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# Elevated Serum Advanced Glycation Endproducts in Obese Indicate Risk for the Metabolic Syndrome: A Link Between Healthy and Unhealthy Obesity?

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## Abstract

### Context:

Although obesity can predispose to the metabolic syndrome (MS), diabetes, and cardiovascular disease, not all obese subjects develop MS, hence the need for new indicators of risk for this syndrome. Advanced glycation end products (AGEs) correlate with factors involved in the MS, including inflammation and insulin resistance (IR). Because AGEs can be derived from food and are modifiable, it is important to determine whether they are a risk factor for MS.

### Objective:

The objective of this study was to assess the association of endogenous and exogenous AGEs with MS criteria.

### Design:

The following data were collected in a cross-sectional study of subjects with and without the MS: serum AGEs (sAGEs) and mononuclear cell AGEs, metabolites, pro- and antiinflammatory markers, body fat mass measures, including abdominal magnetic resonance imaging, and caloric and dietary AGE (dAGE) consumption.

### Setting:

The study was conducted in the general community.

### Participants:

Participants included 130 MS and 139 non-MS subjects of both sexes, older than 50 years.

## Results:

sAGEs ($^{\epsilon}$N-carboxymethyllysine, methylglyoxal) were markedly elevated in obese persons with more than one other MS criteria but not in obese without MS criteria. sAGEs directly correlated with markers of IR (HOMA) and inflammation (leptin, TNFα, RAGE) and inversely with innate defenses (SIRT1, AGE receptor 1 [AGER1], glyoxalase-I, adiponectin). sAGEs correlated with dAGEs but not with calories, nutrient consumption, or fat mass measures. Consumption of dAGE, but not of calories, was markedly higher in MS than in non-MS.

## Conclusion:

High sAGEs, a modifiable risk factor for IR, may indicate risk for the MS, type 2 diabetes, and cardiovascular disease. High dietary AGE consumption and serum AGE levels may link healthy obesity to at-risk obesity.


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The Metabolic Syndrome (MS) was first described as a group of risk factors for type 2 diabetes (T2D) and cardiovascular disease (CVD). The factors include insulin resistance (IR), obesity, hypertension, and dyslipidemia (1,–3). These conditions are each associated with chronic oxidant stress and inflammation (OS/Inflam) (3), the cause of which remains poorly understood. The general consensus is that there is a continuum between risk for the MS features and progression to overt T2D or CVD. Obesity is a most challenging condition, in part due to the difficulty of cost effectively identifying and treating those obese who are at risk for developing T2D and CVD (4, 5).

Advanced glycation endproducts (AGEs) or glycotoxins are a group of prooxidant, cytotoxic compounds that contribute to chronic inflammation and diabetic complications (6,–8). Although hyperglycemia is traditionally thought to be the major source of AGEs, they can also be diet derived and causally involved in IR and T2D (6). AGEs are present in many animal food products, particularly those processed under high heat, as is often the case with Western diets (6, 9,–12).

A close association has been reported between the AGEs present in the diet (dAGE) and the amounts of food or calories consumed (13). Because the absolute quantities of both AGEs and calories consumed can drive obesity, it has been difficult to sort out the contribution of each of these risk factors. Chronic exposure to a diet with a high content in dAGEs promotes chronic inflammation and IR (6, 13). A direct correlation has been reported between circulating protein-associated AGE markers, such as $^{\epsilon}$N-carboxymethyllysine (CML) or methylglyoxal derivatives, such as MG-H1, proinflammatory factors, and IR in healthy adults (13, 14). High levels of these serum AGE (sAGE) markers were also strongly linked to suppressed levels of innate defense factors, such as sirtuin 1 (SIRT1), a major deacetylase with antiinflammatory and metabolic functions (15) and AGE receptor 1 (AGER1), an AGE receptor with anti-oxidant stress (OS) properties (16). Adult mice, which were exposed for life to an MG-supplemented diet developed visceral adiposity and IR, coupled with an imbalance in innate defense response and inflammation, all absent in age-matched mice fed a low-AGE diet (17, 18). Clinical studies further suggested that the standard AGE-replete diet may be linked to a higher body mass index (BMI), IR, and T2D (10, 17,–22). Other studies in mice have proposed a role for receptors that bind AGEs and promote OS, such as RAGE and Toll-like receptor-2 in adipocyte hypertrophy, indirectly implicating AGEs in obesity and IR (18, 22). However, an inverse association between levels of sAGEs and IR, BMI, or fat mass has also been reported (23, 24); hence, there is a clear need for further studies.

The current cross-sectional study was undertaken in subjects with and without MS criteria to assess the association between established markers of endogenous and exogenous AGEs and their interaction with MS features. The results suggest that serum AGEs, in tandem with inflammatory markers, are elevated in obese persons with one or more features of the MS but not in obese persons without MS criteria. Beyond overnutrition, a high dAGE consumption may link healthy obesity to at-risk obesity.

## Materials and Methods

### Human subjects

Volunteers, aged 50 years or older who presented with at least two of the following five criteria of the MS, based on National Cholesterol Education Program Adult Treatment Panel III (25), were recruited from the New York City urban community surrounding the Mount Sinai School of Medicine: 1) waist circumference (WC) of 102 cm or greater in men and 88 cm or greater in women, 2) blood pressure (BP) of 130/85 mm Hg or greater (or use of anti-BP medication), 3) high-density lipoprotein (HDL)-cholesterol less than 40 mg/dL in men or less than 50 mg/dL in women, 4) triglycerides of 150 mg/dL or greater (or use of medications for high triglycerides, such as fibrates or nicotinic acid), and 5) fasting blood glucose of 100 mg/dL or greater (or use of metformin), but a glycated hemoglobin ($HbA_{1c}$) less than 6.5%. Volunteers were screened with a 3-day AGE-food record and those whose daily intake was 12 AGE Eq/d or greater (n = 130) were invited to participate in the study. As a control population, we selected a group of self-described healthy volunteers of either sex, aged 50 years or older, hereafter referred to as non-MS, recruited from the same urban community. This cohort, which excludes subjects with diabetes, cardiovascular, kidney disease, or cancer, has been previously described in detail (13). All subjects signed a consent form approved by the Mount Sinai School of Medicine Institutional Review Board.

Participants underwent a physical examination and provided their medical history, fasting blood, and a 24-hour urine sample. Patients with the MS also underwent abdominal magnetic resonance imaging (MRI) studies to define the subcutaneous (SAT) and visceral adipose tissue (VAT) distribution (26) (Supplemental Information). Routine blood tests were performed in the hospital clinical laboratory. Renal function was estimated from the clearance of endogenous creatinine: creatinine clearance (milliliters per minute) = (urine volume in milliliters per minute × urine creatinine concentration in milligrams per deciliter)/serum creatinine concentration in milligrams per deciliter.

### Dietary intake

Assessment of daily dietary AGE content was based on 3-day food records that emphasized cooking methods and was estimated from a database of approximately 560 foods that lists AGE values (9) and was expressed as AGE equivalents (Eq) per day (1 AGE equivalent = 1000 kilounits). The 3-day food record was defined as the estimated amount of food and beverages consumed at home or away from home, based on established guidelines developed to assist in estimating portions. Nutrient intakes were estimated from food records using a nutrient software program (Food Processor version 10.1; ESHA Research).

### AGE determination

AGEs in serum, urine, and peripheral mononuclear cell (PMNC) lysates were determined by well validated competitive ELISAs based on non-cross-reactive monoclonal antibodies (mabs) for protein-bound CML (4G9 mab) and protein-bound MG derivatives, ie, hydroimidazolone MG-H1 (3D11 mab), characterized by HPLC, and used as immunogens (27, 28). The resulting values thus reflect relatively stable protein- or peptide-associated CML and MG and not the free compounds.

### Statistical analysis

Abdominal obesity was defined as a waist circumference of 102 cm or greater in men and 88 cm or greater in women. Data are reported as means ± SEM for continuous variables and as percentages of total for categorical variables, unless otherwise specified. The Kolmogorov-Smirnov goodness-of-fit test was used to test for normal distributions. Variables not normally distributed were logarithmically transformed before hypothesis testing. Comparison between the means was made using a Student's *t* test or an ANOVA, depending on the number of groups. Associations between variables were explored using simple linear

regression and Spearman correlation coefficients. Tests were considered significant if the two-sided value was $P < .05$. Analyses were carried out using SPSS version 20.

Further methodological details are provided as Supplemental Information.

## Results

### General description of the population

The MS cohort included participants with two or more MS features. Subjects with MS had higher weight, WC, BMI, percentage body fat, diastolic BP, and mean levels of fasting blood glucose, homeostasis model assessment index (HOMA) and triglycerides but lower HDL-cholesterol than non-MS subjects (Table 1). Estimated renal function in both MS and non-MS subjects was within normal limits, and there was no proteinuria (Table 1). However, the mean 24-hour urinary excretion of both CML and MG was higher (by >2-fold) in MS than in non-MS subjects (Table 1).

### Diet and AGEs

The consumption of calories, nutrients and dAGEs was significantly higher in MS than in non-MS subjects (Table 1 and Supplemental Table 1). However, the consumption of dAGEs by MS subjects was disproportionally greater than that of calories (46% vs 15%), compared with non-MS subjects (Table 1 and Figure 1A), including those with obesity (Table 2). The dietary AGE intake in MS subjects remained significantly higher, even when expressing dietary AGE per amount of calories ingested (Table 1). Total dAGEs, as well as dietary protein- and fat-associated AGEs, closely correlated with the intake of calories, protein, fat, saturated fat, and, to a lesser degree, carbohydrates (Supplemental Table 2). Dietary AGE intake also correlated with serum (s) CML and sMG in both cohorts (Table 3).

Mean levels of two AGEs in serum (sAGEs) and PMNCs [intracellular AGEs (iAGE)], intracellular CML (iCML) and intracellular MG (iMG), plasma 8-isoprostanes, and leptin were markedly elevated in MS compared with non-MS subjects (Table 1). A strongly positive correlation was found between sCML and sMG in both MS and non-MS subjects. However, the intersection points of each slope differed, in that for any given level of sCML, the corresponding level of sMG was higher in MS subjects relative to non-MS subjects (Figure 1B). There was also a positive correlation between serum and intracellular CML and serum and intracellular MG in MS subjects (Figure 1, b1 and b2).

### Body mass and AGEs

Although there were positive intraindividual and group correlations between WC, BMI, and percentage body fat mass (by bioimpedance), there was no overall correlation between these body mass markers and sAGEs in either the MS or non-MS groups (Figure 1C). Also, there was no correlation between sAGEs and percentage SAT or VAT mass in MS subjects, as defined by MRI (Table 3).

When MS subjects were stratified by number of MS criteria present, the mean levels of sAGEs were markedly and equally increased in obese MS subjects with one or more criteria (Figure 1D). Mean PMNC levels of TNFα were also twice as high in obese subjects with one or more MS criteria (Figure 1E).

Because WC is an important predictor of the MS, we compared data from MS subjects, most of whom had at least a high WC, with non-MS subjects with a high WC (Table 2). sAGEs, iAGEs, urinary AGEs, markers of inflammation, as well metabolic indices were distinctly elevated in the MS group but not in non-MS subjects despite a high WC (Table 2). Similar results were obtained for other body mass indices, eg, BMI or percentage body fat.

### Inflammation, innate defenses, and AGEs

PMNC levels of proinflammatory RAGE and TNFα were higher in MS than in non-MS subjects, whereas the levels of the antiinflammatory SIRT1 were decreased (Table 1). Mean PMNC mRNA levels of glyoxalase-I were also decreased in MS, compared with non-MS subjects (Table 1). MS subjects had lower fasting blood glucose, fasting plasma insulin, $HbA_{1c}$, HOMA, leptin, and PMNC TNFα than those reported in diabetic patients (21).

Strongly positive correlations were found between sAGEs (CML and MG) and markers of OS/Inflam (8-isoprostanes, leptin, PMNC TNFα protein, and RAGE mRNA) in MS subjects and non-MS subjects ( Table 3). When the relationships of sAGEs with metabolic or inflammatory factors, namely HOMA, leptin, 8-isoprostanes, and TNFα were examined together, the trajectories of each parameter, although positive in both cohorts, were distinct for MS and non-MS groups, indicating a substantially higher level of sCML and sMG as well as OS/Inflam and IR markers in the MS than in the non-MS groups (Figure 2, A–D). By comparison, significant negative correlations were noted in the MS cohort between levels of sAGEs (sCML and sMG) and levels of innate defenses (SIRT1, AGER1, adiponectin, and glyoxalase) (Figure 2, E and F, and Table 3). Similar trends were observed in non-MS subjects, except for AGER1 mRNA that correlated positively with sAGEs in this cohort (Table 3) (6, 29).

### Sex, race, ethnicity, and AGEs

Men with MS displayed higher BMI, percentage body fat, and VAT (by MRI) than women with MS, but a similar WC (Table 4). Men had a higher caloric intake (20% greater than women) and dAGE consumption (42% greater than women). No significant sex differences were found in the levels of sAGEs, pro- or anti-OS/Inflam markers, metabolic or renal function parameters (except for a higher HDL and urinary AGE excretion in women) (Table 4).

Of the 130 MS participants, 40% were African American, 37% Caucasian, 4% Asian, and 18% of mixed or undetermined race. Twenty-one percent considered themselves as Hispanics. We observed no significant racial or ethnic differences in any parameters assessed.

## Discussion

We report that subjects with MS display markedly elevated serum levels of two distinct markers of protein-bound AGEs, sCML and sMG, both of which strongly correlate with markers of inflammation and impaired metabolism. Although overall sAGEs were not associated with markers of fat mass, in the presence of obesity and one or more MS criteria, sAGE levels were markedly higher, as was dietary AGE consumption. Thus, high sAGE levels in obese adults could serve as a signal of an impending transition from benign obesity to the MS. Given that sAGEs are a modifiable, nontraditional risk factor, these findings may aid in the timely and targeted prevention of the risk for MS, if confirmed in prospective or interventional studies.

Because the MS subjects in this study did not have unbalanced diabetes ($HbA_{1c}$ levels < 6.5%), hyperglycemia could be ruled out as the cause of the excessive sAGEs (13, 19, 20, 30). Although sAGEs were strongly associated with HOMA and leptin levels, two indicators of IR tied to obesity, they did not directly correlate with measures of body fat, WC, BMI, and total and percentage fat mass by impedance or with VAT and SAT by MRI. An obvious source for the surplus sAGEs was the diet because the levels of AGEs in serum strongly correlated with those of the same AGE markers in the diet of both cohorts, even after adjusting for nutrient consumption (13, 14). Because circulating AGEs have further been identified as a modifiable factor causally linked to chronic OS/Inflam and IR, which underlie the MS (23), the current evidence implicates high sAGEs as a risk factor for the MS.

Both caloric and dAGE consumption were higher in subjects with MS, consistent with their higher fat mass compared with non-MS. Although it is possible that increased energy intake, such as fat, can promote OS and endogenous AGE levels, the amount of dAGEs consumed by MS subjects was considerably

greater (>46%) than that consumed by non-MS. Foods rich in high-protein and -fat AGEs often consist of animal-derived products prepared under dry heat, as typified by Western diets, the preference for which is owed to the abundance of flavorful AGEs (9,–12, 30). Habitual preference of such foods in excess can result in a modest elevation of sAGEs and inflammation, even without frank obesity (14, 19, 30). Exogenously driven elevated sAGEs could thus act as initiators of cellular OS/Inflam, secondarily leading to newly formed cell-derived iAGEs. This conclusion is supported herein by the strong correlations found between sAGEs and iAGEs, TNFα, and RAGE in PMNCs, used here as surrogates of tissue cells (14, 29, 31).

sAGEs and markers of OS/Inflam were not elevated in obese subjects who did not have other MS features, often referred to as metabolically healthy (1, 2, 4, 5), consistent with the view that increased body fat is not necessarily indicative of risk for the MS. AGE levels were, however, strikingly elevated in obese MS subjects, even with only one more MS feature, a group not traditionally included in the MS (1, 2, 32). The same subjects also displayed the highest titers of TNFα, consistent with evidence that high levels of AGEs promote inflammation and IR, thus risk of T2D or CVD (1,–6). In this context, superphysiological levels of sAGEs in otherwise healthy obese subjects could signal transition to other components of the MS cluster, such as high BP, dyslipidemia, or subclinical CVD and define early risk for MS. Furthermore, beyond overnutrition, a history of exposure to AGE-enriched foods may reveal an important clue and a temporal link between healthy and unhealthy or MS-prone obesity (4,–6).

The current clinical findings mirror those from studies in mice, which had been exposed for life to increased levels of specific dietary AGEs (MG). These mice developed visceral adiposity, IR, and altered innate immunity and metabolism (28). Similarly, in the current study, high sAGE levels in the MS cohort negatively tracked with protective factors, such as SIRT1, an important regulator of insulin action and fat mobilization (15, 33), antiinflammatory adiponectin (34), AGER1, a receptor that opposes AGEs and OS and RAGE overexpression (35) as well as glyoxalase-I, a key MG-degrading enzyme (36). Functional depletion of these genes may further augment MS-PMNC iAGEs, TNFα, and RAGE (21, 28, 31). Similar, albeit weaker, correlations were also evident in non-MS subjects, arguing in favor of a dynamic continuum between healthy and unhealthy obese, who are prone to the MS (14).

The changes in gene expression found in the PMNCs of MS subjects in this study were indicative of a proinflammatory macrophage (M1-like) phenotype, similar to that observed in T2D subjects (21, 29, 38). However, the absence of hyperglycemia represents an important difference between subjects with T2D and the current subjects with MS. AGEs could indeed serve as stimuli for the observed changes in PMNCs, and these, in turn, could modify the metabolic response of adipocytes (18, 28). These findings offer strong support to the postulate that circulating immune cells, like macrophages, are active participants in tissue changes (28, 37, 38) and that these changes could be elicited as a result of persistent excess of sAGEs (29).

Multiple traits can promote the MS, including race, ethnicity, and genetic variants (39). Because a major difference between the MS and non-MS cohorts was the amount of dAGEs consumed, the expression of each of these traits and role in the MS could be augmented in a setting of high external AGEs. This concept deserves attention, in light of evidence, which reveals a difference between overconsumption of nutrients and that of dAGEs. Because dAGE consumption is a determinant of sAGEs and their downstream effects, it may represent a diet-based risk factor that is distinct from overnutrition but evidently modifiable (6).

We found no sex differences with respect to sAGEs, iAGEs, or markers of pro- and anti-OS/inflam, $HbA_{1c}$, IR, and lipid levels, except for HDL. This could be partially due to the small study size and overrepresentation of women.

The current study differs in several aspects from other reports, including selection criteria, age, sex, assessment of AGEs, the use of study-specific selection criteria, and MRI for fat tissue distribution (24, 25). In addition, unlike other studies, dAGEs, calories, and nutrient intakes were assessed based on a large

AGE database and validated dietary tools, which we developed (6, 9, 14, 23). Our findings fail to confirm an inverse relationship between body weight and sAGE levels (23, 24). We, however, found that sAGE levels in healthy obese subjects who did not have the MS were lower than in obese subjects with more than one MS criteria. Thus, classification of the MS could also explain some of the data disparity. The current study relies on the immunoreactivity of two distinct protein-AGEs, the levels of which are found internally consistent with their well-defined biological properties across cellular, animal, and human studies (14, 19, 27, 28, 30, 31). In conclusion, high levels of circulating AGEs in MS may reflect the net result of several dynamic processes: high and sustained dAGE intake, increased endogenous or iAGE production, and decreased tissue AGE catabolism. Long-term exposure to dAGEs may be crucial in the chronic inflammation that underlies risk for the MS and thus T2D or CVD, a concept that deserves further testing in interventional trials. Circulating AGEs may be a useful biomarker for the early detection of obese persons at risk for the MS as well as a means to monitor the efficacy of interventions.

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## Footnotes

Abbreviations:

AGE advanced glycation endproduct
AGER1 AGE receptor 1
BMI body mass index
BP blood pressure
CML $^{\epsilon}$N-carboxymethyllysine
CVD cardiovascular disease
dAGE dietary AGE
$HbA_{1c}$ glycated hemoglobin
HDL high-density lipoprotein
HOMA homeostasis model assessment index
iAGE intracellular AGE
iCML intracellular CML
iMG intracellular MG
IR insulin resistance
mab monoclonal antibody
MG methylglyoxal
MRI magnetic resonance imaging
MS metabolic syndrome
OS oxidant stress
OS/Inflam OS and inflammation
PMNC peripheral mononuclear cell
RAGE receptor for AGEs
s serum
sAGE serum AGE
SAT subcutaneous adipose tissue
SIRT1 sirtuin 1
T2D type 2 diabetes
VAT visceral adipose tissue
WC waist circumference.

## References

1. Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among U.S. Adults. Diabetes Care. 2004;27(10):2444–2449.

2. Lutsey PL, Steffen LM, Stevens J. Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. Circulation. 2008;117(6):754–761. [PubMed: 18212291]

3. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860–867. [PubMed: 17167474]

4. Roberson LL, Aneni EC, Maziak W, et al. Beyond BMI: The “metabolically healthy obese” phenotype, its association with clinical/subclinical cardiovascular disease and all-cause mortality—a systematic review. BMC Public Health. 2014;14:14. [PMCID: PMC3890499] [PubMed: 24400816]

5. Stefan N, Haring HU, Hu FB, Schulze MB. Metabolically healthy obesity: epidemiology, mechanisms, and clinical implications. Lancet Diabetes Endocrinol. 2013;1(2):152–162. [PubMed: 24622321]

6. Vlassara H, Striker GE. AGE restriction in diabetes mellitus: a paradigm shift. Nat Rev Endocrinol. 2011;7(9):526–539. [PMCID: PMC3708644] [PubMed: 21610689]

7. Kilhovd BK, Juutilainen A, Lehto S, et al. Increased serum levels of advanced glycation endproducts predict total, cardiovascular and coronary mortality in women with type 2 diabetes: a population-based 18 year follow-up study. Diabetologia. 2007;50(7):1409–1417. [PubMed: 17479244]

8. Tan KC, Chow WS, Ai VH, Metz C, Bucala R, Lam KS. Advanced glycation end products and endothelial dysfunction in type 2 diabetes. Diabetes Care. 2002;25(6):1055–1059. [PubMed: 12032114]

9. Uribarri J, Woodruff S, Goodman S, et al. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J Am Diet Assoc 2010;110(6):911–916.e912. [PMCID: PMC3704564] [PubMed: 20497781]

10. Birlouez-Aragon I, Saavedra G, Tessier FJ, et al. A diet based on high-heat-treated foods promotes risk factors for diabetes mellitus and cardiovascular diseases. Am J Clin Nutr. 2010;91(5):1220–1226. [PubMed: 20335546]

11. Finot PA. Historical perspective of the Maillard reaction in food science. Ann NY Acad Sci. 2005;1043:1–8. [PubMed: 16037216]

12. Nguyen HT, van der Fels-Klerx HJ, van Boekel MAJS. N-epsilon-(carboxymethyl)lysine: a review on analytical methods, formation, and occurrence in processed food, and health impact. Food Rev Int. 2014;30(1):36–52.

13. Vlassara H, Cai W, Goodman S, et al. Protection against loss of innate defenses in adulthood by low advanced glycation end products (AGE) intake: role of the antiinflammatory AGE receptor-1. J Clin Endocrinol Metab. 2009;94(11):4483–4491. [PMCID: PMC2775660] [PubMed: 19820033]

14. Uribarri J, Cai W, Pyzik R, et al. Suppression of native defense mechanisms, SIRT1 and PPARγ, by dietary glycoxidants precedes disease in adult humans; relevance to lifestyle-engendered chronic diseases. Amino Acids. 2014;46(2):301–309. [PMCID: PMC3795943] [PubMed: 23636469]

15. Liang F, Kume S, Koya D. SIRT1 and insulin resistance. Nat Rev Endocrinol. 2009;5(7):367–373. [PubMed: 19455179]

16. Lu C, He JC, Cai W, Liu H, Zhu L, Vlassara H. Advanced glycation endproduct (AGE) receptor 1 is a negative regulator of the inflammatory response to AGE in mesangial cells. Proc Natl Acad Sci USA. 2004;101(32):11767–11772. [PMCID: PMC511050] [PubMed: 15289604]

17. Mark AB, Poulsen MW, Andersen S, et al. Consumption of a diet low in advanced glycation end products for 4 weeks improves insulin sensitivity in overweight women. Diabetes Care. 2014;37(1):88–95. [PubMed: 23959566]

18. Monden M, Koyama H, Otsuka Y, et al. Receptor for advanced glycation end products regulates adipocyte hypertrophy and insulin sensitivity in mice: involvement of Toll-like receptor 2. Diabetes. 2013;62(2):478–489. [PMCID: PMC3554382] [PubMed: 23011593]

19. Tahara N, Yamagishi S, Matsui T, et al. Serum levels of advanced glycation end products (AGEs) are independent correlates of insulin resistance in nondiabetic subjects. Cardiovasc Ther. 2012;30(1):42–48. [PubMed: 20626403]

20. Gaens KH, Goossens GH, Niessen PM, et al. Nϵ-(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(6):1199–1208. [PubMed: 24723555]

21. Uribarri J, Cai W, Ramdas M, et al. Restriction of advanced glycation end products improves insulin resistance in human type 2 diabetes: potential role of AGER1 and SIRT1. Diabetes Care. 2011;34(7):1610–1616. [PMCID: PMC3120204] [PubMed: 21709297]

22. Song F, Hurtado del Pozo C, et al. RAGE regulates the metabolic and inflammatory response to high-fat feeding in mice. Diabetes. 2014;63(6):1948–1965. [PMCID: PMC4030112] [PubMed: 24520121]

23. Sebekova K, Krivosikova Z, Gajdos M. Total plasma Nϵ-(carboxymethyl)lysine and sRAGE levels are inversely associated with a number of metabolic syndrome risk factors in non-diabetic young-to-middle-aged medication-free subjects. Clin Chem Lab Med. 2014;52(1):139–149. [PubMed: 23509221]

24. Semba RD, Arab L, Sun K, Nicklett EJ, Ferrucci L. Fat mass is inversely associated with serum carboxymethyl-lysine, an advanced glycation end product, in adults. J Nutr. 2011;141(9):1726–1730. [PMCID: PMC3159057] [PubMed: 21775524]

25. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): final report. Circulation 2002;106(25):3143–3421. [PubMed: 12485966]

26. Bonekamp S, Ghosh P, Crawford S, et al. Quantitative comparison and evaluation of software packages for assessment of abdominal adipose tissue distribution by magnetic resonance imaging. Int J Obes (Lond). 2008;32(1):100–111. [PMCID: PMC3096530] [PubMed: 17700582]

27. Cai W, Gao QD, Zhu L, Peppa M, He C, Vlassara H. Oxidative stress-inducing carbonyl compounds from common foods: novel mediators of cellular dysfunction. Mol Med. 2002;8(7):337–346. [PMCID: PMC2040002] [PubMed: 12393931]

28. Cai W, Ramdas M, Zhu L, Chen X, Striker GE, Vlassara H. Oral advanced glycation endproducts (AGEs) promote insulin resistance and diabetes by depleting the antioxidant defenses AGE receptor-1 and sirtuin 1. Proc Natl Acad Sci USA. 2012;109(39):15888–15893. [PMCID: PMC3465382] [PubMed: 22908267]

29. de Kreutzenberg SV, Ceolotto G, Papparella I, et al. Downregulation of the longevity-associated protein sirtuin 1 in insulin resistance and metabolic syndrome: potential biochemical mechanisms. Diabetes. 2010;59(4):1006–1015. [PMCID: PMC2844808] [PubMed: 20068143]

30. Poulsen MW, Bak MJ, Andersen JM, et al. Effect of dietary advanced glycation end products on postprandial appetite, inflammation, and endothelial activation in healthy overweight individuals. Eur J

Nutr. 2014;53(2):661–672. [PubMed: 23929260]

31. Vlassara H, Uribarri J, Cai W, et al. Effects of sevelamer on HbA1c, inflammation, and advanced glycation end products in diabetic kidney disease. Clin J Am Soc Nephrol. 2012;7(6):934–942. [PMCID: PMC3362316] [PubMed: 22461535]

32. Ford ES. Prevalence of the metabolic syndrome in US populations. Endocrinol Metab Clin North Am. 2004;33(2):333–350. [PubMed: 15158522]

33. Yoshizaki T, Milne JC, Imamura T, et al. SIRT1 exerts anti-inflammatory effects and improves insulin sensitivity in adipocytes. Mol Cell Biol. 2009;29(5):1363–1374. [PMCID: PMC2643824] [PubMed: 19103747]

34. Takemura Y, Ouchi N, Shibata R, et al. Adiponectin modulates inflammatory reactions via calreticulin receptor-dependent clearance of early apoptotic bodies. J Clin Invest. 2007;117(2):375–386. [PMCID: PMC1770947] [PubMed: 17256056]

35. Torreggiani M, Liu H, Wu J, et al. Advanced glycation end product receptor-1 transgenic mice are resistant to inflammation, oxidative stress, and post-injury intimal hyperplasia. Am J Pathol. 2009;175(4):1722–1732. [PMCID: PMC2751567] [PubMed: 19779136]

36. Brouwers O, Niessen PM, Ferreira I, et al. Overexpression of glyoxalase-I reduces hyperglycemia-induced levels of advanced glycation end products and oxidative stress in diabetic rats. J Biol Chem. 2011;286(2):1374–1380. [PMCID: PMC3020745] [PubMed: 21056979]

37. Yoshizaki T, Schenk S, Imamura T, et al. SIRT1 inhibits inflammatory pathways in macrophages and modulates insulin sensitivity. Am J Physiol Endocrinol Metab. 2010;298(3):E419–E428. [PMCID: PMC2838524] [PubMed: 19996381]

38. Liu J, Hickson DA, Musani SK, et al. Dietary patterns, abdominal visceral adipose tissue, and cardiometabolic risk factors in African Americans: the Jackson heart study. Obesity (Silver Spring). 2013;21(3):644–651. [PMCID: PMC3478414] [PubMed: 23592674]

39. Scott RA, Fall T, Pasko D, et al. Common genetic variants highlight the role of insulin resistance and body fat distribution in type 2 diabetes, independently of obesity. Diabetes 2014;63(12):4378–4387. [PMCID: PMC4241116] [PubMed: 24947364]

## Figures and Tables

### Table 1.

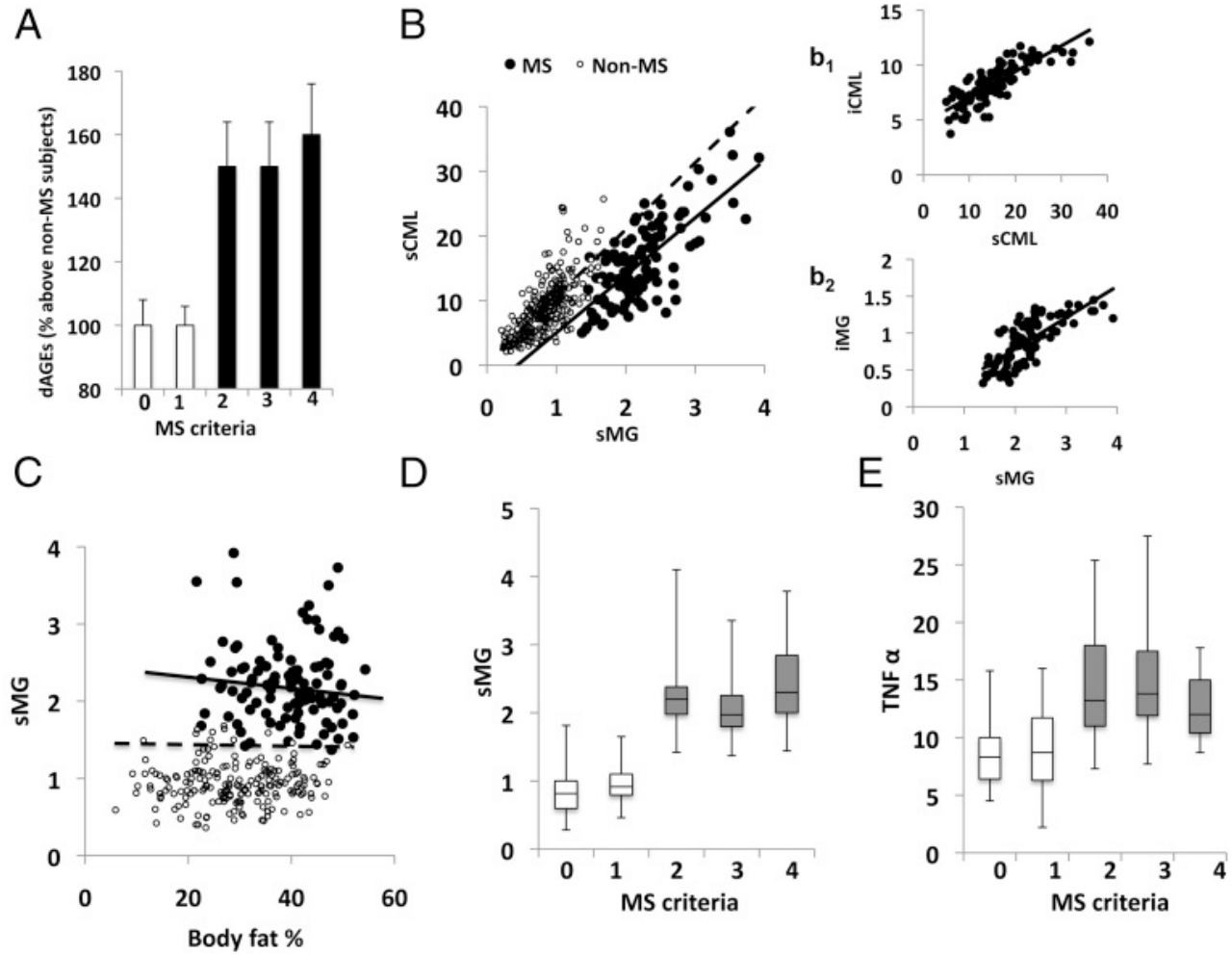
Baseline Characteristics of the Study Groups

| Parameters | Non-MS (n = 137) | MS (n = 130) | *P* Value |
|---|---|---|---|
| Age, y | 68.5 ± 0.7 | 60.3 ± 0.6 | <.001 |
| Sex, % men | 30 | 32 | .877 |
| BP, systolic, mm Hg | 126 ± 1.5 | 129 ± 1.3 | .112 |
| BP, diastolic, mm Hg | 69 ± 1 | 76 ± 1 | <.001 |
| Weight, kg | 72 ± 2 | 89 ± 2 | <.001 |
| BMI, $kg/m^2$ | 26.3 ± 0.5 | 33.2 ± 0.6 | <.001 |
| Waist, cm | 93 ± 1.5 | 109 ± 1.0 | <.001 |
| Body fat, % | 31 ± 0.8 | 40 ± 0.7 | <.001 |

| Parameters | Non-MS (n = 137) | MS (n = 130) | *P* Value |
|---|---|---|---|
| Subcutaneous fat area, $cm^2$ | NA | 224 ± 9 | NA |
| Subcutaneous fat, % | NA | 29 ± 1 | NA |
| Visceral fat area, $cm^2$ | NA | 122 ± 6 | NA |
| Visceral area, % | NA | 16 ± 1 | NA |
| FBG, mg/dL | 83 ± 1 | 89 ± 1 | <.001 |
| FPI, μU/mL | 6.6 ± 0.3 | 14.1 ± 0.6 | <.001 |
| Glucose AUC | NA | 273 ± 6 | NA |
| Insulin AUC | NA | 149 ± 9 | NA |
| $HbA_{1c}$, % | NA | 5.88 ± 0.04 | NA |
| HOMA-IR | 1.34 ± 0.07 | 3.10 ± 0.14 | <.001 |
| Triglycerides, mg/dL | 91 ± 4 | 134 ± 8 | <.001 |
| HDL cholesterol, mg/dL | 67 ± 1.6 | 56 ± 1.4 | <.001 |
| Serum CML, U/mL | 9.2 ± 0.4 | 16.7 ± 0.6 | <.001 |
| Serum MG, nmol/mL | 0.89 ± 0.03 | 2.26 ± 0.05 | <.001 |
| iCML, μ/mg protein | 7.5 ± 0.6 | 8.6 ± 0.2 | <.001 |
| iMG, nmol/mg protein | 0.80 ± 0.05 | 1.02 ± 0.03 | <.001 |
| 8-Isoprostane, pg/mL | 151 ± 8 | 206 ± 10 | <.001 |
| Leptin, ng/mL | 19.5 ± 2 | 28.6 ± 1 | <.001 |
| Adiponectin, μg/mL | 10 ± 0.8 | 9.2 ± 0.3 | .426 |
| AGER1, mRNA | 188 ± 12 | 188 ± 8 | .987 |
| RAGE, mRNA | 360 ± 23 | 485 ± 20 | <.001 |
| SIRT1, mRNA | 356 ± 17 | 258 ± 10 | <.001 |
| Glyoxalase, mRNA | 70 ± 7 | 25 ± 1 | <.001 |
| TNFα, pg/mg protein | 8.8 ± 0.3 | 14.6 ± 0.4 | <.001 |
| Diet calories, kcal/d | 1769 ± 63 | 2034 ± 61 | <.001 |
| dAGE, AGE/Eq · d | 13 ± 1 | 19 ± 1 | <.001 |
| dAGE/dCalories | 7.2 ± 0.3 | 9.0 ± 0.4 | <.001 |
| Creatinine clearance, mL/min | 96 ± 3 | 101 ± 3 | .232 |
| Urinary protein per gram creatinine, mg/g | 65 ± 4 | 62 ± 5 | .456 |
| Urinary microalbumin per gram creatinine, mg/g | NA | 13 ± 3 | NA |
| uCML/creatinine, U/g | 35 556 ± 2425 | 77 034 ± 4165 | <.001 |
| uMG per gram creatinine, nmol/g | 366 ± 49 | 866 ± 56 | <.001 |

Abbreviations: dAGE/dCalories, dAGE × 1000/diet calories; FBG, fasting blood glucose; FPI, fasting plasma insulin; glucose AUC, area under the curve for glucose values at 0, 60 and 120 min; HOMA-IR, homeostasis model assessment index of insulin resistance; insulin AUC, area under the curve for insulin values at 0, 60 and 120 min; NA, not assessed; uCML/creatinine, urinary CML in units divided per urinary creatinine in grams; uMG per gram creatinine, urinary MG in nanomoles divided per urinary creatinine in grams; Data are shown as mean ± SEM. *P* values are the statistical significant differences between MS and non-MS subjects.

## Figure 1.




A, Dietary AGE intake in MS and non-MS subjects. Daily dietary AGE intake expressed as percentage above that in non-MS subjects taken as 100%. [score 0: non-MS with normal WC; score 1: non-MS with high WC; score 2–4: MS subjects with two or more MS criteria (only one subject displayed all five features of the MS and was not included)]. B, Relationship of serum MG and serum CML in persons with MS (straight line) and non-MS (dashed line). Both parameters were assessed simultaneously and in the fasting state (MS, r = 0.704, $P < .001$; non-MS, r = 0.733, $P < .001$). Insets: b1, Relationship of serum CML and iCML in MS subjects. Both parameters were assessed simultaneously and in the fasting state (r = 0.809, $P < .001$; non-MS). b2, Relationship of sMG and iMG in MS subjects. Both parameters were assessed simultaneously and in the fasting state (r = 0.802, $P < .001$; non-MS). C, Relationship of fasting serum MG levels and percentage body fat determined (by bioimpedance) in persons with MS (solid line) and non-MS (dashed line). Both parameters were assessed simultaneously and in the fasting state (MS, r = −0.074, $P = .414$; non-MS, r = 0.174, $P = .073$). D, Serum MG (sMG) levels according to components of the MS. Data are shown as box plots denoting levels of sMG in persons with or without MS [score 0: non-MS with normal WC; score 1: non-MS with high WC; score 2–4: MS subjects with two or more MS criteria (only one subject displayed all five features of the MS and was not included)]. E, TNFα levels according to components of the MS. Data are shown as box plots denoting TNFα protein measured in PMNCs from each of the groups shown in panel B. Differences of means in panels A, D, and E were not significant (NS) between score 0 and 1 or between score 2, 3, and 4 but were significant between each of scores 2, 3, or 4 and scores 0 and 1.

## Table 2.

Selected Parameters Comparing MS Subjects With Non-MS Subjects With a Large WC[a]

| Parameters | Non-MS (n = 58) | MS (n = 123) | *P* Value |
|---|---|---|---|
| Age, y | 70 ± 1 | 60.3 ± 0.6 | <.001 |
| BMI, kg/m$^2$ | 29.5 ± 0.5 | 33.2 ± 0.6 | <.001 |
| Body fat, % | 35 ± 1 | 40 ± 0.7 | <.001 |

| Parameters | Non-MS (n = 58) | MS (n = 123) | *P* Value |
|---|---|---|---|
| Waist, cm | 104 ± 2 | 109 ± 1 | .013 |
| FBG, mg/dL | 85 ± 1 | 90 ± 1 | <.001 |
| FPI, μU/mL | 7.3 ± 0.5 | 14.1 ± 0.6 | <.001 |
| HOMA-IR | 1.56 ± 0.10 | 3.07 ± 0.16 | <.001 |
| Triglycerides, mg/dL | 105 ± 6 | 134 ± 8 | .006 |
| HDL cholesterol, mg/dL | 60 ± 2 | 56 ± 2 | .088 |
| Serum CML, U/mL | 9.8 ± 0.4 | 15.9 ± 0.6 | <.001 |
| Serum MG, nmol/mL | 0.93 ± 0.03 | 2.23 ± 0.05 | <.001 |
| iCML, μ/mg protein | 6.9 ± 0.8 | 8.6 ± 0.2 | <.001 |
| iMG, nmol/mg protein | 0.71 ± 0.07 | 1.02 ± 0.03 | <.001 |
| 8-Isoprostane, pg/mL | 151 ± 10 | 201 ± 11 | .002 |
| Leptin, ng/mL | 23 ± 3 | 28 ± 1 | .044 |
| Adiponectin, μg/mL | 9.3 ± 1 | 9.4 ± 0.3 | .937 |
| AGER1, mRNA | 199 ± 18 | 186 ± 9 | .533 |
| RAGE, mRNA | 410 ± 37 | 470 ± 21 | .167 |
| SIRT1, mRNA | 351 ± 25 | 260 ± 11 | <.001 |
| TNFα, pg/mg protein | 9 ± 0.5 | 14.5 ± 0.4 | <.001 |
| dCal, kcal/d | 1835 ± 94 | 2096 ± 67 | .024 |
| dAGE, AGE Eq/d | 13 ± 1 | 19 ± 1 | <.001 |
| Creatinine clearance, mL/min | 103 ± 4 | 98 ± 3 | .322 |
| uProtein/creatinine, mg/g | 85 ± 7 | 62 ± 5 | .008 |
| uCML/g, U/g | 33 830 ± 2879 | 77 034 ± 4165 | <.001 |
| uMG/g, nmol/g | 366 ± 63 | 866 ± 56 | <.001 |

Abbreviations: FBG, fasting blood glucose; FPI, fasting plasma insulin; HOMA-IR, homeostasis model assessment index of insulin resistance; uCML/creatinine, urinary CML in units divided per urinary creatinine in grams; uMG/creatinine, urinary MG in nmol divided per urinary creatinine in grams. Data are shown as mean ± SEM. *P* value are the statistical significant differences between MS and non-MS subjects.

[a]Large WC was defined as greater than 102 cm in males and greater than 88 cm in females.

## Table 3.

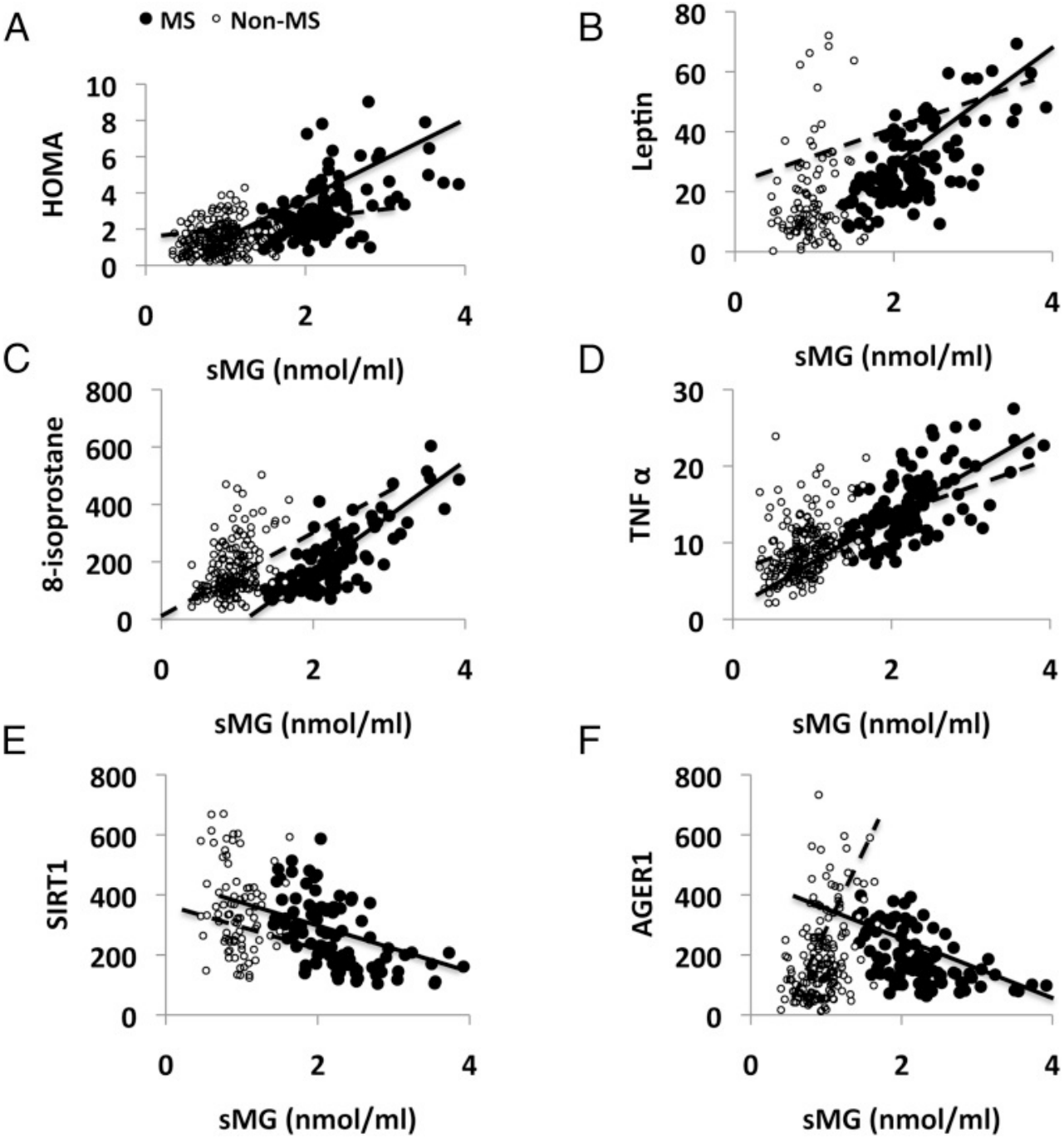
Univariate Associations Between sAGEs and Select Body Mass, Proinflammatory, and Innate Defense Parameters in Study Populations

| | Non-MS | | MS | |
|---|---|---|---|---|
| | r | *P* Value | R | *P* Value |
| sCML | | | | |
| sMG | 0.733 | .001 | 0.704 | .001 |
| 8-Isoprostane | 0.594 | .001 | 0.757 | .001 |
| TNFα | 0.489 | .001 | 0.710 | .001 |
| VCAM1 | 0.474 | .001 | 0.756 | .001 |

| | | Non-MS | | MS | |
|---|---|---|---|---|---|
| | | r | *P* Value | R | *P* Value |
| | Leptin | 0.213 | .057 | 0.608 | .001 |
| | RAGE | 0.634 | .001 | 0.735 | .001 |
| | AGER1 | 0.543 | .001 | −0.514 | .001 |
| | SIRT1 | −0.334 | .002 | −0.807 | .001 |
| | Adiponectin | −0.306 | .005 | −0.486 | .001 |
| | HOMA | 0.207 | .003 | 0.445 | .001 |
| | BMI | 0.050 | .595 | −0.051 | .570 |
| | Percentage body fat | 0.155 | .112 | 0.018 | .841 |
| | WC | −0.005 | .956 | −0.061 | .502 |
| | SAT | NA | NA | 0.097 | .344 |
| | VAT | NA | NA | −0.183 | .072 |
| | dAGE | 0.590 | .001 | 0.194 | .031 |
| | iCML | −0.566 | .001 | 0.809 | .001 |
| | iMG | −0.241 | .116 | 0.606 | .001 |
| sMG | | | | | |
| | 8-Isoprostane | 0.594 | .001 | 0.784 | .001 |
| | TNFα | 0.489 | .001 | 0.654 | .001 |
| | VCAM1 | 0.474 | .001 | 0.649 | .001 |
| | Leptin | 0.262 | .018 | 0.677 | .001 |
| | RAGE | 0.409 | .001 | 0.661 | .001 |
| | AGER1 | 0.336 | .001 | −0.508 | .002 |
| | SIRT1 | −0.255 | .002 | −0.619 | .001 |
| | Adiponectin | −0.200 | .073 | −0.535 | .001 |
| | HOMA | 0.230 | .001 | 0.464 | .001 |
| | BMI | 0.087 | .352 | −0.091 | .570 |
| | Percentage body fat | 0.160 | .102 | −0.074 | .841 |
| | WC | 0.041 | .675 | −0.061 | .502 |
| | SAT | NA | NA | 0.033 | .747 |
| | VAT | NA | NA | −0.052 | .610 |
| | dAGE | 0.471 | .001 | 0.193 | .032 |
| | iCML | −0.404 | .007 | 0.577 | .001 |
| | iMG | 0.029 | .854 | 0.802 | .001 |

Abbreviations: BMI, body mass index; NA, not assessed; SAT, percentage subcutaneous fat as assessed by MRI; VAT, percentage visceral fat as assessed by MRI; VCAM1, vascular cell adhesion molecule 1.

## Figure 2.




Fasting sMG levels plotted against markers of insulin resistance, inflammation, and OS in MS (solid lines) and non-MS subjects (dashed lines) (A–D) and against markers of innate defense mechanisms (E and F). A, sMG vs HOMA (MS: r = 0.464, $P < .001$; non-MS: r = 0.230; $P < .001$). B, sMG vs plasma leptin (MS: r = 0.677; $P < .001$; non-MS: r = 0.262; $P = .018$). C, 8-Plasma isoprostanes (MS, r = 0.784; $P < .001$; non-MS, r = 0.594; $P < .001$). D, PMNC TNFα protein (MS, r = 0.654; $P < .001$; non-MS, r = 0.489; $P < .001$). E, sMG vs AGER1 mRNA (MS, r = −0.508; $P = .002$; non-MS, r = 0.336; $P < .001$). F, sMG vs SIRT1 mRNA (MS, r = −0.619; $P < .001$; non-MS, r = −0.255; $P = .002$).

## Table 4.

Differences Between Men and Women in Both Study Groups

| Parameter | Non-MS | | | MS | | |
|---|---|---|---|---|---|---|
| | Men | Women | *P* Value[a] | Men | Women | *P* Value[b] |

| | | | | | | |
|---|---|---|---|---|---|---|
| Age | 68 ± 1 | 69 ± 1 | .874 | 60.4 ± 1.1 | 60.3 ± 0.7 | .901 |
| Weight | 85 ± 3 | 66 ± 2 | <.001 | 94 ± 2 | 88 ± 2 | .037 |
| BMI | 27.8 ± 0.7 | 25.8 ± 0.6 | .029 | 31.5 ± 0.6 | 34.1 ± 0.8 | .009 |
| Waist | 105 ± 3 | 88 ± 1 | <.001 | 111 ± 1.4 | 109 ± 1.3 | .345 |
| Body fat | 25 ± 1 | 34 ± 1 | <.001 | 32 ± 1 | 44 ± 0.5 | <.001 |
| Subcutaneous fat, $cm^2$ | NA | NA | NA | 158 ± 9 | 261 ± 12 | <.001 |
| Subcutaneous fat, % | NA | NA | NA | 19 ± 1 | 34 ± 1 | <.001 |
| Visceral fat, $cm^2$ | NA | NA | NA | 164 ± 11 | 98 + 6 | <.001 |
| Visceral fat, % | NA | NA | NA | 20 ± 1 | 13 ± 1 | <.001 |
| FBG | 84 ± 2 | 82 ± 1 | .550 | 90 ± 2 | 89 + 1 | .700 |
| FPI | 7 ± 0.7 | 6 ± 0.4 | .277 | 14 ± 1 | 14 + 0.8 | .689 |
| $HbA_{1c}$ | NA | NA | NA | 5.84 ± 0.07 | 5.89 ± 0.05 | .518 |
| HOMA-IR | 1.50 ± 0.15 | 1.29 ± 0.08 | .294 | 3.20 ± 0.20 | 3.04 ± 0.19 | .554 |
| Triglycerides | 89 ± 6 | 91 ± 5 | .853 | 148 ± 11 | 126 ± 10 | .136 |
| HDL cholesterol | 56 ± 3 | 72 ± 2 | <.001 | 49 ± 3 | 60 ± 2 | <.001 |
| Serum CML | 9.3 ± 0.6 | 9.1 ± 0.4 | .732 | 17.1 ± 1.0 | 16.7 ± 0.7 | .690 |
| Serum MG | 0.92 ± 0.05 | 0.86 ± 0.03 | .227 | 2.30 ± 0.09 | 2.24 ± 0.06 | .556 |
| iCML | 6.8 ± 1 | 7.8 ± 0.7 | .431 | 8.7 ± 0.3 | 8.5 ± 0.2 | .683 |
| iMG | 0.83 ± 0.14 | 0.79 ± 0.05 | .834 | 1.06 ± 0.05 | .99 ± 0.04 | .329 |
| 8-Isoprostane | 139 ± 13 | 157 ± 10 | .278 | 210 ± 18 | 204 ± 12 | .790 |
| Leptin | 17 ± 3 | 21 ± 2 | .347 | 26 ± 2 | 30 ± 1.5 | .083 |
| Adiponectin | 11 ± 2 | 10 ± 1 | .575 | 9.3 ± 0.5 | 9.2 ± 0.4 | .852 |
| AGER1 | 172 ± 22 | 196 ± 15 | .361 | 200 ± 15 | 182 + 9 | .340 |
| RAGE | 304 ± 31 | 384 ± 30 | .070 | 493 ± 35 | 480 ± 24 | .775 |
| SIRT1 | 334 ± 25 | 365 ± 22 | .353 | 257 ± 18 | 258 ± 13 | .959 |
| TNFα | 9 ± 0.6 | 9 ± 0.4 | .683 | 15 ± 0.7 | 14 ± 0.5 | .322 |
| dCal | 1840 ± 133 | 1741 ± 71 | .518 | 2360 ± 115 | 1867 ± 64 | <.001 |
| dAGE | 12 ± 1 | 13 ± 1 | .644 | 26 ± 2 | 15 ± 1 | <.001 |
| Creatinine clearance | 97 ± 4 | 88 ± 3 | .101 | 109 ± 6 | 96 ± 3 | .091 |
| uProtein/creatinine* | 53 ± 1 | 86 ± 1 | .003 | 79 ± 14 | 53 ± 3 | .088 |
| uMicroalbumin/creatinine* | NA | NA | NA | 17 ± 5 | 11 ± 3 | .301 |
| uCML/creatinine | 28 827 ± 4337 | 38 606 ± 2867 | .065 | 64 302 ± 5603 | 80 871 ± 5252 | .033 |
| uMG/creatinine | 317 ± 63 | 387 ± 65 | .439 | 806 ± 84 | 897 ± 75 | .420 |

Abbreviations: HOMA-IR, homeostasis model assessment index of insulin resistance; NA, not assessed; uMicroalbumin/creatinine, urinary microalbumin/urinary creatinine (milligrams per day); uProtein/creatinine, urinary protein/urinary creatinine (milligrams per day); Data are shown as mean ± SEM. A gender × MS interaction was tested and found nonstatistically significant except for the following: weight ($P = .004$), BMI ($P = .004$), waist ($P = .001$), dietary calories ($P = .012$), dietary AGEs ($P = .001$), and urinary protein/creatinine ($P = .002$).

[a]Statistical difference between genders in non-MS cohort.
[b]Statistical difference between genders in MS cohort.