Brief report

Obesity is associated with an increased risk of monoclonal gammopathy of undetermined significance among black and white women

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Obesity and black race have been associated with excess risk of multiple myeloma. The association of obesity with monoclonal gammopathy of undetermined significance (MGUS) is unknown. Further, it is not known whether the increased risk of multiple myeloma and MGUS in blacks is related to socioeconomic status, genetic susceptibility, or both. We screened 1000 black and 996 white women (range, 40-79 years) of similar socioeconomic status for MGUS; the aim of the study was to assess MGUS risk in relation to obesity and race. A total of 39 (3.9%) blacks and 21 (2.1%) whites had MGUS. On multivariate analysis, obesity (odds ratio [OR] = 1.8; *P* = .04), black race (OR = 1.8; *P* = .04), and increasing age (> 55 vs < 43 years; OR = 2.5; *P* = .03) were independently associated with an excess risk of MGUS. Our findings support the hypothesis that obesity is etiologically linked to myelomagenesis. The 2-fold excess of MGUS among blacks compared with whites of similar socioeconomic status supports a role for susceptibility genes in MGUS. (*Blood*. 2010;116(7): 1056-1059)

Introduction

Multiple myeloma (MM) is a neoplasm of plasma cells characterized by an overproduction of monoclonal immunoglobulins.[1] Monoclonal gammopathy of undetermined significance (MGUS) is characterized by the presence of a monoclonal immunoglobulin (M-protein) without evidence of MM or other lymphoproliferative malignancies.[2] MM is consistently preceded by MGUS.[3]

Prior studies show racial disparity patterns in the epidemiology of both MGUS and MM.[4] Compared with whites, MGUS and MM are 2- to 3-fold more common in blacks and in Africans.[4] In addition, MGUS and MM are associated with familial clustering.[5,6]

Obesity is associated with a 1.5- to 2-fold elevated risk of developing MM.[7-9] This is of particular interest given that elevated levels of the proinflammatory cytokine interleukin-6 have been found in obese persons,[10] and interleukin-6 has well-known proliferative and antiapoptotic effects on monoclonal plasma cells.[11] In addition, insulin-like growth factors play a role in obesity,[10] and insulin-like growth factor-I has growth/survival effects on monoclonal plasma cells.[12]

We speculated that obesity might increase the risk of MGUS, or, alternatively, that obesity may increase the risk for transformation from MGUS to MM. In this large screening study, we assessed the role of obesity and race in relation to MGUS risk.

Methods

This study was based on the population-based Southern Community Cohort Study (SCCS) cohort (Table 1).[13] The 1996 SCCS subjects made available for inclusion in this study had already been randomly selected within the SCCS strata for another project of obesity biomarkers (Table 1). All participants provided informed consent in accordance with the Declaration of Helsinki, and the protocol was approved by appropriate institutional review boards of all participating institutions.

All serum samples were analyzed in an identical fashion and in the same laboratory as the population-based study of MGUS in Olmsted County, MN (Table 2).[2,14,15]

Statistical analysis

Characteristics for different racial groups were compared using χ^2 test statistics. Unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between MGUS and subject characteristics were estimated using logistic regression.

Results and discussion

The median age was 48 years (range, 40-79 years; Table 1). Per sampling strategy, 50% were obese based on self-reported height and weight (medical record–abstracted weight and height available for approximately 25% of the cohort was very highly concordant with the self-reported values; Pearson correlation greater than 0.95 for body mass index). Socioeconomic status (SES) tended to be low, with 73% of the women not attending any college and 60% having annual household incomes less than $15 000. Nineteen percent of the women reported a history of diabetes mellitus.

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Table 1. Selected characteristics of study participants at screening

Variable	Blacks	Whites
Total n (%)	1000 (100)	996 (100)
Median age, y (range)	48 (40-79)	48 (40-79)
Age group, y, n (%)		
Less than 43	202 (20.2)	224 (22.5)
43-47.99	284 (28.4)	263 (26.4)
48-54.99	259 (25.9)	235 (23.6)
55 or more	255 (25.5)	274 (27.5)
BMI* group, kg/m^2, n (%)		
Less than 25	249 (24.9)	248 (24.9)
25-29.99	251 (25.1)	249 (25.0)
30-34.99	250 (25.0)	250 (25.1)
35 or higher	250 (25.0)	249 (25.0)
Education status, n (%)		
Did not attend college	736 (73.6)	718 (72.1)
Attended at least some college	264 (26.4)	278 (27.9)
Annual household income, n (%)		
Less than $15 000	622 (62.2)	594 (59.6)
At least $15 000	369 (36.9)	398 (40.0)
Household size, n (%)		
1 person	204 (20.4)	229 (23.0)
2 persons	307 (30.7)	356 (35.7)
3 persons	202 (20.2)	189 (19.0)
4 or more persons	287 (28.7)	222 (22.3)
Cigarette smoking, n (%)		
Current smoker	378 (37.8)	444 (44.6)
Former smoker	204 (20.4)	223 (22.4)
Never smoked	417 (41.7)	327 (32.8)
Diabetes mellitus, n (%)		
Yes	220 (22.0)	164 (16.5)

This study was based on the large population-based SCCS cohort, which has been described previously (www.southerncommunitystudy.org).[13] In brief, at entry into the SCCS, trained interviewers administered a comprehensive in-person baseline interview that elicited information, such as demographics, anthropometry, medication use, and medical history. Participants were asked to donate a blood sample at study enrollment. A 20-mL venous blood sample was donated by 59% of those eligible to provide one. The blood was separated into its components and stored at −86°C. The 1996 SCCS subjects made available for inclusion in this study were drawn from a stratified random sample selected by the SCCS for another project of obesity biomarkers and reflect the combination of 2 previously sampled groups. The first group of 395 women (enrolled from 2002 to 2004) had been randomly selected within strata defined by race (black/white), smoking status (never, former, current), and body mass index (BMI, 18-24.99 kg/m^2, 25-29.99 kg/m^2, 30-45 kg/m^2). The second group (n = 1605, enrolled from 2002 to 2006) represents a similarly stratified random sample by race (black/white), BMI (18.5-24.99 kg/m^2, 25.0-29.99 kg/m^2, 30.0-34.99 kg/m^2, 35.0-44.99 kg/m^2), and menopausal status (premenopausal/postmenopausal). Four women were removed because they had a recorded preceding lymphoproliferative malignancy,[14] resulting in our final study population of 1996 subjects.

*All study subjects had information on self-reported weight and height. As stated in "Results and discussion," for approximately 25% of the cohort, medical record-abstracted weight and height (measured on the day of study enrollment at the community health center) were also available. When we compared BMI values calculated from self-reported height and weight compared with BMI calculated from the medical record data, we found a very high concordance (Pearson correlation > 0.95). This provides the assurance about the reliability of the self-report.

MGUS, obesity, and race

MGUS was detected in the serum of 60 (3.0%) of the 1996 participants. More specifically, 39 (3.9%) blacks and 21 (2.1%) whites were found to have MGUS, yielding a crude 1.9-fold (95% CI, 1.1-3.2; $P = .02$) higher risk of MGUS among blacks (vs whites; Table 2). Although it is well known that MM is 2- to 3-fold more common among blacks than whites,[4] the literature indicating an excess of the precursor MGUS among blacks is restricted to a small number of studies.[4,16-18] On multivariate analysis, we found obesity (OR = 1.8; 95% CI, 1.03-3.1; $P = .04$), black race (OR = 1.8; 95% CI, 1.04-3.1; $P = .04$), and increasing age (OR = 2.5; 95% CI, 1.1-5.7; $P = .03$ for age > 55 years compared with age < 43 years) to be associated with an increased risk of MGUS (Table 2). Using educational status and household income as proxy markers for SES, we found no significant association between these variables and MGUS (Table 2). Neither was a medical history of diabetes mellitus associated with an increased risk of MGUS in the multivariate analysis. Our novel finding that MGUS was twice as common among obese versus nonobese women, and independent of race, supports the hypothesis that obesity is etiologically linked to myelomagenesis. Furthermore, it suggests that the previously observed 2-fold increased risk of MM among obese persons[7-9] may be because they are more likely to develop MGUS, which in turn puts them at risk for developing MM.

In contrast to prior studies, we had access to extensive questionnaire data with which to evaluate the effect of several potential confounders of the race-MGUS association. We were specifically interested in assessing confounding by SES, following up on inconsistent findings from prior studies, with some showing elevated risks of MM associated with lower SES (based on education and income status) among both blacks and whites,[19,20] some showing elevated risk of MM mortality with higher social class,[21,22] and other studies finding no association between SES and MM.[23] In the present study, the doubling of risk for blacks was virtually unchanged when we included obesity, education status, and income status in the same multivariate model. Our findings therefore suggest that the racial difference is not an artifact of differences in SES, and strengthen the hypothesis that other factors are involved, including perhaps a role for susceptibility genes in myelomagenesis.[4,6,24,25]

Among black women with MGUS (n = 39), the isotype of the monoclonal immunoglobulin was immunoglobulin G (IgG) in 79%, IgA in 8%, IgM in 8%, and biclonal in 5% (Table 3). In the 21 white women with MGUS, the isotype of the monoclonal immunoglobulin was IgG in 71%, IgM in 19%, IgA in 0%, biclonal

Table 2. Factors associated with MGUS risk*

	Univariate model			Multivariate model		
Variable	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Black race	1.88	1.10-3.23	.021§	1.80	1.04-3.11	.037§
Obesity	1.75	1.03-2.99	.039§	1.80	1.03-3.14	.039§
Age group, y						
43-47.99	0.87	0.33-2.28	.78	0.84	0.32-2.21	.73
48-54.99	1.75	0.74-4.13	.20	1.58	0.66-3.78	.30
55 or older	2.81	1.26-6.25	.011§	2.50	1.10-5.68	.028§
Low education status†	2.15	1.05-4.40	.036§	1.83	0.88-3.84	.11
Low annual household income‡	1.42	0.81-2.49	.23	1.16	0.65-2.08	.62
Diabetes mellitus	1.69	0.95-3.00	.073	1.07	0.58-2.00	.82

Models included variables for age (in 4 categories: < 43, 43-47, 48-54, 55 or older), race/ethnicity (black/white), education status (attended vs not attended any college), household size (1, 2, 3, 4 or more household members), obesity (yes/no), and annual household income (> vs < $15 000). Obesity was defined as BMI > 30.0 kg/m^2. BMI was calculated from self-reported current weight and height. In subanalyses, when we examined the influence of demographic factors, smoking status, and use of antidiabetes medication (insulin as well as oral antidiabetes drugs), our main findings remained virtually the same (data not shown).

*Electrophoresis was performed on agarose gel (REP, Helena Laboratories). The agarose strip was inspected by a technician and by 2 of the authors (R.A.K., J.A.K.). Any serum with a discrete band or thought to have a localized band was subjected to immunofixation (Hydrasys and Hydragel, Sebia).[15] MGUS was defined in accordance with previous definition,[14] which was identical to the definition used in the Olmsted County, MN prevalence study.[2]

†Did not attend any college.

‡Less than $15 000 per year.

§$P < .05$.

Table 3. MGUS characteristics by race

Variable	Blacks (n = 1000)	Whites (n = 996)
Total n (%)	39 (100)	21 (100)
M-protein concentration,* g/dL, median (range)	0.82 (0.39-1.14)	0.55 (0.38-1.04)
M-protein isotype,† n (%)		
IgG	31 (79.5)	15 (71.4)
IgA	3 (7.7)	0
IgM	3 (7.7)	4 (19.1)
Biclonal	2 (5.1)	1 (4.8)
Triclonal	0	1 (4.8)
Serum light-chain type,† n (%)		
κ	21 (53.8)	10 (47.6)
λ	17 (43.6)	9 (42.8)
Biclonal	1 (2.6)	1 (4.8)
Triclonal	0	1 (4.8)
M-protein concentration,† g/dL, n (%)		
Immeasurable	29 (74.4)	16 (76.2)
Less than 0.49	1 (2.6)	2 (9.5)
0.50-0.99	7 (17.9)	2 (9.5)
More than or equal to 1.00	2 (5.1)	1 (4.8)
Age group,† y, n (%)		
Less than 50	14 (35.9)	7 (33.3)
More than or equal to 50	25 (64.1)	14 (66.7)

*Excluding cases with immeasurable M-protein concentration.
†None of the racial differences was significant (χ^2 test).

in one patient, and triclonal in one patient. This is in accord with prior studies reporting a significantly lower prevalence of IgM MGUS and Waldenström macroglobulinemia among blacks compared with whites.[26,27]

More than 70% of the MGUS cases, independent of race, had a very small (unquantifiable) monoclonal Ig (Table 2). This fraction is very high compared with a prior MGUS screening study in Olmsted County, MN (12%).[2] Interestingly, despite earlier thinking that MGUS is probably not present before the age of 50 years,[2] we detected MGUS in 21 subjects in the 40- to 50-year age group, accounting for 35% of our MGUS cases (Table 2). The reported differences across studies may be the result of variations in environmental exposures and obesity status, which may result in differing immune responses.

Strengths of our study include its base in a well-described cohort with carefully obtained baseline data and blood specimens. The very similar SES of the black and white women included in the study also limited, by design, the potential for SES to confound the association between MGUS and race. Differential accuracy in the reporting of body size measurements or other important variables in our analysis was minimized as this risk factor information was collected before blood draw and serum protein analysis. Limitations of our study include the lack of access to clinical or pathologic details regarding the MGUS cases. The cross-sectional nature of the study also precludes assessment of temporality and the drawing of causal inferences.

In conclusion, we found a 2-fold increased risk of MGUS associated with both obesity and with black race, supporting the hypothesis that obesity is etiologically linked to myelomagenesis and further strengthening evidence of the racial difference in MGUS, possibly signifying a role for susceptibility genes in MGUS. Future research is needed to better understand underlying biologic mechanisms of our observations.

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Authorship

Contribution: O.L., W.J.B., and L.B.S. had full access to all the data in the study, had final responsibility for the decision to submit the article for publication, oversaw all aspects of the study, participated in the study conception and design, interpreted the data, drafted the manuscript, managed all revisions to the manuscript, and obtained funding for the study; R.A.K. and J.A.K. reviewed all serum protein electrophoretic patterns; and R.M.P. was primarily responsible for the statistical analysis and takes responsibility for the accuracy of the data analysis. All authors participated in the study design and interpretation of the data, made important intellectual contributions to the manuscript, and read, gave comments, and approved the final version of the manuscript.

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