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Serum levels of soluble Receptor for Advanced Glycation End-products and metabolic syndrome: the Northern Manhattan Study

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Abstract

Objective—Recent studies have shown a strong link between serum soluble Receptor for Advanced Glycation End-products (sRAGE) levels and cardiovascular risk factors and disease. What is less clear is the relationship between metabolic risk factors and sRAGE levels. Here, we tested the hypothesis that lower sRAGE levels may be associated with the metabolic syndrome (MetS) in an urban multi ethnic population.

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Materials/Methods—From the Northern Manhattan Study (NOMAS), we included 1101 stroke-free participants (mean age: 71±9 years, 60% women, 64% Hispanic, 18% black, 16% white). Serum sRAGE was measured by ELISA. Quantile regression analysis was performed to evaluate the association between sRAGE and MetS components and MetS, after adjusting for sociodemographics, smoking status and kidney function.

Results—The median (interquartile) sRAGE was 899 (647-1248)pg/ml, 42% had metabolic syndrome. The prevalence of unfavorable metabolic factors was 50% for waist circumference (WC), 81% for blood pressure, 39% for fasting glucose, 35% for reduced high density lipoproteins (HDL), and 23% for triglycerides. After adjustment, the median sRAGE levels were at least 120 pg/ml lower in those who had elevated WC (p<.0001), blood pressure (p=0.0014), and fasting glucose (p<0.0001), and those who had 2 or more unfavorable metabolic factors. No relationship was seen between sRAGE levels and elevated triglycerides or reduced HDL levels. Interaction and stratified analyses revealed that the association of sRAGE with MetS was more prominent in Hispanics compared to whites, and displaying no association with components of MetS in blacks.

Conclusions—sRAGE levels were mainly associated with MetS factors related to obesity, diabetes and hypertension, and displayed variation with ethnicity in a multi-ethnic population. Further studies of sRAGE, MetS and their relationship to cardiovascular disease are warranted.

Keywords

Metabolic syndrome; RAGE; biomarker; cardiovascular disease; diabetes

Introduction

The metabolic syndrome (MetS) is a complex disorder characterized by a cluster of cardiovascular risk factors including obesity, hyperglycemia, dyslipidemia and hypertension [1]. Recent estimates are that a quarter of the adult population worldwide have MetS [1]. MetS is estimated to be associated with a ~5-fold risk of developing diabetes and 1.5-4-fold risk of cardiovascular disease (CVD) and stroke [1;2]. Moreover, in the Northern Manhattan Study (NOMAS), we have previously shown MetS to be associated with an increased risk of stroke and vascular events, especially amongst Hispanics [2]. Therefore, understanding further the mechanisms underlying MetS and its heightened risk for diabetes and CVD in different ethnic groups is essential.

The Receptor for Advanced Glycation End-products (RAGE) has been implicated to play a pivotal role in metabolic and cardiovascular disease status [3]. Studies in rodent models have revealed that inhibiting RAGE using a soluble ligand binding decoy (sRAGE) or gene knockout, reduces diabetes and CVD, and highlighting RAGE as a viable therapeutic target for metabolic disease states [3]. Furthermore, recent studies have shown that in addition to its role in the vasculature, RAGE affects adipocyte hypertrophy and insulin sensitivity [45]. Data from human cohort studies have established that serum endogenous soluble RAGE is a biomarker for diabetes and CVD [3]. However, few studies to date have thoroughly evaluated the relationship between serum sRAGE levels and MetS, especially amongst different ethnic groups [6-8]. Therefore, the purpose of our study was to investigate the association of MetS and its components with sRAGE in the multi-ethnic NOMAS study.

Subjects and methods

Study population

A total of 1,101 subjects who had sRAGE assessment were included from the NOMAS study, a well-defined race/ethnically diverse community-based cohort that consist of 3,298 stroke-free participants at baseline and 199 stroke-free subjects recruited in 2003. Detailed methods of NOMAS subject recruitment and characterization have been previously described in depth [9]

Definition of MetS

MetS was defined as previously described in NOMAS based on the modified ATP III criteria proposed by the National Cholesterol Education Program [2]. These criteria require 3 or more of the following: (1) fasting glucose≥100 mg/dL or on diabetes medication; (2) waist circumference (WC)>40 inches for men, >35 inches for women; (3) elevated blood pressure (SBP≥130 mmHg or DBP≥85 mmHg) or on medication for hypertension; (4) triglycerides (TG) ≥150 mg/dL; and (5) HDL Cholesterol <40 mg/dL for men, <50 mg/dL for women

Laboratory procedures

Total sRAGE in participants was measured in serum using the Human RAGE Quantikine ELISA (R&D Systems), as previously described [10]. This ELISA measures the total sRAGE pool in serum and plasma samples using a monoclonal antibody raised against the whole recombinant extracellular human sRAGE protein [3]. The minimal level of detection was 0.05 ng/ml as per manufacturer's instructions and the intra- and interassay coefficients of variation with this ELISA were 6% and 10%, respectively.

Statistical analysis

Wilcoxon/Kruskal-Wallis test was used to examine the association between sample characteristics and sRAGE levels, whereas quantile regression analysis was performed to evaluate the association between sRAGE and metabolic syndrome and its components, after adjusting for sociodemographics (including age, sex, education status and health insurance), smoking status and kidney function (eGFR). Interaction and stratified analyses were also performed to assess whether the associations between sRAGE and metabolic factors varied among race-ethnic groups. All data analyses were conducted using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

The characteristics of the study sample and their association with sRAGE levels are presented in Table 1. Of 1,101 subjects, the prevalence of individual metabolic factors was found to be as follows: 50% presented with elevated WC, 81% with elevated blood pressure, 35% with low HDL, 23% with TG ≥150 mg/dL, and 39% with elevated fasting glucose. For MetS, 42% of participants presented with 3 or more risk factors, 28% with 2 risk factors and 30% no or 1 risk factor. The median (interquartile range) sRAGE was 899 pg/ml (647–1248 pg/ml). Univariate analysis revealed lower sRAGE levels to be significantly associated with

increased WC, elevated BP and hyperglycemia (Table 1). No association was observed between sRAGE levels and triglyceride or HDL levels. sRAGE levels were lower with increasing MetS risk factors (Table 1).

We next performed multivariable analysis to test if these relationships observed with MetS and its components persisted. Quantile regression analysis was first performed to adjust for age, sex, race-ethnicity, education, health insurance status, smoking status and eGFR and showed that the median sRAGE levels were at least 120 pg/ml lower in those who had elevated WC ($p<.0001$), blood pressure ($p=0.0014$), and fasting glucose ($p<0.0001$), and in those who had 2 or more unfavorable metabolic factors; the levels were not related to elevated triglycerides and reduced HDL levels (Table 2). Interaction and stratified analyses revealed that the association of sRAGE with central obesity, hyperglycemia and blood pressure was more pronounced in Hispanics compared to whites and blacks, with blacks displaying no associations between sRAGE and MetS components (Table 2). Further, MetS was significantly associated with sRAGE only in Hispanics.

Discussion

In this multi-ethnic community based study, we demonstrate for the first time that not only are lower sRAGE levels associated with metabolic syndrome, but they are also lower in proportion to the number of metabolic components. In addition, the association of sRAGE with central obesity, hyperglycemia and blood pressure varies by race-ethnicity. These data further support the role of RAGE as a risk factor for metabolic and vascular disease and extend this observation to minority populations.

Since its isolation in 1992 as a receptor for the late products of non-enzymatic glycation, formed under hyperglycemic states, RAGE has been demonstrated to be a key molecule driving metabolic and inflammatory disease states [3]. Although a body of work has implicated its role in cardiovascular disease states including atherosclerosis, heart failure, stroke and diabetic vascular diseases, recent data suggests a role for RAGE underlying metabolic disease [3-5]. Using either soluble RAGE decoys or gene knockout, various groups have shown an effect for RAGE on weight gain, abdominal fat levels, adipocyte size and a concomitant relationship in these models with development of CVD [4;5]. In human cohort studies, measurement of serum sRAGE levels has revealed relationships not only with CVD, but also with metabolic components/disease including diabetes, obesity, and hypertension [3]. Most recently, work from a number of groups has demonstrated an association between sRAGE levels and MetS [6-8]. This therefore highlights sRAGE levels as a potential biomarker of the developing metabolic disease and future cardiovascular disease. Previous studies from our group have shown a relationship in the multi-ethnic NOMAS community based study between sRAGE levels and risk of subclinical vascular disease 10. Furthermore, we have demonstrated that in NOMAS, MetS is a strong risk factor for stroke and vascular events [2]. Here, we extend these observations to a relationship between sRAGE and MetS, particularly in Hispanic NOMAS participants.

In the current study we found that lower sRAGE levels were strongly associated with a number of components of the MetS including increasing BMI, central obesity, blood

pressure and plasma glucose levels. Interestingly, no relationship was observed with lipid components of the metabolic syndrome. When combined, a step-wise relationship between lower sRAGE levels and increased metabolic components was seen, with a clear relationship with low sRAGE and MetS observed. Data from our group and others have demonstrated clear differences in sRAGE levels between different ethnic groups [10-12], with minority groups including Hispanics and blacks displaying significantly lower sRAGE levels compared to whites or Asians. To extend these data to sRAGE and MetS, we performed stratified analysis by ethnicity. Our data indicated that in Hispanics and whites, associations were seen between sRAGE levels and multiple components of MetS. However, in blacks no relationship was seen with sRAGE levels and more than one component of MetS (blood pressure). Our data are in keeping with prior studies that demonstrate a relationship between lower sRAGE and increasing BMI, hypertension, diabetes and most recently the MetS in non-diabetic Non-Hispanic White Europeans and Asians [3;6-8;13]. Whilst the relationship between sRAGE and MetS has been previously explored, our study is novel due to the following reasons; 1. This is the first study to investigate sRAGE and MetS in a multi-ethnic community based population. All prior studies on sRAGE and MetS were on either whites or Asian populations [6-8]; 2. All prior studies were of relatively small sample sizes compared to our study here [6-8]; 3. The study by Momma et al only focused on the esRAGE splice variant not the total circulating pool [7]; 4. None of these studies performed any multivariate adjusted analysis of sRAGE and MetS as we demonstrated in Table 2. Therefore due to these key differences between our current study and the prior published studies, the current study represents a novel and more thorough analysis of the relationship of sRAGE and MetS.

These data also raise interesting points with respect to the question of the relationship between sRAGE, metabolic disease, diabetes and CVD risk. There are contrasting data that demonstrate the relationship of sRAGE with CVD risk and disease. In studies of long-term diabetes (type 1 and 2), a positive relationship between sRAGE and CVD [12;14;15] has been seen. Conversely, in general community based cohorts, an inverse relationship between sRAGE and CVD risk has been observed [10;11;13;16]. Further clinical and biological studies are needed to investigate how and why these contrasting differences are sRAGE levels are seen, and whether persistent chronic disease (eg. diabetes) affects the role of sRAGE as a biomarker. It is possible that confounding factors affecting sRAGE levels not analyzed or corrected for in these studies may explain these differences. To-date, in addition to metabolic components, race:ethnicity and kidney function other factors to affect sRAGE levels include age, smoking and medication use (anti-diabetic medication, statins, ACE inhibitors) [17-20]. In the case of medication use on sRAGE, multiple studies have demonstrated these latter classes of drugs increase sRAGE levels and therefore may affect data particularly in diabetic populations where these medications are frequently used [17-20]. Furthermore, recent studies have revealed a genetic influence on sRAGE levels, and may therefore further explain differences seen between studies [21;22]. Future studies to address all these points are needed.

Strengths of the current study include the large population studied, inclusion of a multi-ethnic group living in the same community, and various measures of metabolic syndrome. Limitations include that the current study is cross-sectional and limits causal inferences,

with a relatively small sample size for non-Hispanic blacks and whites. However, our subgroup analysis numbers exceed those of prior analysis between sRAGE and MetS [3;6-8]. In addition, the measurement of sRAGE and MetS components were only performed once, which does not account for changes over time. Further, the method used to measure sRAGE levels measures the total serum pool of soluble RAGE which includes the isoform resulting from ectodomain shedding (cleaved RAGE) and alternative splicing (esRAGE) [3]. Therefore future studies should measure the alternatively spliced isoform separately to assess whether changes occur in cleavage versus spliced soluble RAGE forms.

In conclusion, lower sRAGE levels were associated with MetS and individual components of the metabolic syndrome, with clear differences between ethnic groups. These data suggest that sRAGE may serve as a useful marker and therapeutic target of metabolic and cardiovascular disease, depending on the stage of / underlying chronic disease. Further studies are required to investigate this relationship and to investigate the role of RAGE and its soluble isoforms in metabolic disease.

Abbreviations

BMI	body mass index
eGFR	estimated glomerular filtration rate
HDL	high density lipoproteins
MetS	metabolic syndrome
NOMAS	Northern Manhattan Study
RAGE	Receptor for Advanced Glycation End-products
TG	triglycerides
WC	waist circumference
WHR	waist:hip ratio

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Table 1

Sample characteristics and sRAGE levels

	n (%)	sRAGE (pg/ml) Median (IQR)	P*
Age			0.0102
<70 years	525 (47.7)	870.6 (639.7 - 1174.9)	
≥70 years	576 (52.3)	940.5 (660.3 - 1308.9)	
Sex			0.2876
Men	443 (40.2)	871.2 (642.9 - 1209.4)	
Women	658 (59.8)	926.1 (652.1 - 1265.2)	
Race-ethnicity			<.0001
Hispanic	708 (64.3)	889.8 (655.3 - 1227.7)	
Non-Hispanic Black	197 (17.9)	757.4 (511.0 - 1076.3)	
Other	26 (2.4)	888.7 (639.7 - 1233.0)	
Non-Hispanic White	170 (15.4)	1120.5 (861.8 - 1631.0)	
High school education			0.0953
No	593 (53.9)	870.6 (643.7 - 1224.6)	
Yes	508 (46.1)	935.0 (660.3 - 1264.2)	
Medical insurance status			0.0100
No	318 (28.9)	847.1 (626.2 - 1154.1)	
Yes	783 (71.1)	928.4 (661.3 - 1282.4)	
Smoking			0.0972
Never	518 (47.0)	928.6 (654.0 - 1250.4)	
Former	461 (41.9)	895.6 (662.2 - 1243.0)	
Current	122 (11.1)	814.6 (586.6 - 1249.2)	
eGFR			<.0001
<60	222 (20.3)	1007.2 (754.1 - 1340.2)	
60-<90	644 (58.9)	896.7 (646.7 - 1271.4)	
≥90	227 (20.8)	793.7 (601.0 - 1110.0)	
BMI, kg/m^2			<.0001
<25	272 (24.7)	1043.3 (733.2 - 1311.6)	
25-<30	464 (42.1)	908.6 (660.9 - 1236.9)	
≥30	365 (33.2)	830.4 (617.6 - 1125.5)	
WHR >0.9 for men, >0.85 for women			0.0079
No	308 (28.0)	956.4 (684.8 - 1311.6)	
Yes	793 (72.0)	871.7 (641.3 - 1209.4)	
WC>40 inches for men, >35 inches for women			<.0001
No	552 (50.1)	959.7 (688.3 - 1308.4)	
Yes	549 (49.9)	850.1 (625.9 - 1141.6)	
SBP≥130 mmHg or DBP≥85 mmHg or on BP medication			0.0012
No	208 (18.9)	1004.2 (754.7 - 1333.4)	

	n (%)	sRAGE (pg/ml) Median (IQR)	P*
Yes	893 (81.1)	870.4 (641.9 - 1209.4)	
TG ≥150 mg/dL			0.3671
No	846 (76.8)	896.9 (642.9 - 1233.0)	
Yes	255 (23.2)	908.4 (673.2 - 1265.2)	
HDL<40 mg/dL for men, <50 mg/dL for women			0.6362
No	713 (64.8)	909.9 (637.9 - 1233.0)	
Yes	388 (35.2)	877.3 (661.7 - 1261.7)	
Fasting glucose≥100 mg/dL or on diabetes medication			0.0051
No	674 (61.2)	936.7 (674.5 - 1279.7)	
Yes	427 (38.8)	842.2 (620.1 - 1191.6)	
No. having metabolic factors			0.0054
0-1	330 (30.0)	974.9 (686.9 - 1341.9)	
2	312 (28.3)	877.0 (638.5 - 1185.0)	
≥3	459 (41.7)	858.1 (634.5 - 1208.3)	

* based on Wilcoxon/Kruskal-Wallis Test.

Table 2

Relationship between sRAGE level and metabolic factors

	All subjects (n = 1,101)		non-Hispanic white (n= 170)		non-Hispanic black (n = 197)		Hispanic (n = 708)	
	Change in sRAGE levels (95% CI)*	P	Change in sRAGE levels (95% CI)*	P	Change in sRAGE levels (95% CI)*	P	Change in sRAGE levels (95% CI)*	P
WC>40 inches for men, >35 inches for women (yes vs. no)	−163 (−221, −107)	<.0001	−234 (−456, −14)	0.0327	−29 (−162, 104)	0.6701	−168 (−236, −101)	<.0001
SBP≥130mmHg or DBP≥85 mmHg or on BP medication (yes vs. no)	−124 (−200, −48)	0.0014	−50 (−275, 175)	0.6634	−174 (−329, −18)	0.0286	−117 (−211, −22)	0.0154
Fasting glucose≥100 mg/dL or on diabetes medication (yes vs. no) ‡	−120 (−180, −59)	<.0001	−223 (−415, −31)	0.0232	8 (−156, 173)	0.9206	−97 (−164, −30)	0.0048
TG ≥150 mg/dL (yes vs. no)	10 (−61, 82)	0.7865	79 (−141, 299)	0.4797	26 (−153, 205)	0.7722	14 (−74, 102)	0.7531
HDL<40 mg/dL for men, <50 mg/dL for women (yes vs. no)	3 (−56, 63)	0.9123	−29 (−254, 196)	0.8007	143 (−12, 298)	0.0698	−33 (−102, 37)	0.3537
No. having metabolic factors								
0-1	Reference (n=330, median=975)		Reference (n=74, median=1276)		Reference (n=71, median=764)		Reference (n=176, median=963)	
2	−100 (−177, −23)	0.0107	−159 (−403, 85)	0.2011	−92 (−219, 36)	0.1596	−76 (−175, 23)	0.1317
≥3	−143 (−214, −72)	<.0001	−214 (−479, 51)	0.1128	2 (−162, 167)	0.9773	−139 (−230, −49)	0.0027

*Based on median regression stratified by race-ethnicity and adjusted for age, sex, education, health insurance status, smoking and eGFR

‡p value for the interaction with race-ethnicity < 0.05 based on median regression in the whole sample by excluding 26 other subjects.