Serum β-Glucuronidase Activity in Response to Fruit and Vegetable Supplementation: A Controlled Feeding Study

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Abstract

Background: **Fruit and vegetable (F&V) intake may lower the risk of some cancers. One hypothesized, but understudied, chemopreventive mechanism is that plant food constituents inhibit β-glucuronidase, an acid hydrolase that deconjugates glucuronides.**

Methods: **We conducted a crossover feeding trial in 63 healthy women and men ages 20 to 40 years to examine the effect of diet on serum β-glucuronidase activity. Participants were randomized to two 2-week experimental diets with an intervening washout period: a diet high in selected citrus fruit, crucifers, and soy (F&V) and a diet devoid of fruits, vegetables, and soy (basal). Serum β-glucuronidase activity was measured during the preintervention, F&V, and basal periods. Linear mixed models were used to obtain effect estimates and 95% confidence intervals (95% CI).**

Results: **We observed statistically significantly higher β-glucuronidase activity during the F&V than the basal diet (ratio, F&V versus basal diet, 1.09; 95% CI, 1.05-1.13; $P < 0.01$). These results were probably due to decreased β-glucuronidase activity during the basal diet (ratio, basal period versus preintervention, 0.93; 95% CI, 0.87-0.98; $P = 0.01$) rather than increased enzyme activity during the F&V diet (ratio, F&V period versus preintervention, 1.01; 95% CI, 0.96-1.06; $P = 0.64$). Response to the experimental diet did not differ by sex ($P_{interaction} = 0.30$), but there was a suggestion of a short-term diet effect at 8 versus 15 days ($P_{interaction} = 0.06$).**

Conclusion: **This intervention of selected F&V did not lower β-glucuronidase activity. Further investigation is needed regarding what other foods and phytochemicals may influence β-glucuronidase activity and effect modifiers of this relation.** (Cancer Epidemiol Biomarkers Prev 2008;17(7):1808–12)

Introduction

Fruit and vegetable (F&V) intake may lower risk of some human cancers (1, 2). One hypothesized, but understudied, mechanism is the inhibition of the acid hydrolase, β-glucuronidase, found in most tissues, such as the liver, kidney, spleen, intestinal epithelium, and endocrine and reproductive organs (3). β-Glucuronidase cleaves glucuronic acid from substrates (e.g., drug and nondrug xenobiotics, steroid hormones, and other endogenous compounds), making them less water-soluble and less able to be excreted. β-Glucuronidase may increase cancer risk, because potential carcinogens and promoting agents, once deglucuronidated, have the ability to recirculate and interact with cells.

Plant food constituents, such as D-glucaric acid, may act as nontoxic β-glucuronidase inhibitors in humans (4) and thus lower cancer risk. D-Glucaric acid is converted into D-glucaro-1,4-lactone, which competitively inhibits β-glucuronidase and has been shown to reduce chemical carcinogen-mediated mammary, liver, and skin tumors in animals (5-7). The effect of D-glucaric acid in preventing human cancer is unknown. Among commonly consumed plants, citrus and cruciferous foods are rich in D-glucaric acid (8).

Previously, we conducted a cross-sectional pilot study of 83 men and 120 women to examine dietary associations with serum β-glucuronidase activity (9). We used serum β-glucuronidase because it reflects tissue β-glucuronidase resulting from cell turnover, particularly from the liver, which is the major source of the enzyme, and because serum collection requires minimally invasive methods. We found that β-glucuronidase activity was significantly inversely associated with intakes of plant protein, fruit, dietary fiber ($r = -0.24$ to -0.30; $P < 0.01$), the botanical groupings of Cucurbitaceae, Rosaceae, and Leguminosae (correlation, $r = -0.16$ to -0.19; $P < 0.05$), and serum α-carotene, β-carotene, and β-cryptoxanthin ($r = -0.18$ to -0.26; $P \leq 0.01$).

No human intervention study has examined this relation. We thus conducted a crossover feeding trial to compare the effects of a diet high in selected F&V with a diet devoid of F&V on serum β-glucuronidase activity. Based on earlier investigations of D-glucaric acid and our observational pilot study results, we hypothesized that a plant-rich diet would lower β-glucuronidase activity.

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Materials and Methods

The investigation was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board. Informed written consent was obtained from all participants.

Participants and Covariate Data. Participants were recruited from 193 individuals who had met the selection criteria for and completed an initial cross-sectional study (10). Because of the aims of the parent study (10), participants were also recruited based on the UDP-glucuronosyltransferase (UGT). Of the 111 eligible for the feeding study, 72 consented and were randomized. Of these, 8 withdrew and 1 was noncompliant with the diet. Before the intervention, each participant provided demographic and health-related information and baseline data on dietary intake over the past 3 months.

Feeding Study Design. Participants were randomized and blocked on sex and UGT1A1 genotype. Using a crossover study design, participants consumed two 2-week (14 days) experimental diets assigned in random order, with an intervening washout phase of at least 2 weeks when individuals resumed their habitual diet. The basal experimental (control) diet was low in phytochemicals and contained low-fiber refined foods, without fruits, vegetables, herbs, or spices (menu presented in ref. 10). The F&V experimental diet consisted of the basal diet supplemented with crucifers (broccoli, cabbage, and radish sprouts), citrus fruits (grapefruit/orange segments, grapefruit/orange juice, and dried orange peel), and soy foods (tofu, soy nuts, and soy milk). Crucifers and citrus fruits contain D-glucaric acid and therefore were likely to decrease β-glucuronidase activity. We did not find literature suggesting that soy foods influence β-glucuronidase; soy was of interest to the parent study. For the F&V diet, individuals were dosed with F&V according to body weight (10) and consumed ~10 daily total servings. Both basal and F&V diets provided similar percent energy from carbohydrate (56%), protein (16%), and fat (28%). Nutrient intakes were calculated using the Nutrition Data System for Research software version V4.05_33 (Nutrition Coordinating Center, University of Minnesota).

Participants were instructed to eat only prescribed, study-provided beverages and foods. Compliance, as assessed by 24-h urinary excretion of isoflavones and isothiocyanates and by daily food check-off forms, was high (10).

Determination of Serum β-Glucuronidase Activity. Before the intervention and at days 8 and 15 of each feeding period, morning blood (after 10 h of fasting) was collected for serum. β-Glucuronidase activity from serum was determined using the following method modified from the Sigma β-glucuronidase kit (Sigma-Aldrich), because the kit had been discontinued. Serum (50 μL) was used in the assay with a corresponding reduction in the volumes of the enzyme substrate, the acetate buffer, and water. The volume of the AMP buffer (stop reagent) was reduced by 20%. Serum was incubated with phenolphthalein glucuronic acid (Sigma), the β-glucuronidase substrate, at pH 4.5 for 4 h at 37°C. At exactly 4 h, the reaction was stopped using an alkaline buffer 0.1 mol/L AMP buffer (Sigma; pH 11). Under standard conditions, β-glucuronidase cleaves phenolphthalein glucuronic acid liberating free phenolphthalein. A DU650 spectrophotometer (Beckman Instruments) was used to monitor the intensity of the resulting pink color, which is proportional to β-glucuronidase activity. We determined enzyme activity, expressed as μg phenolphthalein released/mL serum/h at 37°C, from standard curves. The intra-assay and interassay coefficient of variation were 2.9% and 5.7%, respectively.

Statistical Analysis. Before analyses, β-glucuronidase activity was log transformed to improve normality. A linear mixed model was used to examine the effect of F&V on β-glucuronidase activity and whether the relation differs by subgroups of sex and days (8 or 15). We adjusted for sex, days on experimental diet, UGT1A1 genotype (one of the recruitment factors), order of assigned experimental diet, carryover effect, β-glucuronidase activity during the preintervention period, and two-way interactions between sex, days on experimental diet, UGT1A1 genotype, and experimental diet. The back-log-transformed least-square means and their associated 95% confidence intervals (95% CI) were reported. Our main effect measure, the ratio of enzyme activity

Table 1. Baseline characteristics of female and male participants

	Total (n = 63)	Women (n = 31)	Men (n = 32)	P*
Age, y	29.5 ± 5.57	28.8 ± 5.48	30.3 ± 5.65	0.29
Weight, kg	68.9 ± 12.0	62.2 ± 10.2	75.5 ± 9.98	<0.01
Height, m	1.72 ± 0.10	1.65 ± 0.08	1.78 ± 0.08	<0.01
Body mass index, kg/m^2	23.3 ± 2.61	22.8 ± 2.82	23.7 ± 2.35	0.14
Race, n (%)				
Caucasian	68	65	72	0.59
Asian	25	32	19	0.25
Other	6	3	9	0.61
Habitual servings/d †				
Fruits	2.47 ± 2.08	2.45 ± 2.06	2.50 ± 2.13	0.87
Vegetables	1.87 ± 1.21	2.14 ± 1.30	1.61 ± 1.08	0.07
Citrus fruits	0.82 ± 1.10	0.85 ± 1.35	0.80 ± 0.82	0.82
Cruciferous vegetables	0.34 ± 0.40	0.30 ± 0.28	0.38 ± 0.50	0.67

NOTE: Values for continuous variables are mean ± SE, and values for categorical variables are percentages.
*We tested whether the baseline data were statistically different by sex by computing two-sample t tests for continuous variables and the Fisher's exact test for the race variable; dietary intakes were log transformed before hypothesis testing to improve normality. $P < 0.05$ was considered statistically significant.
†Servings were calculated based on the standardized serving sizes from the Dietary Guidelines for Americans.

Table 2. Effect of experimental diets on serum β-glucuronidase activity, stratified by sex and day on experimental diet

	Experimental diets		Ratio of F&V and basal diets[†] (95% CI)
	Basal diet* (μg/mL/h)	F&V diet* (μg/mL/h)	
All participants, averaged both days	5.43 ± 0.15	5.91 ± 0.17	1.09 (1.05-1.13)[‡]
Women[§]	5.19 ± 0.21	5.75 ± 0.23	1.11 (1.05-1.17)[‡]
Men[§]	5.69 ± 0.23	6.06 ± 0.25	1.07 (1.01-1.13)[‡]
Day 8	5.44 ± 0.17	6.15 ± 0.19	1.13 (1.07-1.20)[‡]
Day 15	5.42 ± 0.17	5.67 ± 0.18	1.05 (0.99-1.11)

*Back-log-transformed least-square mean ± SE of serum β-glucuronidase activity. Means are adjusted for sex, days on experimental diet, UGT1A1 genotype, order of assigned experimental diet, carryover effect, β-glucuronidase activity during the preintervention period, two-way interactions between sex, days on experimental diet, UGT1A1 genotype, and experimental diet.

†Ratio was calculated by exponentiating the difference of the log-transformed adjusted, least-square means.

‡Serum β-glucuronidase activity was significantly higher during F&V than during basal diet ($P < 0.05$).

§β-Glucuronidase activity averaged over days 8 and 15 of experimental diet.

during each diet, was calculated by back-transforming (exponentiating) the difference of the log-transformed means from each diet. All statistical tests were two-sided with $P < 0.05$ considered statistically significant. Additional details are provided in the table footnotes. Analyses were conducted using SAS version 9.0 (SAS Institute).

Results

Sixty-three healthy, nonsmoking men and women, ages 20 to 40 years, completed both feeding periods (Table 1). They were mostly Caucasian (68%) and Asian (25%). Their mean baseline body mass index was within normal range, with men being taller ($P < 0.01$) and heavier ($P < 0.01$) than women. Men and women had statistically similar preintervention dietary intakes of F&V (Table 1) even after adjusting for weight (data not shown), reporting, on average, approximately four daily servings. Men had higher preintervention β-glucuronidase activity (6.89 μg/mL/h) than women (5.02 μg/mL/h, $P < 0.01$).

Table 2 shows the effect of F&V on mean β-glucuronidase activity. Contrary to our hypothesis, participants had significantly higher mean β-glucuronidase activity on F&V than on the basal diet (ratio, F&V versus basal diet, 1.09; 95% CI, 1.05-1.13; $P < 0.01$). Seventy-six percent had higher β-glucuronidase activity on F&V than on the basal diet, whereas 24% had lower levels. Response to diet appeared stronger for women than men (Table 2), but the test of interaction was not statistically significant ($P_{interaction} = 0.30$). There was also a suggestion of a short-term effect; the F&V diet was associated with a significant increase in β-glucuronidase activity half-way through the intervention on day 8 (ratio, F&V versus basal, 1.13; 95% CI, 1.07-1.20; $P < 0.01$), but this relation was attenuated on day 15 (ratio, 1.05; 95% CI, 0.99-1.11; $P = 0.12$; $P_{interaction} = 0.06$). Order of diet assignment (F&V-basal or basal-F&V) had no effect on β-glucuronidase activity ($P = 0.70$). Moreover, we did not observe specific responses among individuals that would allow for stratification of responder and nonresponder groups.

Because the F&V results were unexpected, we subsequently examined the change in β-glucuronidase activity from the preintervention to each experimental diet period (Table 3). β-Glucuronidase activity during the F&V period was not significantly different than the preintervention period (ratio, F&V period versus preintervention, 1.01; 95% CI, 0.96-1.06; $P = 0.64$). However, during the basal diet, there was a statistically significant 7% decrease in β-glucuronidase activity compared with the preintervention diet (ratio, basal period versus preintervention, 0.93; 95% CI, 0.87-0.98; $P = 0.01$), suggesting that our main finding was due to a decline in β-glucuronidase activity during the basal (control) diet. In subgroup analyses, this decline was slightly stronger for women (ratio, 0.90; 95% CI, 0.83-0.98) than men (ratio, 0.96; 95% CI, 0.87-1.04). The increase in β-glucuronidase activity from preintervention to day 8 during the F&V diet was attenuated on day 15. The magnitude of these changes was small.

Discussion

In this randomized crossover study, we examined the effect of a diet rich in selected F&V on serum β-glucuronidase activity compared with a basal diet devoid of F&V. Comparing F&V and basal diets, we observed an increase in β-glucuronidase activity. However, on further analysis, we attribute this result to a decline in β-glucuronidase activity during the basal diet from the habitual, preintervention diet levels.

We originally hypothesized that a plant-rich diet would lower β-glucuronidase activity. During the F&V diet, participants were fed citrus and cruciferous foods naturally rich in D-glucaric acid, a possible inhibitor of β-glucuronidase. Broccoli and grapefruit, for instance, contain ~350 mg/100 g D-glucaric acid and oranges have ~129 mg/100 g D-glucaric acid (8). However, not all D-glucaric acid may be bioavailable to lysosomes, where β-glucuronidase mostly resides (11). Additionally, other botanical groupings, not investigated here such as Cucurbitaceae (squash, melons), Rosaceae (stone-fruit), and Leguminosae (legumes), may be relevant, as suggested by our pilot results of habitual diet (9).

During the basal diet (averaged days 8 and 15), the decrease in β-glucuronidase activity from preintervention levels was interesting and needs further evaluation. One explanation may be that foods eaten habitually before the intervention contained constituents that maintain β-glucuronidase activity and the removal of these foods (basal diet) lowered activity. Our results,

Table 3. Serum β-glucuronidase activity during preintervention and experimental periods, stratified by sex and day on experimental diet

	Preintervention diet* (μg/mL/h)	Experimental diets		Ratio of basal and preintervention diets† (95% CI)	Ratio of F&V and preintervention diets† (95% CI)
		Basal diet* (μg/mL/h)	F&V diet* (μg/mL/h)		
All participants, averaged both days	5.89 ± 0.34	5.46 ± 0.06	5.96 ± 0.06	0.93 (0.87-0.98)‡	1.01 (0.96-1.06)
Women§	5.02 ± 0.40	4.50 ± 0.40	5.01 ± 0.46	0.90 (0.83-0.98)‡	1.00 (0.93-1.08)
Men§	6.89 ± 0.51	6.58 ± 0.49	7.05 ± 0.51	0.96 (0.87-1.04)	1.02 (0.96-1.09)
Experimental day 8	5.89 ± 0.34‖	5.49 ± 0.07	6.22 ± 0.06	0.93 (0.87-1.00)	1.06 (1.00-1.11)‡
Experimental day 15	5.89 ± 0.34‖	5.45 ± 0.06	5.72 ± 0.06	0.93 (0.86-0.99)‡	0.97 (0.92-1.02)

*Geometric mean ± SE of β-glucuronidase activity; means were unadjusted because paired *t* tests were used to compare values.
†Experimental diet versus preintervention ratios were calculated by exponentiating the difference of the log-transformed (unadjusted) geometric means. Paired *t* tests, inherently adjusting for within-person characteristics, were used to calculate the significance of the ratios.
‡Serum β-glucuronidase activity was significantly different for the preintervention than the experimental diet ($P < 0.05$).
§For experimental diets, data stratified by sex represent values averaged over days 8 and 15 of experimental diet.
‖Preintervention β-glucuronidase activity was sample at one time point.

although statistically significant, were small and the clinical relevance of these small changes on cancer risk is unknown.

In subgroup analyses, we observed a tendency for a stronger response on day 8 versus day 15, supporting an acute response to diet. This is consistent with the short-term effects of cruciferous vegetable feeding on acetaminophen conjugation (12) and oltipraz administration on the induction of detoxification enzymes (13). However, it is unknown whether the body adapts to elevated exposure over the long-term. There may be transient, short-term responses to our 2-week dietary alterations that are different from responses to longer (>14-day) interventions.

This is the first human intervention study examining dietary supplementation on β-glucuronidase activity. Strengths of this investigation include (*a*) controlled diets in which the plant foods were dosed according to body weight to minimize confounding by weight, (*b*) inherent adjustment for confounding and between-person differences as each person acted as his/her own control, and (*c*) high participant adherence to experimental diets. Lower β-glucuronidase activity (reviewed in ref. 3) has been associated with higher D-glucaric acid (4, 11), caloric restriction (14), silymarin (milk thistle extract; ref. 15), *Ganoderma lucidum* (16), and the calcium modulating xenobiotics A23187 (17) and thapsigargin (17). Conversely, increased β-glucuronidase activity (reviewed in ref. 3) has been associated with male sex (9, 18), higher body mass index (18), older age (3, 18), pathologic conditions (cancer, liver disease, and tuberculosis; ref. 3), tobacco exposure (19), and spironolactone, a drug inducer of microsomal enzymes such as UGT (20). Our restriction to healthy, nonsmoking, and nonmedicated participants minimized the effect of these and other nonintervention factors on β-glucuronidase activity. A study limitation is our reliance on serum β-glucuronidase, which are lower than tissue levels. Moreover, day-to-day, within-person variability in β-glucuronidase activity would attenuate our results. However, in our pilot study in which we had two baseline measures of β-glucuronidase activity, the between-person coefficient of variation (46%) was higher than the within-person coefficient of variation (8%). Although there is no established range of human β-glucuronidase activity, enzyme activity in this current study was similar to that of our pilot after taking into account different assay temperatures.

The mechanisms underlying human β-glucuronidase induction are largely unknown. Analysis of the human β-glucuronidase gene suggests the presence of binding sites for three ubiquitous transcription factors with putative regulating roles: nuclear factor-κB, activating protein-2, and specificity protein 1 (cited in ref. 21). The possible β-glucuronidase-lowering effects of silymarin (15), A23187 (17), and thapsigargin (17) may be mediated by nuclear factor-κB (22) and activating protein-2 (21); expression of nuclear factor-κB may, in turn, be induced by phytochemicals (23). Moreover, specificity protein 1 sites may prevent portions of the gene from becoming methylated (24). Three β-glucuronidase polymorphisms, whose frequencies in the general population still require quantification, have been associated with altered enzyme activity (18), and several isoforms of both microsomal and lysosomal origin have been identified (25), raising questions regarding whether the diet response varies by these factors.

In conclusion, we did not detect an effect of F&V supplementation on β-glucuronidase activity but rather observed a small decrease in enzyme activity during the control diet devoid of F&V. There are many unresolved questions and further investigation is needed regarding what other foods and phytochemicals may influence β-glucuronidase activity and the effect modifiers for this relation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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