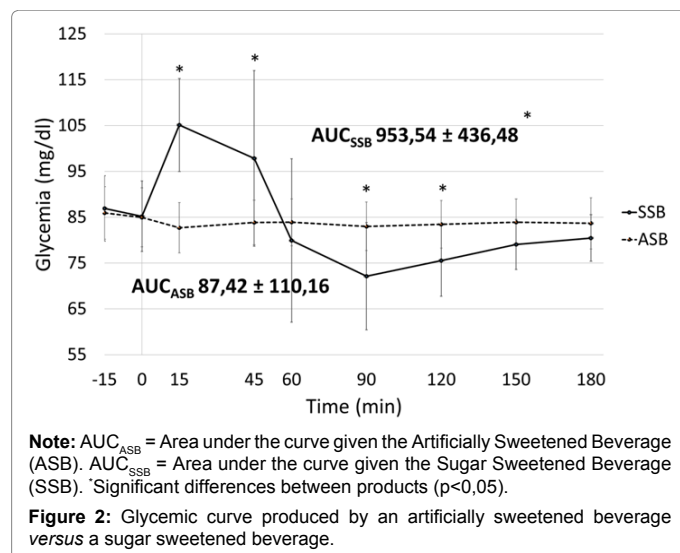
Note: AUC: Area under the Curve; ASB: Artificially Sweetened Beverage; SD: Standard Deviation; CV: Coefficient of Variation; SSB: Sugar Sweetened Beverage. *P-value <0.05.

Table 2: AUC of glucose for the artificially sweetened drink and the sugar sweetened drink and coefficients of intra and between-individual variation.

Beverage Volunteer	Artificially sweetened			Sugar sweetened		
	Blood Insulin AUC (x ± SD)			Blood Insulin AUC (x ± SD)		
1	6	±	9	1411	±	106
2	26	±	35	2551	±	522
3	36	±	51	2561	±	1613
4	10	±	17	1120	±	325
5	60	±	74	3457	±	1449
6	4	±	8	1071	±	280
7	6	±	5	1336	±	300
8	15	±	13	1130	±	351
9	159	±	112	1002	±	430
Average	36*	±	50	1738*	±	887
Median	15		17	1336		351

Note: AUC: Area under the Curve; ASB: Artificially Sweetened Beverage; SD: Standard Deviation; CV: Coefficient of Variation; SSB: Sugar Sweetened Beverage. *P-value <0.05.

Table 3: AUC of insulin for the artificially sweetened beverage and sugar sweetened drink.



showed that sucralose, at concentrations of 1-5 mM, stimulates the secretion of GLP1 and gastric inhibitory polypeptide (GIP), in a dose-dependent manner [32,33], studies in animals did not demonstrate this effect. In healthy adults, delivery of an intragastric solution containing different doses of sucralose, to skip the cephalic phase, had no effect on insulin, GLP-1 and GIP incretin secretion [32,34,35]. Studies delivering an intragastric solution of aspartame or Acek or sucralose also had no effect on insulin or GLP-1 secretion in healthy subjects.

There is agreement that the intake of NAS solutions without a glucose load have no effect on insulin secretion. These results are comparable to those of the present study. However, all these studies are short term and after an acute consumption of the drink. Thus, we can conclude that NAS have no cephalic or subsequent effect on insulin secretion, since neither the route of administration (oral or feeding tube) nor the type of NAS had any effect on insulin secretion. On the contrary, in some studies [9,25,26,27] the provision of NAS along with a load of glucose increases the secretion of insulin and incretins in healthy adults, therefore, generating in the long term greater risk of developing IR or T2D. The postulated mechanism is that NAS, when given along with a glucose load, interact with sweet taste receptors of the gut, generating an increase in glucose uptake and triggering the secretion of insulin by increasing the secretion of GLP-1 [9].

Finally, we observed a high intra- and inter-individual variability of insulin AUC with ASB. We do not have a clear explanation for this. However, every time our group has carried out studies measuring glucose and insulin curve for a standard meal, we observed high intra and inter-individual variations. Probably this variation of the glycaemic and insulinemic response is subject dependent [30].

Conclusion

We observed no effect of NAS on insulin secretion in the short term.

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