ORIGINAL RESEARCH

CURRENT DEVELOPMENTS IN NUTRITION

Nutrition in Health and Disease

Soluble Receptor for Advanced Glycation End Products (sRAGE) Isoforms Predict Changes in Resting Energy Expenditure in Adults with Obesity during Weight Loss

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ABSTRACT

Background: Accruing evidence indicates that accumulation of advanced glycation end products (AGEs) and activation of the receptor for AGEs (RAGE) play a significant role in obesity and type 2 diabetes. The concentrations of circulating RAGE isoforms, such as soluble RAGE (sRAGE), cleaved RAGE (cRAGE), and endogenous secretory RAGE (esRAGE), collectively sRAGE isoforms, may be implicit in weight loss and energy compensation resulting from caloric restriction.

Objectives: We aimed to evaluate whether baseline concentrations of sRAGE isoforms predicted changes (Δ) in body composition [fat mass (FM), fat-free mass (FFM)], resting energy expenditure (REE), and adaptive thermogenesis (AT) during weight loss.

Methods: Data were collected during a behavioral weight loss intervention in adults with obesity. At baseline and 3 mo, participants were assessed for body composition (bioelectrical impedance analysis) and REE (indirect calorimetry), and plasma was assayed for concentrations of sRAGE isoforms (sRAGE, esRAGE, cRAGE). AT was calculated using various mathematical models that included measured and predicted REE. A linear regression model that adjusted for age, sex, glycated hemoglobin (HbA1c), and randomization arm was used to test the associations between sRAGE isoforms and metabolic outcomes.

Results: Participants ($n = 41$; 70% female; mean ± SD age: 57 ± 11 y; BMI: 38.7 ± 3.4 kg/m^2) experienced modest and variable weight loss over 3 mo. Although baseline sRAGE isoforms did not predict changes in ΔFM or ΔFFM, all baseline sRAGE isoforms were positively associated with ΔREE at 3 mo. Baseline esRAGE was positively associated with AT in some, but not all, AT models. The association between sRAGE isoforms and energy expenditure was independent of HbA1c, suggesting that the relation was unrelated to glycemia.

Conclusions: This study demonstrates a novel link between RAGE and energy expenditure in human participants undergoing weight loss. This trial was registered at clinicaltrials.gov as NCT03336411. *Curr Dev Nutr* 2022;6:nzac046.

Keywords: precision nutrition, caloric restriction, resting metabolic rate, metabolic adaptation, energy balance

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Abbreviations used: AGE, advanced glycation end product; *Ager*, advanced glycation end product specific receptor; AT, adaptive thermogenesis; CGM, continuous glucose monitor; cRAGE, cleaved receptor for advanced glycation end products; esRAGE, endogenous secretory receptor for advanced glycation end products; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; HbA1c, glycated hemoglobin; RAGE, receptor for advanced glycation end products; REE, resting energy expenditure; REEp, predicted resting energy expenditure; RQ, respiratory quotient; sRAGE, soluble receptor for advanced glycation end products; $\dot{V}CO_2$, maximal carbon dioxide production; $\dot{V}O_2$, maximal oxygen consumption; WHR, waist-to-hip ratio; %BF, percentage body fat.

Introduction

In the United States, overweight and obesity continue to increase, with >85% of the population predicted to have obesity by 2050 (1). Current treatments of obesity are focused principally on caloric restriction, pharmacological intervention, and bariatric surgery. Although behavioral lifestyle interventions are effective at reducing body weight and improving cardiometabolic outcomes, key challenges remain in deciphering the biological underpinnings that mediate weight loss and that hinder weight loss maintenance. Differences in adaptations to caloric restriction, including a complex set of feedback mechanisms that collectively slow resting energy expenditure (REE), may explain some of the variability in long-term weight loss success and individual variability (2). An observed response to caloric restriction and weight loss is adaptive thermogenesis (AT), which is a reduction in energy expenditure related to improved cellular energy efficiency that is independent of changes in fat mass (FM) and fat-free mass (FFM). AT persists in the weight-reduced state (3) and during the dynamic process of negative energy balance, and may limit the ability to effectively maintain weight loss (4).

A potential biological mechanism underlying between-subjects variability in weight loss after caloric restriction is the accumulation of advanced glycation end products (AGEs) and their interactions with the central cellular receptor for advanced glycation end products (RAGE). RAGE transduces the signals of its ligands such as AGEs, which accumulate in diabetes and obesity (5). Expression of RAGE is higher in obese than in lean human adipose tissue; although plasma concentrations of carboxymethyllysine AGEs are reduced in obesity, this is proposed to be mediated by the "trapping" of AGE ligands by high expression of RAGE in adipose tissue (5). With weight loss, plasma carboxymethyllysine AGE concentrations rise owing to reduced adipose RAGE expression and consequent reductions in RAGE-mediated AGE trapping. Serum concentrations of AGEs are inversely correlated with fat mass (FM) in adults (6). In contrast, plasma concentrations of other specific AGEs, such as carboxyethyllysine, are higher in obese than in lean humans (5). In separate studies, weight loss induced by low-calorie diets resulted in a reduction in circulating AGEs (7–9). These differences in the pattern of plasma/serum AGEs after weight loss likely reflect that AGEs are a heterogeneous group of structures that bind multiple receptors; hence, the dynamics of the changes in their concentrations in response to weight loss may vary (10).

Beyond direct measures of tissue RAGE expression, RAGE may be tracked in plasma and serum; total soluble RAGE (sRAGE) measures cell surface cleaved RAGE (cRAGE) and the product of an mRNA splice variant, endogenous secretory RAGE (esRAGE). sRAGE isoforms are hypothesized to bind RAGE ligands and, thereby, block their activation of cell surface RAGE. sRAGE is considered a novel biomarker to identify people with obesity who may benefit from weight management interventions (10); however, evidence from surgical and medical weight loss studies on the directionality of sRAGEs in weight loss is mixed (11–15).

Data in mice suggest a link between RAGE and energy expenditure. Song et al. (16) found that mice globally devoid of advanced glycation end product specific receptor (*Ager*; the gene encoding RAGE) fed a high-fat diet were protected from diet-induced obesity and exhibited a higher energy expenditure than wild-type *Ager*-expressing control mice, despite no differences in caloric intake or physical activity. In addition, mice devoid of adipocyte *Ager* displayed reduced weight gain and significantly lower FM after consumption of a high-fat diet, higher energy expenditure, and higher adipose tissue expression of uncoupling protein 1 (*Ucp1*) (17). The mechanisms were traced to RAGE-dependent suppression of protein kinase A activities in brown and white adipocytes. Collectively, these studies in mice uncovered unanticipated roles for RAGE in the regulation of energy expenditure and prompted us to seek evidence for such relations in human subjects.

Although prior studies have shown a relation between sRAGEs and body weight after diet-induced weight loss (14), few reported associated changes in body composition (15), and no study to date has assessed potential relations between sRAGE isoforms, REE, and AT during weight loss. Therefore, the aim of this secondary analysis was to determine whether concentrations of baseline sRAGE isoforms predicted changes (Δ) in body composition (FM and FFM), REE, and AT after 3 mo of a weight loss intervention. In particular, we hypothesized that sRAGE isoforms would be positively associated with ΔFM and ΔREE at 3 mo. Furthermore, we examined the association between sRAGE isoforms and metabolic outcomes (e.g., body composition, REE, adipokines) at baseline and 3 mo, and determined the relation between ΔsRAGEs and metabolic outcomes.

Methods

Design

The data included constituted a secondary analysis utilizing a subgroup of participants in the Personal Diet Study (NCT03336411), a behavioral weight loss intervention. The study was a 2-arm, parallel-group, randomized clinical trial. The purpose of the Personal Diet Study was to compare 2 weight loss interventions: *1*) a low-fat or Standardized diet and *2*) a Personalized diet using a gut microbiome–derived machine learning algorithm that predicts an individual's postprandial glycemic response (18). The primary objective of the parent study was to compare the Standardized and Personalized dietary recommendations on percentage weight loss at 6 mo. Participants were adults between 18 and 80 y old, with a BMI (in kg/m^2) ≥27, diagnosed with prediabetes (>5.6%) or type 2 diabetes, and having a glycated hemoglobin (HbA1c) <8.0%, treated with lifestyle alone or lifestyle plus metformin. The parent cohort (the Personal Diet Study) was part of a larger center project (American Heart Association, Strategically Focused Research Network on Obesity) that also included a clinical study in a bariatric cohort undergoing sleeve gastrectomy. Therefore, for this secondary analysis we selected participants with a baseline BMI ≥ 35, because this threshold is an indication for bariatric surgery, to undergo additional measures on sRAGE isoforms in order to eventually make comparisons with the bariatric cohort. This study was reviewed and approved for human subjects research by the NYU Grossman School of Medicine Institutional Review Board (#17-00741). All participants signed an informed consent before random assignment. A detailed description of exclusion criteria and details regarding the Personalized and Standardized arms has been published previously (19).

Data collection

Measurements were obtained at baseline and 3 mo at the Clinical Research Center of the New York University Clinical and Translational Science Institute. Participants in both arms were provided with hypocaloric targets (−500 kcal/d) based on REE measurements from indirect calorimetry with a physical activity factor of 1.4. Participants in both arms received the same behavioral weight loss counseling intervention and self-monitored dietary intakes using the same mobile phone app.

For the purposes of this secondary analysis, the main outcomes included FM, REE, and AT. Additional outcomes included body weight, BMI, waist-to-hip ratio (WHR), fat mass index (FMI), fat-free mass (FFM), fat-free mass index (FFMI), percentage body fat (%BF), respiratory quotient (RQ), and plasma leptin and adiponectin concentrations.

Anthropometrics.

Height was measured to the nearest 1 cm using a portable stadiometer (SECA 213, Seca GmBH & Co. KG), and body weight was measured in light clothing without shoes to the nearest 0.1 kg using a Stow-A-Weigh scale (Scale Tronix, Welch Allyn). All measurements were performed in a fasted state.

Body composition, REE, and metabolic adaptation.

Body composition was assessed using bioelectrical impedance analysis (InBody 270, InBody, Inc.). Indexes for body composition (FMI and FFMI) were calculated from absolute values of FM and FFM by adjusting for body height squared (m^2), as calculated for BMI. Before REE measurement, participants were asked to confirm the following: *1*) no vigorous physical activity within the previous 48 h, *2*) a minimum of 8 h fast, and *3*) no use of caffeine or nicotine products on the day of testing. Participants were directed to lie supine for 10 min, during which the flow meter and gas analyzer were calibrated per the manufacturer's instructions. Open-circuit indirect calorimetry was performed using a COSMED Quark RMR® metabolic cart with flow-dilution canopy hood (COSMED). Maximal oxygen consumption ($\dot{V}O_2$) and maximal carbon dioxide production ($\dot{V}CO_2$) were measured for 20 min after a 5-min run-in stabilization period. Participants were instructed to abstain from sleeping and talking during the test. Gas exchange variables ($\dot{V}O_2$ and $\dot{V}CO_2$) were measured every 10 s. REE was calculated from the Weir equation and expressed in kcal/d (20). RQ was determined by dividing $\dot{V}CO_2$ by $\dot{V}O_2$. REE was determined using the first steady-state period where both $\dot{V}O_2$ and $\dot{V}CO_2$ were ≤10% CV (21). For those who did not meet these criteria, we used the $\dot{V}O_2$ and $\dot{V}CO_2$ from the 5-min period after the initial 10-min measurement period. To assess the validity of the test, the range of RQ was determined and compared to the physiologic range (0.67–1.3).

AT was used to detect differences in REE that are independent of changes in body composition (FM and FFM). Given the lack of standardization of methodologies to assess AT in REE, we calculated AT using various equations as described by Nunes et al. (22). More specifically, AT was assessed with 3 mathematical approaches, which varied in the calculation of predicted REE (REEp) as follows:

1) REEp1 = a prediction equation using baseline FM, FFM, sex, and age as independent predictors;
2) REEp2 = a prediction equation using baseline FFM as an independent predictor; and
3) REEp3 = a prediction equation using baseline FM and FFM as independent predictors.

AT was then calculated using measured REE (REE via indirect calorimetry) and 1 of the 3 aforementioned calculations of REEp. We used 3 models to estimate AT: *1*) in model A, AT was assessed simply by subtracting REEp from REE at 3 mo. *2*) In model B, AT was calculated by subtracting REEp from REE at 3 mo ($REE_{3mo} - REEp_{3mo}$) and subtracting REEp from REE at baseline ($REE_{baseline} - REEp_{baseline}$). Therefore, AT is equal to $[(REE_{3mo} - REEp_{3mo}) - (REE_{baseline} - REEp_{baseline})]$. *3*) In model C, percentage AT (%AT) was calculated as 100∗[(REE/REEp) – 1] after 3 mo; therefore, AT is assessed as $(\%AT/100)*REE_{baseline}$. Models are labeled alphabetically, with the respective equation to estimate REEp given a numeral (e.g., Model A1).

Glycemia.

Multiple indexes of glycemia were obtained. HbA1c was analyzed using HPLC (Variant II Turbo analyzer, Bio-Rad Laboratories, Inc.). Plasma was collected in lithium heparin–coated tubes for analysis of fasting glucose and fasting insulin by quantitative enzymatic hexokinase/glucose-6-phosphate dehydrogenase (G-6-PDH) assay (Abbott Architect, Abbott Laboratories) and chemiluminescent microparticle immunoassay (Abbott Architect, Abbott Laboratories), respectively. Glucose and insulin concentrations were used in the HOMA-IR (HOMA2, Diabetes Trials Unit, University of Oxford). Furthermore, participants wore continuous glucose monitors (CGMs; Abbott FreeStyle Libre Pro) for ≤14 d. Participants were blinded to the CGM data and were asked not to take aspirin while wearing the CGM. As per the manufacturer's instructions, the first 48 h of readings of each CGM were removed from analysis. Measures of glycemic variability included mean amplitude of glycemic excursions and CV using EasyGV version 9.0.R2 (Nathan R Hill, University of Oxford).

Human sRAGE and esRAGE concentrations.

Plasma total sRAGE concentrations were measured using a commercially available ELISA (R&D ELISA, DRG00). The AsOne International ELISA (K-1009-1) measures only esRAGE. From this, we calculated cell surface cleaved (c) sRAGE (total sRAGE – esRAGE) = cRAGE. For total sRAGE, each unique sample was analyzed in duplicate (50 μL/replicate). The sensitivity of the assay was 16.14 pg/mL, with an assay range of 78–5000 pg/mL. There was <0.5% cross-reactivity with other molecules. The intra-assay precision (CV) was ∼5.7% and the interassay precision (CV) was ∼7.7%. For esRAGE, each unique sample was analyzed in duplicate (20 μL/replicate). The linear range of the esRAGE measurements was 0.05–3.2 ng/mL. The inter- and intra-assay CVs for esRAGE were <10% and <4.4%, respectively. For every experiment, standards were included as per the manufacturer's instructions.

Adipokine concentrations.

Plasma concentrations of leptin were measured with the Milliplex Human Metabolic Hormone Panel V3 (HMH3-34K; Millipore, Sigma) according to the manufacturer's instructions. The range of detection per the standard curve is 137–100,000 pg/mL; sensitivity for detection of

leptin is 52 pg/mL; and accuracy is 87%. The intra-assay precision is <10% CV and the interassay precision is <20% CV. There is no known or negligible cross-reactivity between the antibodies for the detection of leptin and any of the other analytes in this specific panel. Plasma concentrations of adiponectin were measured with the Milliplex Human Adipokine Magnetic Bead Panel 1 (HADK1MAG-61K; Millipore, Sigma) according to the manufacturer's instructions. The range of detection per the standard curve is 26–400,000 pg/mL; sensitivity for detection of adiponectin is 21 pg/mL, and accuracy is 89%. The intra-assay precision is <10% CV and the interassay precision is <15% CV. There is no known or negligible cross-reactivity between the antibodies for the detection of adiponectin and any of the other analytes in this specific panel.

Statistical analyses

As a secondary analysis, the association of sRAGE isoforms with anthropometric, body composition, energy expenditure, glycemic, and adipokine outcomes (collectively called metabolic outcomes) was investigated using a selected subsample in the Personal Diet Study. First, we examined the concentrations of sRAGE isoforms (sRAGE, esRAGE, cRAGE) with each metabolic outcome at baseline and 3 mo. Second, we examined baseline sRAGE isoform concentrations with each metabolic outcome at 3 mo. Third, we examined the association between baseline sRAGE isoform concentrations and the changes (Δ) in each metabolic outcome (3 mo minus baseline). Finally, we examined the association between ΔsRAGE isoform concentrations and the change in each metabolic outcome between baseline and 3 mo. A linear regression model was used for the analysis at a single time point; to consider the correlation of longitudinal measurements for data with >1 time point, a linear mixed-effect model was fitted instead.

Because the original data came from a randomized trial, we first conducted a full regression model that included the randomization arm and the interaction between sRAGE isoform concentrations and randomization arm (Standardized compared with Personalized) to determine whether the studied associations differed in the 2 arms. In addition, in the full regression model, we adjusted for age, sex, and HbA1c. Because we were unable to measure AGEs owing to limited sample availability, we used HbA1c as a surrogate marker for long-term glycemia. If the full model indicated no significant interaction between sRAGE isoform concentrations and the randomization arm, both arms were collapsed into a single group and the arm was adjusted for in a simplified model without the interaction term. Otherwise, we fitted the linear regression model in the 2 arms separately (adjusted for age, sex, and HbA1c).

Results

The final sample included 41 participants (n = 12 males, n = 29 females). **Figure 1** shows the flow of the participants through the trial. **Table 1** presents baseline characteristics in the combined sample and by randomly assigned arm. A total of $n = 7$ participants reported the use of thyroid medications at baseline; however, any subjects reporting a history of hyperthyroidism were excluded from the study and, aside from age, there were no significant differences in baseline characteristics between those reporting thyroid medications and those not taking thyroid medications (**Supplemental Table 1**).

Metabolic outcomes are presented in **Table 2**, which only includes participants ($n = 33$) with both baseline and 3-mo data (**Supplemental Table 2** shows the sample sizes at each time point). **Supplemental Table 3** presents the full sample of participants' metabolic outcomes. Weight loss at 3 mo was modest and variable among all participants (**Supplemental Figure 1**) with a change in mean body weight of −1.7%± 4.0%. Baseline REE was not significantly associated with Δbody weight; however, there was a positive association between ΔREE and Δbody weight ($R = 0.37$; $P = 0.04$). There was a trend in the change in mean FM (−1.3 ± 3.4 kg; $P = 0.05$) and there was a significant decrease in mean REE (−157.8 ± 308.0 kcal/d; $P < 0.01$). **Supplemental Table 4** presents the mean and range of AT for each model.

The full model indicated no significant interaction between any of the sRAGE isoforms (sRAGE, esRAGE, cRAGE) and randomization arm for FM, REE, and AT; therefore, both arms were collapsed into a single group and the arm was adjusted for in a simplified model without the interaction term. In the case of baseline esRAGE, there was a significant interaction effect with both ΔFFM and ΔFFMI, which indicated that the association between baseline esRAGE and ΔFFM/ΔFFMI was different between arms. The post hoc analysis revealed a significant association between baseline esRAGE concentrations and ΔFFM for the Standardized ($P = 0.02$) but not the Personalized arm ($P = 0.20$).

The full linear regression model that included the interaction term between any of the sRAGE isoforms and the randomization arm revealed significant associations for the glycemic outcomes, which are described in **Supplemental Text 1**. **Table 3** reports the linear mixed model examining the associations between any of the sRAGE isoform concentrations and metabolic outcomes at both baseline and 3 mo. All sRAGE isoform concentrations were positively associated with body weight, hip circumference, FM, leptin, and adiponectin. However, when FM was adjusted for body size (e.g., FMI), the associations were lost. sRAGE and cRAGE concentrations were negatively associated with WHR. **Table 4** reports baseline sRAGE isoform concentrations and metabolic outcomes at 3 mo. All sRAGE isoform concentrations were positively associated with FM at 3 mo. Baseline sRAGE and cRAGE concentrations were positively associated with hip circumference and only baseline cRAGE concentrations were negatively associated with WHR at 3 mo. Baseline esRAGE concentrations were positively associated with REE and leptin. The ΔsRAGE isoform concentrations were not significantly associated with ΔFM, ΔREE, or any of the other metabolic outcomes (**Supplemental Table 5**).

The linear regression model revealed that baseline sRAGE isoform concentrations did not predict ΔFM at 3 mo (**Table 5**). Baseline sRAGE isoform concentrations were significantly associated with ΔREE. More specifically, for every unit (1-pg/mL) increase in baseline sRAGE, esRAGE, and cRAGE concentrations, there was a positive 0.526-, 1.816-, and 0.561-kcal/d ΔREE, respectively. In other words, a 100-pg/mL increase in baseline values for sRAGE, esRAGE, and cRAGE concentrations translated to ΔREE of 52.6 kcal/d, 181.6 kcal/d, and 56.1 kcal/d, respectively, when comparing 3 mo with baseline results. AT was associated with sRAGE isoforms depending on the specific AT model (**Table 6**). Baseline esRAGE was significantly associated with AT when using model A1, but not models A2 and A3. All baseline sRAGE isoforms were significantly associated with AT at 3 mo using models B1–B3. In model C, there was only a significant association between baseline esRAGE and AT in model C1.

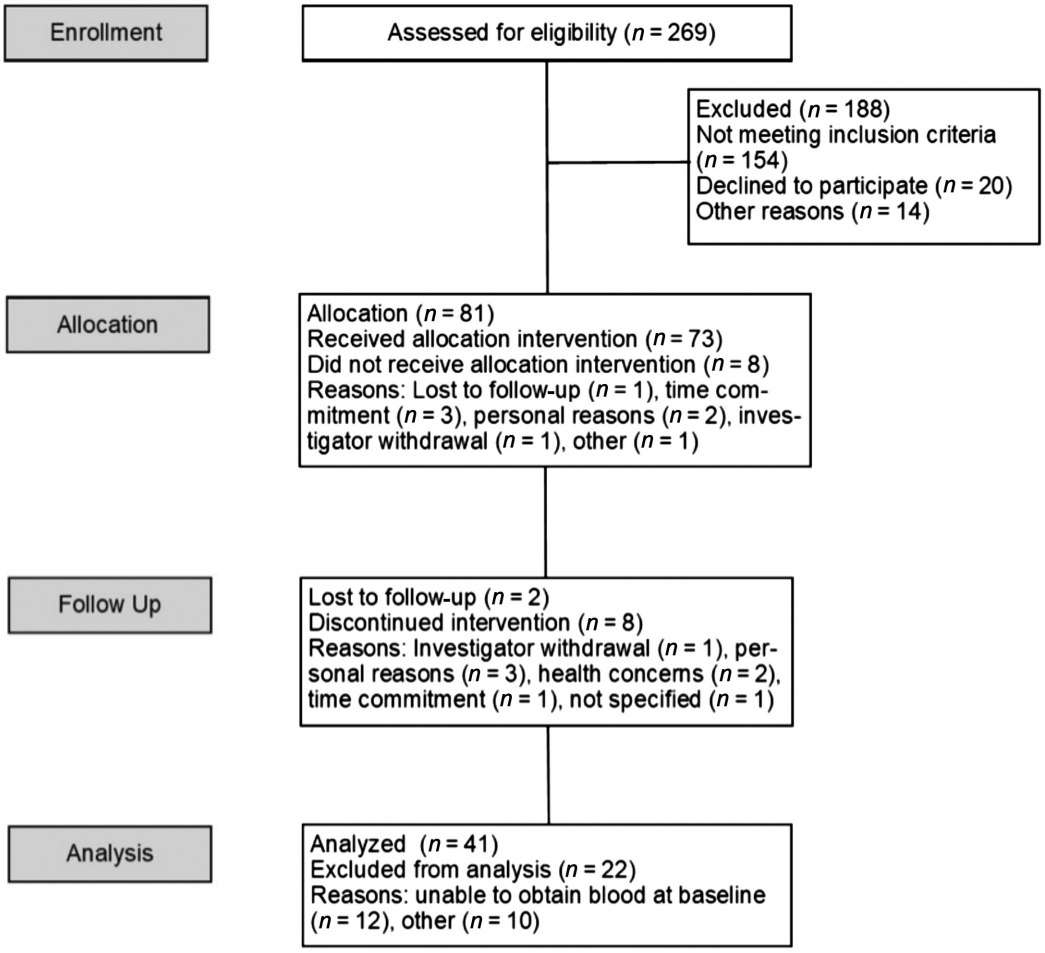

FIGURE 1 Flow of participants through the 3-mo dietary intervention. The flow diagram includes the 2 arms (Standardized and Personalized) collapsed into a single group.

Discussion

The physiologic effects of RAGE include the activation of proinflammatory signals (e.g., NF-κB) and increased production of proinflammatory cytokines, adhesion molecules, and RAGE itself, which are associated with increased risks of cardiovascular disease, diabetes, and obesity (5, 23). Because adults with obesity have higher expression of RAGE protein in adipose tissue than their lean counterparts, the relation between

TABLE 1 Baseline characteristics[1]

Variable	All (n = 41)	Standardized (n = 16)	Personalized (n = 25)
Age, y	57 ± 11	59 ± 10	56 ± 11
Sex, female	70.7	50.0	84.0
Ethnicity, non-Hispanic	82.9	93.8	76.0
Race			
White	53.7	75.0	40.0
African American	22.0	12.5	28.0
Other	24.3	12.5	32.0
Height, cm	165.4 ± 8.1	167.5 ± 6.8	164.1 ± 8.7
Weight, kg	106.0 ± 13.0	106.9 ± 10.6	105.4 ± 14.5
BMI, kg/m^2	38.7 ± 3.4	38.1 ± 2.2	39.1 ± 3.9
HbA1c, %	5.8 ± 0.65	5.9 ± 0.73	5.8 ± 0.6

[1]Values are means ± SDs or percentages. Race: "other" includes Asian, Native Hawaiian or Other Pacific Islander, American Indian, Alaska Native Asian, or Unknown. HbA1c, glycated hemoglobin.

TABLE 2 Changes in metabolic outcomes from baseline to 3 mo[1]

Variable	Baseline ($n = 33$)	3 mo ($n = 33$)	Δ	*P* value
Weight, kg	107.2 ± 11.7	105.5 ± 12.7	−1.72 ± 4.2	0.02*
BMI, kg/m^2	38.7 ± 2.9	38.0 ± 3.0	−0.66 ± 1.6	0.02*
WHR	0.94 ± 0.1	0.94 ± 0.1	0 ± 0.0	0.92
Body fat, %	43.7 ± 6.3	43.2 ± 6.6	−0.51 ± 1.9	0.17
FM, kg	46.8 ± 6.2	45.5 ± 6.9	−1.29 ± 3.4	0.05
FMI, kg/m^2	17.0 ± 3.2	16.5 ± 3.2	−0.49 ± 1.3	0.05
FFM, kg	61.1 ± 11.8	60.7 ± 12.3	−0.41 ± 2.2	0.32
FFMI, kg/m^2	21.7 ± 2.4	21.6 ± 2.6	−0.17 ± 0.8	0.27
REE, kcal/d	1941.4 ± 387.0	1783.6 ± 307.1	−157.8 ± 308.0	<0.01*
RQ	0.83 ± 0.1	0.87 ± 0.1	0.04 ± 0.2	0.60
Leptin, ng/mL	28.8 ± 19.1	26.2 ± 23.2	−2.56 ± 10.6	0.32
Adiponectin, ng/mL	74.3 ± 94.4	72.5 ± 90.3	−1.81 ± 79.3	0.68
sRAGE, pg/mL	710.0 ± 282.3	703.9 ± 268.5	−6.09 ± 176.8	0.88
esRAGE, pg/mL	157.7 ± 88.9	147.8 ± 111.2	−9.85 ± 60.0	0.48
cRAGE, pg/mL	552.3 ± 228.1	556.1 ± 213.4	3.76 ± 153.1	0.92
Fasting glucose, mg/dL	100.6 ± 22.0	97.4 ± 13.2	−3.19 ± 15.9	0.69
Fasting insulin, mg/dL	14.0 ± 6.4	12.5 ± 4.9	−1.47 ± 4.8	0.24
HOMA-IR	3.4 ± 1.8	3.0 ± 1.4	−0.42 ± 1.5	0.47
GV, %CV	19.3 ± 4.5	18.6 ± 4.1	−0.7 ± 3.7	0.37
MAGE, mg/dL	57.7 ± 20.7	50.7 ± 18.3	−6.9 ± 17.2	0.07

[1]Values are mean ± SD unless otherwise indicated. Data from subjects with baseline and 3-mo time points were included. Sample sizes varied by outcome and are presented in Supplemental Table 1. cRAGE, cleaved receptor for advanced glycation end products; esRAGE, endogenous secretory receptor for advanced glycation end products; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; GV, glycemic variability; MAGE, mean amplitude of glycemic excursions; REE, resting energy expenditure; RQ, respiratory quotient; sRAGE, soluble receptor for advanced glycation end products; WHR, waist-to-hip ratio.
*The level of significance was set at $P < 0.05$.

FM and RAGE is particularly interesting. In individuals with obesity, sRAGE concentrations are reported to be lower than in lean individuals (11, 24) and total sRAGE concentrations are negatively associated with BMI (25, 26). Increases in sRAGE isoform concentrations have been observed after significant reductions in FM (15). Therefore, although we predicted that baseline sRAGE concentrations would be associated with ΔFM, our results are not in line with our original hypothesis. Of interest, the associations between sRAGE isoforms and ΔREE demonstrate a link between energy partitioning during negative energy balance and RAGE as possible feedback mechanisms. Based on these findings, esRAGE concentrations may be specific to changes in REE; however, future studies are required to determine if expression of RAGE in adipose tissue after weight loss correlates with ΔREE. Moreover, the exact mechanisms that regulate formation of the mRNA splice variant esRAGE are largely unknown; esRAGE may act as a decoy to prevent activation of cell surface RAGE signaling cascades (27).

Compensatory responses in REE during negative energy balance that are independent of changes in FM and FFM (i.e., AT) may attenuate weight loss (4, 28, 29). Therefore, identifying predictors of metabolic adaptation may contribute to better treatment of obesity and weight management (30). The findings from our study linking sRAGE isoforms and AT were mixed and depended on the mathematical models used to predict AT. In models A1, B1, and C1, there was a significant association between baseline esRAGE and AT. Each of these models predicted REE using sex and age as predictors; however, it is important to note that in distinct studies, the contribution of sex to the variance in REE has not been shown to be significant (31). In addition, it has been demonstrated that age contributes very little (~2%) to the variance in REE, because a recent study found that both REE and total energy expenditure are relatively stable over one's lifetime (32). Age has been shown not to be a significant predictor of AT (33); therefore, predicting REE using only FFM and FFM plus FM may be optimal for our models. Collectively, our results indicate a nonsignificant association between baseline sRAGE isoforms and AT only in models using predicted REE from FFM alone or FFM plus FM (that is, models A2, A3, C2, and C3). Moreover, the application of model B, which adjusts for baseline measures of AT, may be considered the strongest methodological approach to estimating AT (22). Interestingly, all baseline sRAGE isoforms were positively associated with AT in models B1–B3. The largest magnitude of AT was associated with baseline esRAGE and is consistent with ΔREE. Despite these significant findings, the physiologic relevance of AT and sRAGE isoforms requires future exploration to confirm these findings.

There is variability in the response of sRAGEs after weight loss (11, 14, 15). Others reported a nonsignificant decrease in sRAGE concentrations from baseline to 12 wk in adults undergoing weight loss due to a very-low-calorie diet. A prior study by Hagen et al. (14) found that after weight loss, participants with a greater reduction in BMI had lower baseline sRAGE concentrations. In addition, when stratifying by median weight loss, Miranda et al. (15) found no difference in the change in sRAGE isoform concentrations between those above and below the median weight loss cutoff at 12 wk. However, at 24 wk, those who were above the median weight loss cutoff (e.g., lost more weight) maintained their sRAGE concentrations. In contrast, those who did not lose weight (e.g., were below the median cutoff) experienced a decrease in their cRAGE and esRAGE concentrations at 24 wk.

TABLE 3 Association test of sRAGE isoform concentrations (sRAGE, esRAGE, cRAGE) and anthropometrics, REE, adipokines, and glycemia at baseline and 3 mo by linear mixed-effect model[1]

	sRAGE, pg/mL		esRAGE, pg/mL		cRAGE, pg/mL	
Variable	**Estimate**	***P* value**	**Estimate**	***P* value**	**Estimate**	***P* value**
Body weight, kg	0.012	0.01*	0.037	0.00*	0.012	0.03*
BMI, kg/m^2	0.004	0.02*	0.010	0.02*	0.004	0.05
WC, cm	0.007	0.11	0.012	0.29	0.007	0.10
HC, cm	0.017	0.00*	0.036	0.00*	0.014	0.00*
WHR	−0.000	0.03*	−0.000	0.09	−0.000	0.03*
Body fat, %	0.002	0.34	0.001	0.79	0.003	0.32
FM, kg	0.009	0.018	0.023	0.02*	0.010	0.02*
FMI, kg/m^2	0.003	0.07	0.005	0.17	0.003	0.12
FFM, kg	0.004	0.10	0.008	0.25	0.004	0.15
FFMI, kg/m^2	0.001	0.22	0.002	0.27	0.001	0.36
REE, kcal/d	−0.139	0.16	−0.070	0.82	−0.237	0.09
RQ	0.000	0.49	0.000	0.47	0.000	0.22
Leptin, ng/mL	0.028	0.00*	0.078	0.00*	0.026	0.01*
Adiponectin, ng/mL	0.129	0.01*	0.324	0.00*	0.132	0.04*
Fasting glucose, mg/dL	0.009	0.25	0.039	0.07	0.001	0.52
Fasting insulin, mg/dL	−0.004	0.23	−0.011	0.19	−0.004	0.32
HOMA-IR	−0.000	0.55	−0.000	0.69	−0.000	0.54
GV, %CV	0.003	0.13	0.014	0.03*	0.003	0.32
MAGE, mg/dL	0.012	0.26	0.064	0.03*	0.002	0.62

[1]The fitted model: interested variable ~ RAGE variable + sex + age + month + arm + HbA1c + (1|subject); $P \leq 0.05$; significance shown in bold. cRAGE, cleaved receptor for advanced glycation end products; esRAGE, endogenous secretory receptor for advanced glycation end products; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; GV, glycemic variability; HC, hip circumference; MAGE, mean amplitude of glycemic excursions; REE, resting energy expenditure; RQ, respiratory quotient; sRAGE, soluble receptor for advanced glycation end products; WC, waist circumference; WHR, waist-to-hip ratio.
*The level of significance was set at $P < 0.05$.

In the current study, we did not find a significant association between ΔsRAGE isoform concentrations and ΔFM, ΔREE, and AT. This may be a result of nonsignificant ΔsRAGE isoform concentrations at 3 mo. Regardless, there were suggestions from our data that support prior findings. In particular, Miranda et al. (15) found that greater FM loss was associated with an increase in esRAGE concentrations at 6 mo. Our results showed a negative but nonsignificant relation between ΔFM and ΔesRAGE concentrations at 3 mo (est. = −0.02, $P = 0.24$); however,

TABLE 4 Association test of baseline sRAGE isoform concentrations (sRAGE, esRAGE, cRAGE) and anthropometrics, REE, adipokines, and glycemia at 3 mo by linear regression model[1]

	sRAGE, pg/mL		esRAGE, pg/mL		cRAGE, pg/mL	
Variable	**Estimate**	***P* value**	**Estimate**	***P* value**	**Estimate**	***P* value**
Body weight, kg	0.012	0.07	0.037	0.09	0.014	0.11
BMI, kg/m^2	0.003	0.18	0.008	0.28	0.003	0.22
WC, cm	0.003	0.51	0.010	0.50	0.003	0.57
HC, cm	0.013	0.02*	0.026	0.19	0.017	0.02*
WHR	−0.000	0.06	−0.000	0.46	−0.000	0.04*
Body fat, %	0.005	0.21	0.006	0.66	0.007	0.17
FM, kg	0.014	0.00*	0.036	0.04*	0.016	0.01*
FMI, kg/m^2	0.004	0.09	0.009	0.27	0.005	0.09
FFM, kg	0.003	0.64	0.026	0.24	0.001	0.87
FFMI, kg/m^2	0.000	0.94	0.004	0.35	−0.000	0.82
REE, kcal/d	0.138	0.30	0.862	0.04*	0.092	0.58
RQ	0.000	0.87	0.000	0.28	−0.000	0.82
Leptin, ng/mL	0.027	0.17	0.167	0.01*	0.023	0.33
Adiponectin, ng/mL	0.024	0.77	0.369	0.23	−0.001	0.99
Fasting glucose, mg/dL	0.001	0.89	0.049	0.09	−0.005	0.65
Fasting insulin, mg/dL	−0.000	0.94	−0.004	0.74	−0.000	0.90
HOMA-IR	0.000	0.89	0.001	0.79	−0.000	0.98
GV, %CV	0.002	0.54	0.019	0.15	0.001	0.82
MAGE, mg/dL	0.002	0.17	0.083	0.07	−0.009	0.62

[1]The fitted model: interested variable ~ RAGE variable + sex + age + arm + HbA1c; significance shown in bold. $P \leq 0.05$. cRAGE, cleaved receptor for advanced glycation end products; esRAGE, endogenous secretory receptor for advanced glycation end products; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; GV, glycemic variability; HC, hip circumference; MAGE, mean amplitude of glycemic excursions; REE, resting energy expenditure; RQ, respiratory quotient; sRAGE, soluble receptor for advanced glycation end products; WC, waist circumference; WHR, waist-to-hip ratio.
*The level of significance was set at $P < 0.05$.

TABLE 5 Association test of baseline sRAGE isoform concentrations (sRAGE, esRAGE, cRAGE) and the change in (Δ) anthropometrics, REE, adipokines, and glycemia from baseline to 3 mo by linear regression model[1]

	sRAGE, pg/mL		esRAGE, pg/mL		cRAGE, pg/mL	
Variable	Estimate	*P* value	Estimate	*P* value	Estimate	*P* value
ΔBody weight, kg	0.004	0.22	0.004	0.70	0.006	0.16
ΔBMI, kg/m^2	0.002	0.17	0.002	0.58	0.002	0.14
ΔWC, cm	0.001	0.30	0.005	0.67	0.005	0.26
ΔHC, cm	0.000	0.79	−0.007	0.52	0.002	0.56
ΔWHR	0.000	0.30	0.000	0.21	0.000	0.41
ΔBody fat, %	0.002	0.27	0.001	0.80	0.002	0.20
ΔFM, kg	0.004	0.10	0.006	0.52	0.006	0.08
ΔFMI, kg/m^2	0.002	0.09	0.003	0.45	0.001	0.07
ΔFFM, kg	0.001	0.66	0.002	0.75	0.000	0.68
ΔFFMI, kg/m^2	0.000	0.55	0.001	0.58	0.000	0.59
ΔREE, kcal/d	0.526	0.01*	1.816	0.00*	0.561	0.03*
ΔRQ	−0.000	0.91	0.000	0.21	−0.000	0.53
ΔLeptin, ng/mL	0.016	0.14	0.064	0.11	0.018	0.19
ΔAdiponectin, ng/mL	−0.095	0.21	−0.243	0.42	−0.119	0.21
ΔFasting glucose, mg/dL	−0.006	0.63	−0.057	0.18	−0.002	0.92
ΔFasting insulin, mg/dL	0.008	0.02*	0.024	0.04*	0.011	0.04*
ΔHOMA-IR	0.002	0.12	0.003	0.38	0.003	0.10
ΔGV, %CV	0.004	0.29	0.021	0.04*	0.002	0.61
ΔMAGE, mg/dL	0.012	0.44	0.029	0.53	0.014	0.48

[1]The fitted model: interested variable ~ RAGE variable + sex + age + arm + HbA1c; $P \leq 0.05$; significance shown in bold. cRAGE, cleaved receptor for advanced glycation end products; esRAGE, endogenous secretory receptor for advanced glycation end products; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; GV, glycemic variability; HC, hip circumference; MAGE, mean amplitude of glycemic excursions; REE, resting energy expenditure; RQ, respiratory quotient; sRAGE, soluble receptor for advanced glycation end products; WC, waist circumference; WHR, waist-to-hip ratio.
*The level of significance was set at $P < 0.05$.

there was a negative trend between Δ%BF and ΔesRAGE concentrations ($P = 0.08$), suggesting the possibility that an increase in esRAGE concentrations may be associated with greater changes in %BF. These trends may be explained by a relatively small sample size with baseline and 3-mo data ($n = 19$). Furthermore, the exact mechanism surrounding the ΔesRAGE concentrations after fat loss needs to be further explored. The conversion of *AGER* pre-mRNA to esRAGE may be inhibited during obesity as a result of adipose tissue inflammation or other yet to be defined factors.

The associations of sRAGE isoforms with the main study outcomes were independent of HbA1c and suggest that the expression of the sRAGE isoforms is not directly dependent on glycemia. Typically, although HbA1c assesses glucose control over a few months, it is not possible to infer information about AGE concentrations from this parameter. Although earlier studies in rats suggested correlations between HbA1c and concentrations of the AGE pentosidine per milligram of collagen (34), studies in humans have revealed mixed associations regarding HbA1c and AGE measurements (35–37). HbA1c is a reversible

TABLE 6 Association test of baseline sRAGE isoform concentrations (sRAGE, esRAGE, cRAGE) and AT at 3 mo by linear regression model[1]

	sRAGE, pg/mL		esRAGE, pg/mL		cRAGE, pg/mL	
AT[2]	Estimate	*P* value	Estimate	*P* value	Estimate	*P* value
Model A1	0.130	0.36	1.09	0.01*	0.029	0.87
Model A2	0.036	0.77	0.436	0.25	−0.013	0.93
Model A3	0.032	0.79	0.423	0.26	−0.018	0.91
Model B1	0.605	<0.01*	2.48	<0.01*	0.561	0.04*
Model B2	0.603	<0.01*	2.48	<0.01*	0.557	0.04*
Model B3	0.601	<0.01*	2.47	<0.01*	0.556	0.04*
Model C1	0.180	0.20	1.21	<0.01*	0.091	0.61
Model C2	0.089	0.45	0.608	0.09	0.043	0.77
Model C3	0.085	0.47	0.597	0.10	0.039	0.79

[1]The fitted model: interested variable ~ RAGE variable + arm + HbA1c; $P \leq 0.05$; significance shown in bold. AT, adaptive thermogenesis; cRAGE, cleaved receptor for advanced glycation end products; esRAGE, endogenous secretory receptor for advanced glycation end products; REE, resting energy expenditure; REEp; resting energy expenditure predicted; sRAGE, soluble receptor for advanced glycation end products.
[2]Models are numbered (e.g., A1, A2, A3) based on which model for REEp was used. Model A: AT (kcal/d) = REE3mo − REEp(1,2,3)3mo. Model B: AT (kcal/d) = {[REE3mo − REEp(1,2,3)3mo] – [REEbaseline − REEp(1,2,3)baseline]}. Model C: AT (kcal/d) = (%AT/100)∗$REE_{baseline}$; %AT = 100∗[(REE/REEp) − 1]. REEp1 (kcal/d) = 2331.823 − 11.416∗age − 459.778∗sex [0 = male, 1 = female] + 1.210∗FM [kg] + 8.949∗FFM [kg] ($R^2 = 0.6755$; $P < 0.001$). REEp2 (kcal/d) = 494.86 + 24.44∗FFM [kg] ($R^2 = 0.5076$; $P < 0.001$). REEp3 (kcal/d) = 479.3418 + 0.3112∗FM [kg] + 24.4612∗FFM [kg] ($R^2 = 0.4943$; $P < 0.001$).
*The level of significance was set at $P < 0.05$.

glycation product; in contrast, AGEs are formed irreversibly. Thus, variations in the expression and activities of pre-AGE detoxifying pathways such as glyoxalase 1 may account for the lack of consistent relations between HbA1c and AGE concentrations (38). Hence, although sample limitation in this study precluded measurement of plasma AGEs, differences in HbA1c did not account for the observed associations of sRAGE isoforms with REE and the metabolic endpoints under study.

Despite the relation between sRAGE isoforms and REE, our study had limitations. First, dietary AGEs contribute to the pool of AGEs which can affect RAGE activity. Participants were recommended to reduce caloric intake, which could have reduced dietary AGE exposure. In addition, changes in dietary choices as a result of the interventions could correspond to lower AGE exposure; however, we did not quantify dietary AGEs. Second, thyroid hormone is a regulator of energy expenditure, and although we did not measure thyroid status, we did find that a small percentage ($n = 7$; 17%) of participants self-reported thyroid medications. However, participants were asked if they had history of hyperthyroidism and any subjects replying in the affirmative were excluded from the study. In addition, baseline comparison between those taking thyroid medications and those not taking thyroid medications indicated no significant difference, especially for body composition (FM and FFM) and REE. Third, although REE accounts for the majority of total energy expenditure, AT is characterized also by non-REE (39). Compensatory behavior changes after caloric restriction leading to greater than predicted changes in physical activity energy expenditure may contribute to the individual variability in weight loss (40). Finally, the use of a 4-compartment model in contrast to the 2-compartment model used in our study to estimate body composition may better characterize molecular changes in body composition because FFM represents heterogeneous tissues with varying metabolic rates (41).

In conclusion, our study uncovered a potential new link between energy expenditure during negative energy balance and RAGE in humans. This raises new considerations; for example, do greater changes in REE prevent weight loss and do changes in energy expenditure act, in part, via the RAGE pathway reflected by concentrations of sRAGEs? The contribution of AGEs and the RAGE pathway in energy balance warrants further investigation. To our knowledge, this is the first study to examine the effects of REE and sRAGE isoforms during weight loss. We recommend that future trials *1*) examine the causal relation between sRAGE isoforms and REE, including serial assessment of thyroid function and other metabolic proteins affecting energy expenditure (e.g., Fibroblast growth factor 21); *2*) examine the relation of sRAGE isoforms with total energy expenditure and activity energy expenditure using doubly labeled water techniques; *3*) examine the association of sRAGE isoforms and weight loss maintenance after significant weight loss (>5% body weight loss); and *4*) determine the physiologic relevance of AT and sRAGE isoforms. Irrespective of these points, the present study extends the results of experiments performed in mice to potential associations in human subjects. Studies in mice had uncovered unexpected relations between RAGE activity, obesity, and suppression of energy expenditure; hence, this work in human subjects adds to the growing body of literature examining the role of sRAGEs in metabolic disease and the potential role of RAGE in regulation of the mechanisms mediating weight loss and energy balance. Future trials are needed to confirm and extend our findings.

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Data Availability

Data described in the article, code book, and analytic code will be made available upon request by investigators whose proposed use of the data has been approved by an independent review committee identified for this purpose.

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