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Effect of the consumption of yacon flour and energy-restricted diet on glycation markers, and association between these markers and factors linked to obesity in adults with excess body weight: A randomized, double-blind, placebo-controlled clinical trial

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ABSTRACT

Objectives: Regardless of the positive effect of yacon on metabolic markers, this food contains fructose molecules, which can originate advanced glycation end products (AGEs). High AGEs serum concentrations can contribute to excess body weight. We evaluated the effect of consuming an energy-restricted diet and yacon flour on glycation markers concentrations, and the associations between these markers and factors linked to obesity in adults with excess body weight.

Methods: Twenty-six adults with excess body weight were included in this randomized, parallel, double-blind, placebo-controlled, 6-week clinical trial. Subjects were randomly allocated to the control group (n = 13) or the yacon-flour group (n = 13), and daily consumed a breakfast drink either not containing or containing 25 g of yacon flour (8.7 g of fructooligosaccharides). Energy-restricted diets were prescribed for both groups. Biochemical markers, anthropometric variables, and body composition were evaluated at baseline and the end of the study.

Results: AGEs and early glycation products did not increase in the yacon flour group. Soluble receptor for AGEs (sRAGE) decreased regardless of group. Besides, changes in AGEs were positively associated with changes in body fat (β = 0.04, P = 0.038) and in sRAGE, with insulin (β = 0.02, P = 0.035) and homeostasis model assessment index of insulin resistance (β = 0.01, P = 0.049).

Conclusions: The consumption of 25 g of yacon flour associated with an energy-restricted diet did not increase concentrations of glycation markers. Changes in glycation markers were positively associated with changes in consolidated anthropometric and biochemical markers related to being overweight. Assessing glycation markers may be a useful strategy for monitoring responses to dietary interventions in subjects with excess body weight.

Introduction

Abnormal or excessive accumulation of fat, in people with overweight, constitutes a risk factor for the development of several non-communicable chronic diseases [1,2]. The prevalence of excess body weight has increased, and it has become a major public health problem in many countries [3]. For that reason, there is great interest among the scientific community in identifying strategies capable of preventing or controlling the occurrence of excess body weight.

All authors designed the study. A. M. M. and N. B. M. S. carried out the data collection and analyses. P. V. M. R., A. M. M., N. B. M. S., L. L. O., and R. C. G. A. completed the data and statistical analyses and drafted the manuscript. All authors edited, read, and approved the final manuscript.

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Advanced glycation end products (AGEs) seem to contribute to excess body weight and manifestations of other chronic diseases [4–9]. They can be produced endogenously through the Maillard non-enzymatic reaction between a reducing sugar and a protein, a lipid, or nucleic acids [4,10]. Although AGEs concentrations may increase in the presence of hyperglycemia and oxidative stress [4,11,12], these compounds are also found in food [4].

The contribution of AGEs to excess body weight has mainly been attributed to their ability to bind to the AGEs receptor (RAGE), activating signaling pathways that activate inflammatory processes dependent on nuclear factor κB, causing an increase in proinflammatory cytokines, adhesion molecules, and the expression of RAGE itself [13,14], and suggesting the occurrence of positive inflammatory feedback. Furthermore, the interaction between AGEs and RAGE increases the formation of reactive oxygen species, and AGEs can also lead to loss of protein function after chemical modification [4]. On the other hand, the soluble AGEs receptor (sRAGE) has the same AGE-binding specificity as RAGE, which means it can bind to AGEs, preventing the activation of the inflammation-signaling cascade and the occurrence of oxidative stress [15,16]. Therefore, the adoption of strategies to manage excess body weight, such as lifestyle changes, consumption of energy-restricted diets [17], and inclusion of foods capable of improving body composition and metabolic marker concentrations, may play a role in reducing AGEs concentrations.

Yacon (*Smallanthus sonchifolius*) is an herbaceous plant native to the Andean region of South America, and a rich source of fructooligosaccharides (FOS) and phenolic compounds, particularly chlorogenic acid [18,19]. Apparently owing to its low caloric value and high fiber content, yacon is a promising food supplement that can be used to prevent and treat several chronic diseases, such as diabetes and obesity [20]. However, it contains FOS [18,21], which have short linear chains of fructose molecules [22] that can in turn originate methylglyoxal, a precursor of AGEs [4]. Therefore, the effect of increased yacon consumption on AGEs concentrations is not known.

In a previous study conducted by our research group, we observed that consumption of yacon flour (25; 8.7 g FOS) associated with an energy-restricted diet resulted in greater weight loss and improved body composition in individuals with excess body weight [23]. No human study has investigated the role of yacon consumption on glycation marker concentrations. Therefore, in the present study we evaluated how the consumption of yacon flour and an energy-restricted diet affected glycation marker concentrations, and we investigated the associations between these markers and factors linked to obesity in adults with excess body weight.

Participants and methods

Participants

Eligible participants were men and women (ages 20–59 y) who were excess body weight (body mass index [BMI] 25–34.9 kg/m^2) [24], regularly consumed breakfast, had a mild physical activity level, had food restriction or disinhibition ≤ 14 [25], were not diabetic, and did not have a family history of diabetes or glucose intolerance.

Non-inclusion criteria were cigarette smoking; consumption of more than two doses of alcohol per day (>50 g ethanol/d); use of medications that affect blood glucose or energy metabolism; use of drugs, herbs, or diets to reduce appetite and body weight; gain or loss of at least 5 kg in the 3 months before the beginning of the study; recent change in physical activity level; aversion or intolerance to the foods provided in the study; existence or history of endocrine, cardiovascular, arterial hypertension, liver, or gastrointestinal diseases; eating disorders occurence; pregnancy or lactation; use of laxatives or antibiotics in the 3 months before the beginning of the study; use of probiotics, prebiotics, or symbiotics; and menstrual irregularity in the 3 months before the beginning of the study.

The study protocol was approved by the Universidade Federal de Viçosa, Brazil Human Research Ethics Committee (1.875.372). Subjects signed the informed consent form according to the recommendations of the Declaration of Helsinki [26]. The trial is registered in the Brazilian Registry of Clinical Trials (ReBEC, http://www.ensaiosclinicos.gov.br; identifier RBR-6YH6BQ).

Study design

This was a double-blind, randomized, parallel, 6-week clinical trial. Participants were randomly allocated into the yacon flour group or the control group in a proportion of 1:1. Block randomization technique, used to allocate the subjects into the groups, was applied by a person who was not part of the research group. Energy-restricted diets were prescribed (−500 kcal/d) [27], considering the nutritional composition of the drinks provided during the study. The prescribed diets had a similar content of macronutrients and dietary fiber, according to the Acceptable Macronutrient Distribution Range [28]. Subjects did not receive any guidance on how to prepare the foods consumed during the study, so that they would not be induced to change their AGEs consumption.

Subjects daily consumed in the laboratory 350 mL of a drink breakfast containing 25 g of yacon flour (13.72 ± 3.97 g of total fiber and 8.7 g FOS) or not containing yacon flour (2.63 ± 3.91 g of total fiber and 0 g of FOS). On weekends, subjects received the ingredients of the drink to be consumed at home. The investigators assessed the protocol adherence.The full nutritional composition of these drinks and a chemical characterization of yacon flour have been given elsewhere [23]. All other meals were consumed under free-living conditions. Participants were instructed to maintain their level of physical activity during the study.

Body composition, anthropometry, and biochemical variables, systolic and diastolic blood pressure, and glycation markers (AGEs, early glycation products - EGPs, and sRAGE) were assessed at baseline and after 6 week in each experimental group.

Breakfast drinks

Drinks with and without yacon flour had similar macronutrient and energy contents, differing only in total dietary fiber and FOS [23]. The ingredients used to prepare the drinks were the same, except for the addition (or not) of yacon flour, which was replaced by cornstarch in the control-group drinks so that they would be nutritionally similar to those in the yacon flour group. These drinks also contained fruit pulp, cocoa powder or instant coffee, whole milk powder, sugar, oil, and water. The amount of yacon flour added (25 g) was based on other studies, considering the occurrence of possible undesirable gastrointestinal effects [29–31]. Daily intake of yacon flour was well tolerated, causing no adverse gastrointestinal effects.

Anthropometric, body-composition, and blood-pressure measurements

Body weight was assessed using an electronic platform scale (Model 2096PP/2, Toledo, São Paulo, Brazil) with a capacity of 150 kg and an accuracy of 50 g. Height was measured using a stadiometer with a scale of 0 to 220 cm and a precision of 0.1 cm (Wiso, Chapecó, Brazil). BMI was calculated by dividing body weight by the square of height. Waist and hip circumferences were measured using a flexible inelastic tape. Waist circumference was measured at the smallest circumference, and hip circumference was measured at the highest prominence between the anterior iliac crest and the largest trochanter.

Body fat and fat-free mass were assessed using a dual-energy X-ray absorptiometry scan (Prodigy Advance, GE Healthcare Inc., Waukesha, WI, USA). Blood pressure was assessed in both arms, using an automatic Omron HEM-7200 (Omron Inc., Dalian, China), in duplicate [32].

Biochemical analyses

Venous blood samples were obtained after 12-h overnight fasting. Glucose, triacylglycerol, total cholesterol, and high-density lipoprotein cholesterol concentrations were measured using a colorimetric assay (Bioclin kit, Quibasa, Belo Horizonte, Brazil). Low-density lipoprotein cholesterol concentration was calculated by subtracting high-density lipoprotein cholesterol and 20% of triacylglycerols from total cholesterol [33]. Insulin was determined by chemiluminescent immunoassay (Access Ultrasensitive Insulin, Beckman Coulter, Brea, California, USA). Insulin resistance was calculated using the homeostasis model assessment index of insulin resistance (HOMA-IR) [34].

Glycation marker analyses

Serum concentrations of AGEs were assessed by fluorescence spectroscopy ($\lambda_{emission}$ = 460 nm, $\lambda_{excitation}$ = 370 nm; SpectraMax M2e, SoftMax Pro software, Manufacturer, Location) using 50 μL of serum [35]. The AGEs content of samples was corrected by the amount of protein [36].

Detection of early glycation products (EGPs; glycated hemoglobin, glycated albumin, fructosyl-lyine, furosine, and other glycated plasma proteins) was undertaken to verify the reduction of nitroblue tetrazolium (NBT) [37]. In the NBT test, 20 μL of sample was mixed with 200 μL of NBT solution (100 mM sodium

carbonate buffer [pH 10.8] containing 0.25 mM NBT). The glycation reaction was incubated at 37°C for 30 min, and the reading was performed on a spectrophotometer (absorbance = 525nm; SpectraMax M2e) [35]. That method identifies EGPs concentrations as low as 0.04 mM, with 2.45 and 0.74% coefficients of variation for repeatability and reproducibility [38].

Concentrations of sRAGE were determined using a commercial enzyme-linked immunosorbent assay kit (Human RAGE; Sigma-Aldrich, Location) specific for human sRAGE (intra- and interassay reproducibility coefficients of variation < 10% and < 12%, respectively). Duplicate samples and absorbed sRAGE standards were read at 450 nm (SpectraMax M2e, SoftMax Pro).

Statistical analysis

This study had 81% statistical power, considering the AGEs concentrations after 6 week of intervention, with a 95% confidence interval, type I error of $\alpha = 0.05$, and type II error of $\beta = 0.2$ [39–41]. Statistical analyses were performed using SPSS, version 23.0 (SPSS, Inc., Chicago, IL, USA). The Shapiro–Wilk test was used to assess the normality of the data distribution, with a significance of 5%. Student's *t* test or the Mann–Whitney *U* test was used to identify differences in the changes (deltas) in variables presented by participants in the two groups.

The effect of the intervention was assessed by comparing means of glycation markers between groups after 6 week of intervention, using the generalized estimation equation model. For variables with normal distribution, a connection identification function was used; gamma distribution with a log link was used for variables that did not present normal distribution. An unstructured and robust estimated covariance matrix was used as a work correlation matrix. The Bonferroni post hoc test was used to identify differences by group, time, and their interaction. A threshold of $P < 0.05$ was adopted as the level of statistical significance.

Pearson or Spearman correlation was performed according to the variable's distribution to assess the correlation between changes in glycation markers and changes anthropometric, body composition and biochemicals markers within groups. In addition, the correlations between changes sRAGE and changes biochemical markers for all participants were assessed.

Multiple linear regression was also performed considering change in glycation markers as the independent variable and changes in anthropometric and biochemical markers as dependent variables. A model was estimated for each independent variable (glycation marker), and adjustments were made for the values of the independent and dependent variables at baseline.

Results

Twenty-six participants (15 women, 11 men; mean ± SD BMI, 30.44 ± 2.46 kg/m^2; total body fat, 40.16% ± 6.71%; age, 31.35 ± 8.54 y) were included in this study. The CONSORT participant-selection flow diagram has already been published [23]. After 6 weeks of intervention, changes in body weight and BMI in the yacon group were greater than in the control group (Table 1), and daily consumption of dietary fiber was 25.5 ± 1.4 g in the control group and 38.8 ± 1.9 g in the yacon flour group ($P < 0.05$).

AGEs and EGPs concentrations were not affected by the intervention in either experimental group. On the other hand, sRAGE concentrations declined after the intervention (baseline versus 6 wk) in both groups (Table 2).

Changes in AGEs concentrations were positively correlated with changes in BMI, waist circumference, gynoid body fat, total body fat, and serum triacylglycerols in the yacon flour group. In the control group, they were positively correlated with changes in waist circumference and fat-free mass (Table 3). When we evaluated the association between changes in anthropometric, body composition and biochemical markers (dependent variables) and changes in AGEs concentrations (independent variable) in the yacon flour group, we observed that change in total body fat was positively associated with change in AGEs after adjustment for baseline variables ($\beta = 0.04$, $P = 0.038$; data not shown).

A positive correlation was verified between changes in sRAGE concentration and changes in insulin, HOMA-IR, and triacylglycerols (Fig. 1). In assessing the associations between changes in biochemical markers (dependent variables) and changes in sRAGE concentration (independent variable), we observed that changes in fasting insulin and HOMA-IR were positively associated with change in sRAGE after adjustment for baseline variables ($\beta = 0.02$, $P = 0.035$, and $\beta = 0.01$, $P = 0.049$, respectively; data not shown).

Discussion

To our knowledge, this is the first study to investigate the effect of yacon flour (*Smallanthus sonchifolius*) consumption associated with an energy-restricted diet on glycation marker serum concentrations and factors linked with obesity in adults with excess body weight. Daily consumption of 25 g of yacon flour (8.7 g FOS) for 6 week did not increase AGEs or EGPs concentrations. About 70% to 80% of yacon's dry weight is FOS [18,21], which are fructans made up of short linear chains of fructose molecules [22]. Methylglyoxal, a precursor of AGEs, partly originates from fructose metabolism [4]. Therefore, we did not know whether the ingestion of yacon flour would increase AGEs production.

In a previous study conducted out by our group, we observed that yacon flour consumption resulted in greater reduction in gynoid fat and anthropometric measurements (body weight, gynoid fat, waist circumference, sagittal abdominal diameter, and waist/height index) compared with the control group [23]. We

Table 1
Participant characteristics at baseline and after 6 weeks of intervention, according to experimental group

	Control group (n = 13)			Yacon flour group (n = 13)			
Variable	Baseline	After 6 wks	Δ	Baseline	After 6 wks	Δ	p_{inter}
Body weight, kg	84.93 ± 13.83	83.89 ± 13.54	−1.04 ± 1.69	88.52 ± 15.21	85.95 ± 14.67	−2.57 ± 1.74	0.032*
BMI, kg/m^2	30.08 ± 2.04	29.72 ± 1.92	−0.37 ± 0.58	30.80 ± 2.85	29.91 ± 2.82	−0.89 ± 0.55	0.028*
Fat mass, kg	32.56 ± 5.41	31.51 ± 5.74	−1.22 ± 1.78	36.61 ± 8.15	33.39 ± 7.36	−2.08 ± 1.34	0.202
Fat percentage, %	38.76 ± 5.96	38.07 ± 5.14	−0.96 ± 2.15	44.97 (29.31–49.78)	43.68 (26.55–49.20)	−1.29 ± 1.30	0.659
Waist circumference, cm	100.18 ± 8.19	88.66 ± 9.02	−2.66 ± 1.39	102.62 ± 9.38	88.13 ± 8.45	−3.69 ± 1.32	0.065
Fasting glucose, mg/dL	91.92 ± 5.27	90.92 ± 7.25	−1.00 ± 4.88	89.69 ± 6.91	90.54 ± 7.30	0.85 ± 5.89	0.393
Fasting insulin, μUI/mL	9.29 ± 2.91	7.20 (4.50–19.40)	−0.96 ± 3.33	9.45 ± 2.78	9.10 (5.90–21.10)	0.05 ± 2.85	0.412
HOMA-IR, AU	2.11 ± 0.68	1.64 (0.99–4.79)	−0.21 ± 0.84	2.11 ± 0.72	1.95 (1.12–5.47)	0.06 ± 0.73	0.378
Triacylglycerides, mg/dL	87 (44–263)	94 (48–253)	−4.69 ± 37.02	106 (53–261)	112.23 ± 37.48	−13.15 ± 40.89	0.581
Cholesterol, mg/dL	189 (141–277)	192 (141–301)	−1.00 (−34.00 to 24.00)	178.85 ± 24.02	174.38 ± 27.53	−4.46 ± 22.80	0.670
HDL-cholesterol, mg/dL	50.38 ± 14.50	51.38 ± 12.82	1.00 ± 3.83	48 (33–86)	49 (35–85)	0.15 ± 5.96	0.585
LDL-cholesterol, mg/dL	106 (84–212)	104 (80–221)	−0.31 ± 15.22	104.92 ± 26.91	102.92 ± 30.40	−2.00 ± 15.36	0.780
Systolic blood pressure, mm Hg	112.66 ± 8.43	111.92 ± 7.50	−2.04 ± 6.49	113.96 ± 11.03	110.42 ± 11.11	−2.25 ± 10.76	0.953
Diastolic blood pressure, mm Hg	67.33 ± 7.17	66.54 ± 5.41	−2.77 ± 6.91	69.30 ± 7.86	62 (56–95)	−3.00 (−11.00 to 38.00)	0.979

Data are presented as mean ± SD or median (interquartile range)
BMI, body mass index; HDL, high-density lipoprotein; HOMA-IR: homeostasis model assessment index of insulin resistance; LDL, low-density lipoprotein; P_{inter}, between-groups comparison of Δ values by Student's *t* test or Mann–Whitney *U* test
*$p < 0.05$.

Table 2
Mean ± SD glycation-marker concentrations at baseline and after 6 week of intervention, according to experimental group

Variable	Control group (n = 13)		Yacon flour group (n = 13)	
	Baseline	After 6 weeks	Baseline	After 6 weeks
AGEs, AU/mg	2.18 ± 0.31	2.20 ± 0.32	2.16 ± 0.36	2.05 ± 0.39
EGPs, AU	0.05 ± 0.02	0.05 ± 0.01	0.06 ± 0.03	0.05 ± 0.02
sRAGE, pg/mL	322.52 ± 122.78*	282.38 ± 106.95†	288.53 ± 104.16*	257.19 ± 81.36†

AGEs, advanced glycation end products; EGPs, early glycation products; sRAGE, soluble receptor of AGEs
Different superscript symbols in the same line indicate intragroup difference by the generalized estimating equation model, $p < 0.05$

believe that although yacon flour (FOS) may have caused an increase in AGEs concentrations, the observed reduction in anthropometric characteristics may have caused a reduction in these concentrations. We also believe that weight loss due to the consumption of FOS may have resulted from greater satiety, reducing food intake and dietary AGEs and thus reducing the pool of energy substrate for endogenous AGEs formation. It is also possible that the reduction in visceral adipose tissue observed in our previous study may have led to a lower expression of RAGE, consequently resulting in less binding of AGEs to RAGE [42]. Thus, these opposite effects may have been responsible for the fact that AGEs and EGPs concentrations did not increase.

The consumption of an energy-restricted diet reduced AGEs concentrations in two 3-months randomized clinical trials [43,44] and in a prospective study in individuals with overweight [45]. The divergence in these results and ours may be due to the differences in study duration, type of intervention applied, and method used to assess AGEs concentrations. The percentage of weight loss observed in those studies was 4.3% [43] and 6.7% [45], corresponding to 2.9% in our previous study [23]. Where the present study lasted for 1.5 months (6 week), those studies had durations of 2 [45] and 3 [43,44] months. Therefore, we do not know whether the consumption of yacon flour associated with an energy-restricted diet for more than 6 week would have affected our results. If our study had been conducted for a longer period of time, we probably would have seen greater weight loss, which in turn would stimulate a significant reduction in AGEs concentrations. We must also point out that the techniques used to quantify AGEs concentrations differed between studies. Whereas we and Gugliucci et al. [45] used a technique to quantify total fluorescent AGEs, the other two studies Rodríguez et al. [43] assessed only Nε-carboxymethyllysine (a type of AGEs) concentrations, by enzyme-linked immunosorbent assay [43] and high-performance liquid chromatography [44].

Moreover, in this study, we obtained positive correlations between changes in AGEs concentrations and changes in anthropometric (waist circumference, BMI), body-fat (gynoid body fat, total body fat) and biochemical (triglyceridemia) markers in the yacon flour group. Participants in that group also exhibited greater weight loss and reductions in body-composition markers [23]. These results are interesting because AGEs are seen as new biomarkers, and it is relevant that they correlate with such well-established obesity-related markers. Another study has observed that reductions in AGEs concentrations were also positively correlated with triacylglycerol concentrations, waist circumference, and BMI in overweight participants prescribed an energy-restricted diet [35], as in our study. Our correlation data and those verified by

Table 3
Correlations between changes in AGEs concentration and in anthropometric and biochemical markers, according to experimental group

Variable	Control group (n = 13)		Yacon flour group (n = 13)	
	r	p	r	p
ΔBMI, kg/m^2	0.496	0.085	0.557	0.048*
ΔWaist circumference, cm	0.699	0.008*	0.573	0.041*
ΔGynoid body fat, kg	−0.103	0.777	0.691	0.019*
ΔTotal body fat, kg	−0.271	0.420	0.680	0.015*
ΔLean trunk mass, kg	0.645	0.032*	0.168	0.602
ΔTriacylglycerides, mg/dL	0.554	0.050	0.560	0.046*

AGEs, advanced glycation end product; BMI, body mass index
Pearson or Spearman correlation, according to variable distribution
*$p < 0.05$.

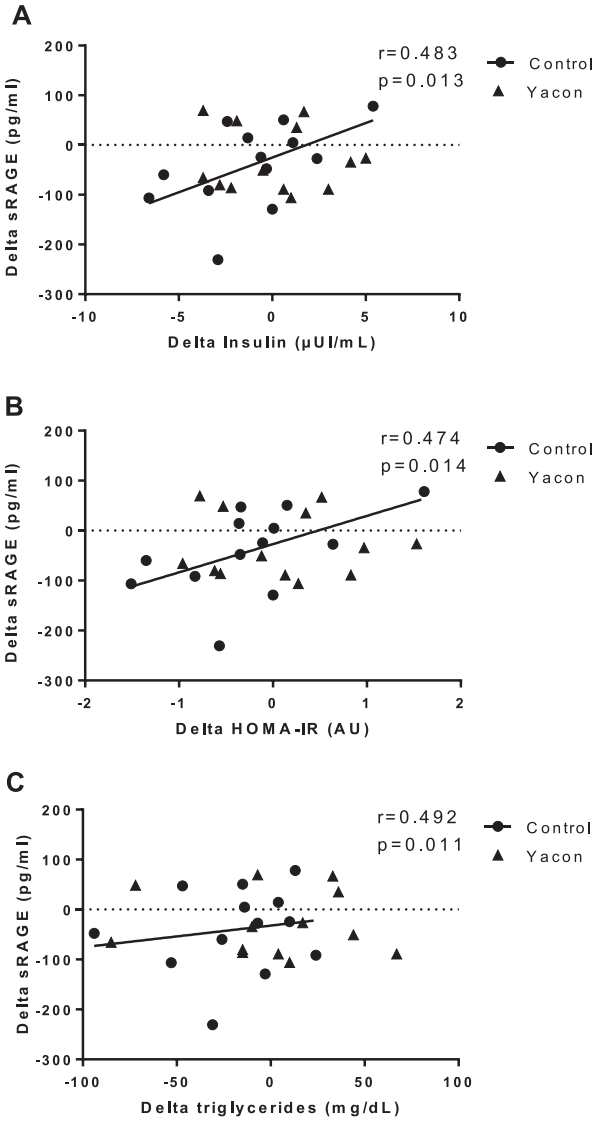

Fig. 1. Pearson or Spearman correlations between changes in concentrations of sRAGE and in biochemical markers (n = 26). sRAGE, soluble receptors of advanced glycation end products.

Gugliucci et al. [45] suggest that loss of visceral and subcutaneous adipose tissue (represented by waist circumference, BMI, and gynoid and total body fat) is related to reductions in AGEs concentrations, suggesting that these tissues may be important in regulating AGEs production and playing a role in the mechanism of the AGEs–RAGE axis.

In adipose tissue cells from participants with obesity, there was an accumulation of carboxymethyllysine and higher RAGE expression compared with adipose tissue from eutrophic participants. RAGE overexpression was higher in visceral adipose tissue than in subcutaneous adipose tissue. Thus, higher AGEs concentrations and the activation of inflammatory pathways are mechanisms involved in adipokine dysregulation, contributing to insulin resistance in obesity [8]. In fact, visceral adipose tissue is an inflammatory fat deposit associated with increased risk of metabolic disease, AGEs accumulation, and RAGE overexpression, all of which are involved in metabolic dysfunction.

We also observed a reduction in sRAGE in both experimental groups and a positive correlation between change in sRAGE and changes in triacylglycerols, insulinemia, and HOMA-IR. Norata et al. [46] showed inverse associations between sRAGE concentration and BMI, waist-to-hip ratio, and fasting blood glucose in healthy participants with excess body weight. The divergence from our results is probably due to the intervention characteristics. Our participants consumed yacon flour and an energy-restricted diet, whereas in that study, no intervention was applied. sRAGE has been considered a new useful biomarker for diagnosis and prognosis of chronic diseases [47]. Apparently it acts as an endogenous inhibitor of RAGE, since it binds to circulating AGEs, and inhibits tissue damage [48]. However, its protective effect and the mechanisms that regulate its concentrations are still under debate. In an epidemiologic study conducted over 4 y, a positive correlation was observed between AGEs and sRAGE concentrations in 184 non-diabetic participants with normal weight [49]. In a cross-sectional study involving 198 subjects with type 2 diabetes mellitus and high risk for vascular complications, a positive association was observed between sRAGE and peripheral neuropathy (a microvascular complication of diabetes) [50]. This indicates that sRAGE does not always have a protective role, since in these studies there was an association between sRAGE and AGEs, which are known to exacerbate inflammation and oxidative stress [51], as well as an association between sRAGE and diabetes complications [46]. Some authors state that sRAGE is associated with inflammation [52–54]. The results of in vitro studies suggest a new role for sRAGE in inflammation mediated by monocytes and in neutrophil survival and differentiation [55]. Therefore, future studies should be conducted to assess the actual role of sRAGE.

In subjects with chronic diseases, increased serum AGEs and RAGE expression are seen because of increased oxidative stress and hyperglycemia. According to some authors, sRAGE concentration may be a biomarker that can be used to reflect the deleterious effects of AGEs [50]. Increased tissue RAGE expression can result in increased sRAGE concentration to neutralize increased AGEs concentrations, thus preventing tissue damage [47,50]. However, the mechanism involved in sRAGE modulation is still not clear and should be further investigated. In the present study, sRAGE concentrations decreased despite AGEs concentrations remaining constant. That result suggests that the mechanism by which sRAGE modulates AGEs concentrations also needs to be further explored.

Some authors have observed body weight loss after energy-restricted diets and bariatric surgery, but different behaviors in terms of sRAGE concentration [56–60]. Consumption of energy-restricted diets for 6 months did not affect sRAGE concentrations in subjects with overweight [56,57], nor did bariatric surgery [58]. However, other authors have observed a reduction in sRAGE concentrations 12 months after bariatric surgery [59]. Another study found an increase in sRAGE concentrations 24 months after bariatric surgery [60]. The results of these studies confirm that future studies should be conducted to clarify the effect of weight loss on sRAGE concentrations. However, we hypothesize that the discrepancies in these results may be due to differences in the duration and type of intervention applied (bariatric surgeries can led to greater loss of body weight than energy-restricted diets). Apparently, AGEs, RAGE, and sRAGE are three elements in a model in balance with positive and negative feedbacks that can be modified by different diseases [47]. However, the mechanisms that regulate their concentrations are still under debate, and little is known about the potential modulating role of diets.

Our study has several strengths. It was a randomized and controlled design. We selected participants without comorbidities, who were overweight or obese (not morbidly obese) and who were not receiving pharmacologic treatment. However, it is possible that the duration of our study was insufficient to result in significant changes in glycation markers, as we discussed earlier. We also quantified only serum glycation markers. Performing tissue analysis would have enabled us to evaluate RAGE expression, which would have allowed us to have a broader view of the effects of weight loss in subjects with excess body weight. Also, serum AGEs concentrations do not reflect total AGEs concentrations in the body; a fraction of AGEs are linked to their receptors present in tissue membranes, which may play a fundamental role in the pathogenesis of several chronic diseases [35]. However, since tissue analysis is more invasive, we did not evaluate the fraction of AGEs linked to such receptors.

Conclusions

The consumption of 25 g of yacon flour associated with an energy-restricted diet for 6 wk did not affect AGEs and EGPs concentrations. Changes in glycation marker concentrations were positively associated with changes in consolidated anthropometric and biochemical markers related to excess body weight. These results suggest that assessing the concentrations of glycation markers may be a useful strategy to monitor responses to dietary interventions in subjects with excess body weight. Future long term studies ($\geq$2 months) are needed to investigate the mechanisms that regulate the concentrations of these glycation markers and the effects of different types of foods in their concentrations.

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References

[1] Blüher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol 2019;15:288–98.
[2] World Health Organization. Obesity and overweight 2020. Available at: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed July 6, 2021.
[3] Chooi YC, Ding C, Magkos F. The epidemiology of obesity. Metabolism 2019;92:6–10.

[4] Matafome P, Rodrigues T, Sena C, Seiça R. Methylglyoxal in metabolic disorders: facts, myths, and promises. Med Res Rev 2017;37:368–403.
[5] Uribarri J, Cai W, Sandu O, Peppa M, Goldberg T, Vlassara H. Diet-derived advanced glycation end products are major contributors to the body's AGE pool and induce inflammation in healthy subjects. Ann N Y Acad Sci 2005;1043:461–6.
[6] Ramasamy R, Vannucci SJ, Yan SSD, Herold K, Yan SF, Schmidt AM. Advanced glycation end products and RAGE: a common thread in aging, diabetes, neurodegeneration, and inflammation. Glycobiology 2005;15:16R–28R.
[7] Song F, Hurtado del Pozo C, Rosario R, Zou YS, Ananthakrishnan R, Xu X, et al. RAGE regulates the metabolic and inflammatory response to high-fat feeding in mice. Diabetes 2014;63:1948–65.
[8] Gaens KHJ, Goossens GH, Niessen PM, van Greevenbroek MM, van der Kallen CJH, Niessen HW, et al. N^{ε}-(carboxymethyl)lysine-receptor for advanced glycation end product axis is a key modulator of obesity-induced dysregulation of adipokine expression and insulin resistance. Arterioscler Thromb Vasc Biol 2014;34:1199–208.
[9] Ueno H, Koyama H, Shoji T, Monden M, Fukumoto S, Tanaka S, et al. Receptor for advanced glycation end-products (RAGE) regulation of adiposity and adiponectin is associated with atherogenesis in apoE-deficient mouse. Atherosclerosis 2010;211:431–6.
[10] Uribarri J, Woodruff S, Goodman S, Cai W, Chen X, Pyzik R, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J Am Diet Assoc 2010;110. 911–16.e12.
[11] Goldin A, Beckman JA, Schmidt AM, Creager MA. Advanced glycation end products: sparking the development of diabetic vascular injury. Circulation 2006;114:597–605.
[12] Miyata T, Wada Y, Cai Z, Iida Y, Horie K, Yasuda Y, et al. Implication of an increased oxidative stress in the formation of advanced glycation end products in patients with end-stage renal failure. Kidney Int 1997;51:1170–81.
[13] Tanaka N, Yonekura H, Yamagishi S, Fujimori H, Yamamoto Y, Yamamoto H. The receptor for advanced glycation end products is induced by the glycation products themselves and tumor necrosis factor-α through nuclear factor-κB, and by 17β-estradiol through Sp-1 in human vascular endothelial cells. J Biol Chem 2000;275:25781–90.
[14] Neeper M, Schmidt AM, Brett J, Yan SD, Wang F, Pan YCE, et al. Cloning and expression of a cell surface receptor for advanced glycosylation end products of proteins. J Biol Chem 1992;267:14998–5004.
[15] Yonekura H, Yamamoto Y, Sakurai S, Petrova RG, Abedin MJ, Li H, et al. Novel splice variants of the receptor for advanced glycation end-products expressed in human vascular endothelial cells and pericytes, and their putative roles in diabetes-induced vascular injury. Biochem J 2003;370:1097–109.
[16] Hudson BI, Carter AM, Harja E, Kalea AZ, Arriero M, Yang H, et al. Identification, classification, and expression of RAGE gene splice variants. FASEB J 2008;22:1572–80.
[17] Bray GA, Heisel WE, Afshin A, Jensen MD, Dietz WH, Long M, et al. The science of obesity management: an Endocrine Society scientific statement. Endocr Rev 2018;39:79–132.
[18] Lachman J, Fernández EC, Orsák M. Yacon [*Smallanthus sonchifolia* (Poepp. et Endl.) H. Robinson] chemical composition and use—a review. Plant Soil Environ 2003;49:283–90.
[19] Silva MFG, Dionísio AP, Abreu FAP, Pinto CO, Silva LMA, de Brito ES, et al. Optimization of enzymatic treatment to produce yacon juice clarified by microfiltration with high levels of chlorogenic acid and fructooligosaccharides. J Food Process Preserv 2018;42:e13641.
[20] Caetano B, de Moura N, Almeida A, Dias M, Sivieri K, Barbisan L. Yacon (*Smallanthus sonchifolius*) as a food supplement: health-promoting benefits of fructooligosaccharides. Nutrients 2016;8:436.
[21] Campos D, Betalleluz-Pallardel I, Chirinos R, Aguilar-Galvez A, Noratto G, Pedreschi R. Prebiotic effects of yacon (*Smallanthus sonchifolius* Poepp. & Endl), a source of fructooligosaccharides and phenolic compounds with antioxidant activity. Food Chem 2012;135:1592–9.
[22] Apolinário AC, de Lima Damasceno BPG, de Macêdo Beltrão NE, Pessoa A, Converti A, da Silva JA. Inulin-type fructans: a review on different aspects of biochemical and pharmaceutical technology. Carbohydr Polym 2014;101:368–78.
[23] Machado AM, da Silva NBM, Chaves JBP, Alfenas RCG. Consumption of yacon flour improves body composition and intestinal function in overweight adults: a randomized, double-blind, placebo-controlled clinical trial. Clin Nutr ESPEN 2019;29:22–9.
[24] Salas-Salvadó J, Rubio MA, Barbany M, Moreno B. Consenso SEEDO 2007 para la evaluación del sobrepeso y la obesidad y el establecimiento de criterios de intervención terapéutica. Med Clin (Barc) 2007;128:184–96.
[25] Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. J Psychosom Res 1985;29:71–83.
[26] World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191–4.
[27] Associação Brasileira para Estudo da Obesidade e Síndrome Metabólica. Diretrizes brasileiras de obesidade 2016. 4th ed. São Paulo: Marcio C. Mancini; 2016.
[28] Institute of Medicine. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (macronutrients). Washington, DC: Paula R. Trumbo; 2005.
[29] Genta S, Cabrera W, Habib N, Pons J, Carillo IM, Grau A, et al. Yacon syrup: beneficial effects on obesity and insulin resistance in humans. Clin Nutr 2009;28:182–7.
[30] Satoh H, Kudoh A, Hasegawa K, Hirai H, Watanabe T. Yacon supplementation reduces serum free fatty acids and tumor necrosis factor alpha concentrations in patients with type 2 diabetes. Diabetol Int 2014;5:165–74.
[31] Scheid MMA, Genaro PS, Moreno YMF, Pastore GM. Freeze-dried powdered yacon: effects of FOS on serum glucose, lipids and intestinal transit in the elderly. Eur J Nutr 2014;53:1457–64.
[32] Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021–104.
[33] Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.
[34] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
[35] Ashraf JM, Ahmad S, Choi I, Ahmad N, Farhan M, Tatyana G, et al. Recent advances in detection of AGEs: immunochemical, bioanalytical and biochemical approaches. IUBMB Life 2015;67:897–913.
[36] Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem 1976;72:248–54.
[37] Johnson RN, Baker JR. The alkaline reducing activity of glycated serum proteins and its relevance to diabetes mellitus. Clin Chem 1986;32:368–70.
[38] Palma-Duran SA, Kontogianni MD, Vlassopoulos A, Zhao S, Margariti A, Georgoulis M, et al. Serum levels of advanced glycation end-products (AGEs) and the decoy soluble receptor for AGEs (sRAGE) can identify non-alcoholic fatty liver disease in age-, sex- and BMI-matched normo-glycemic adults. Metabolism 2018;83:120–7.
[39] Meyer PL. Probability: applications to statistics. 2nd ed. Rio de Janeiro: Technical and Scientific Books; 1983.
[40] Morettin PA, Bussa WO. Basic statistics. 4th ed. São Paulo: Current; 1987.
[41] Magalhães MN, Lima A. Notions of probability and statistics. 3rd ed. São Paulo, Brazil: Publisher of the University of São Paulo (USP); 2001.
[42] Tavares JF, Ribeiro PVM, Coelho OGL, Silva LE, Alfenas RCG. Can advanced glycation end-products and their receptors be affected by weight loss? a systematic review. Obes Rev 2020;21:e13000.
[43] Rodríguez JM, Balich LL, Barnett DB, Acevedo GB, Birn SH, Jaime TJ, et al. Reduction of serum advanced glycation end-products with a low calorie mediterranean diet. Nutr Hosp 2015;31:2511–7.
[44] Deo P, Keogh J, Price N, Clifton P. Effects of weight loss on advanced glycation end products in subjects with and without diabetes: a preliminary report. Int J Environ Res Public Health 2017;14:1553.
[45] Gugliucci A, Kotani K, Taing J, Matsuoka Y, Sano Y, Yoshimura M, et al. Short-term low calorie diet intervention reduces serum advanced glycation end products in healthy overweight or obese adults. Ann Nutr Metab 2009;54:197–201.
[46] Norata GD, Garlaschelli K, Grigore L, Tibolla G, Raselli S, Redaelli L, et al. Circulating soluble receptor for advanced glycation end products is inversely associated with body mass index and waist/hip ratio in the general population. Nutr Metab Cardiovasc Dis 2009;19:129–34.
[47] Maillard-Lefebvre H, Boulanger E, Daroux M, Gaxatte C, Hudson BI, Lambert M. Soluble receptor for advanced glycation end products: a new biomarker in diagnosis and prognosis of chronic inflammatory diseases. Rheumatology 2009;48:1190–6.
[48] Herold K, Moser B, Chen Y, Zeng S, Yan SF, Ramasamy R, et al. Receptor for advanced glycation end products (RAGE) in a dash to the rescue: inflammatory signals gone awry in the primal response to stress. J Leukoc Biol 2007;82:204–12.
[49] Yamagishi S, Adachi H, Nakamura K, Matsui T, Jinnouchi Y, Takenaka K, et al. Positive association between serum levels of advanced glycation end products and the soluble form of receptor for advanced glycation end products in non-diabetic subjects. Metabolism 2006;55:1227–31.
[50] Aubert CE, Michel P-L, Gillery P, Jaisson S, Fonfrede M, Morel F, et al. Association of peripheral neuropathy with circulating advanced glycation end products, soluble receptor for advanced glycation end products and other risk factors in patients with type 2 diabetes. Diabetes Metab Res Rev 2014;30:679–85.
[51] Ribeiro PVM, Tavares JF, Costa MAC, Mattar JB, Alfenas RCG. Effect of reducing dietary advanced glycation end products on obesity-associated complications: a systematic review. Nutr Rev 2019;77:725–34.
[52] Nakamura K, Yamagishi S, Adachi H, Kurita-Nakamura Y, Matsui T, Yoshida T, et al. Serum levels of sRAGE, the soluble form of receptor for advanced glycation end products, are associated with inflammatory markers in patients with type 2 diabetes. Mol Med 2007;13:185–9.
[53] Bopp C, Hofer S, Weitz J, Bierhaus A, Nawroth PP, Martin E, et al. sRAGE is elevated in septic patients and associated with patients outcome. J Surg Res 2008;147:79–83.
[54] Pullerits R, Brisslert M, Jonsson I-M, Tarkowski A. Soluble receptor for advanced glycation end products triggers a proinflammatory cytokine cascade via β2 integrin Mac-1. Arthritis Rheum 2006;54:3898–907.
[55] Wang Y, Wang H, Piper MG, McMaken S, Mo X, Opalek J, et al. sRAGE induces human monocyte survival and differentiation. J Immunol 2010;185:1822–35.

[56] Hagen I, Schulte DM, Müller N, Martinsen J, Türk K, Hedderich J, et al. Soluble receptor for advanced glycation end products as a potential biomarker to predict weight loss and improvement of insulin sensitivity by a very low calorie diet of obese human subjects. Cytokine 2015;73:265–9.
[57] Miranda ER, Fuller KNZ, Perkins RK, Kroeger CM, Trepanowski JF, Varady KA, et al. Endogenous secretory RAGE increases with improvements in body composition and is associated with markers of adipocyte health. Nutr Metab Cardiovasc Dis 2018;28:1155–65.
[58] Parikh M, Chung M, Sheth S, McMacken M, Zahra T, Saunders JK, et al. Randomized pilot trial of bariatric surgery versus intensive medical weight management on diabetes remission in type 2 diabetic patients who do NOT meet NIH criteria for surgery and the role of soluble RAGE as a novel biomarker of success. Ann Surg 2014;260:617–24.
[59] Lorenzi R, Pattou F, Beuscart JB, Grossin N, Lambert M, Fontaine P, et al. Anti-sRAGE autoimmunity in obesity: downturn after bariatric surgery is independent of previous diabetic status. Diabetes Metab 2014;40:356–62.
[60] Brix JM, Höllerl F, Kopp HP, Schernthaner GH, Schernthaner G. The soluble form of the receptor of advanced glycation endproducts increases after bariatric surgery in morbid obesity. Int J Obes 2012;36:1412–7.