Short Communication

Ethnic Disparity in the Relationship between Obesity and Plasma Insulin-Like Growth Factors: The Multiethnic Cohort

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Abstract

Previous studies on the relationship between obesity and circulating insulin-like growth factor (IGF) hormones show inconsistent findings and have not considered the possibility of racial/ethnic–specific differences that may exist. We therefore examined the relationship between obesity status [as measured by body mass index (BMI)] and plasma levels of the IGF proteins, IGF-I, IGF-binding protein 3 (IGFBP-3), and the molar ratio of IGF-I/IGFBP-3 in Whites, African Americans, Latinos, Japanese Americans, and Native Hawaiians from the ongoing Hawaii and Los Angeles Multiethnic Cohort Study. We measured plasma IGF-I and IGFBP-3 by ELISA in a random sample of 811 Multiethnic Cohort participants (53% male, age range = 47-82 at blood draw). In a multivariate regression of IGF-I levels, we found a statistically significant interaction between race/ethnicity and obesity status (P = 0.005). Plasma IGF-I levels declined with increasing BMI most dramatically in Latinos and Japanese. This decline was attenuated in Whites and absent in African-American and Native Hawaiian subjects. In Japanese, the quadratic term (BMI^2) was statistically significant in a multivariate model (P = 0.002). In Latinos, the adjusted least-squares mean IGF-I levels in ng/mL for BMI < 25, 25 to 29.99, and ≥30 were 184.6, 147.7, and 132.7, respectively. No interaction between race/ethnicity and BMI explained the plasma IGFBP-3 levels in these data. These results may help to resolve the uncertainty in the relationship between circulating IGF levels and obesity and highlight the potential importance of racial/ethnic–specific effects among these factors in explaining ethnic disparities in obesity-related cancers. (Cancer Epidemiol Biomarkers Prev 2006;15(11):2298–302)

Introduction

Investigation of the relationships between body fat and insulin-like growth factors (IGF) has clinical significance because this hormonal axis is a plausible mechanism linking obesity to cancer risk (1). Previous studies, however, have been inconsistent with respect to the relationships between adiposity and circulating levels of IGF proteins (2-11). Studies among healthy adults have reported a null association (2-4), a positive association (5), an inverse association (6-9), and a nonlinear association (10, 11) between body mass index (BMI) and IGF-I levels. We are unaware of any study that has looked at possible ethnic differences in the relationship between obesity and circulating IGF-I, and this may be important in addressing the metabolic basis for ethnic differences in cancer risk. Previous work has shown that ethnic differences in circulating IGF levels do exist (12, 13). We have previously reported that IGF-I levels are lower among Latinos, compared with four other major racial/ethnic groups (13). Building upon this previous work in the Multiethnic Cohort, we set out to investigate the relationships between plasma IGF protein levels and obesity, using BMI as an indicator of adiposity, across five racial/ethnic groups (Whites, African Americans, Latinos, Japanese Americans, and Native Hawaiians).

Materials and Methods

Study Subjects. Participants included in these analyses were selected from a large population-based cohort study, the Hawaii and Los Angeles Multiethnic Cohort study (14). The primary aim of this prospective study is to evaluate the dietary and other environmental contributions to the racial/ethnic variability in cancer risk. The Multiethnic Cohort consists of 215,251 men and women, mainly Japanese Americans, Whites, and Native Hawaiians in Hawaii and African Americans and Latinos in Los Angeles. Subjects were recruited between 1993 and 1996 primarily through driver's license files. All participants were between the ages of 47 and 82 at time of blood draw.

Baseline data were collected on cohort participants via a mailed questionnaire that contained five sections: (*a*) background, including medical history and family cancer history; (*b*) diet history; (*c*) medication use; (*d*) physical activity; and for women (*e*), female reproductive history, including use of hormones. Height and weight were self-reported by respondents on the baseline questionnaire, and Quetelet's index (kg/m^2), or BMI, was calculated as a measure of obesity.

For this analysis, blood was collected on a subcohort of about 5,000 randomly selected participants. The draw was completed in the morning, typically at the person's home, after informed consent was obtained. The participation rate for providing a blood sample was 66%. Details of the study have

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been published previously (14). Written informed consent from every subject was obtained. This investigation was approved by the institutional review boards of the University of Southern California and the University of Hawaii.

We measured plasma IGF-I and IGF-binding protein 3 (IGFBP-3) in a random sample of 1,000 of these Multiethnic Cohort participants [100 for each of 10 sex/ethnic groups with equal representation of each 5-year age group at blood draw (>45 years for men and >55 years for women)] who donated a blood sample. Nine hundred sixty subjects had complete IGF-I and IGFBP-3 measurements. One hundred forty-nine subjects were excluded for incomplete questionnaire data for BMI, having prevalent breast, prostate, or colon cancer or use of menopausal hormone therapy at the time of blood draw, leaving 811 subjects for the analysis. The baseline characteristics of these subjects (Table 1) did not differ from those which were described previously (13).

IGF-I and IGFBP-3 Measurements in Plasma. Samples were analyzed blind as to the ethnicity and sex of the participants. To reduce the effect of laboratory variability, each analytic batch included equal numbers of subjects from each ethnic/sex group. IGF-I and IGFBP-3 were measured by ELISA from Diagnostic System Laboratories (Webster, TX). IGF-I assays included an acid-ethanol precipitation of IGF-I binding proteins, to avoid interference of IGFBPs with the IGF-I assay. The overall intra-batch coefficients of variation were <10% for both IGF-related proteins. The average inter-batch coefficients of variation were 13.94% and 10.35% for IGF-I and IGFBP-3, respectively.

Statistical Analysis. Building on previous gender-stratified work on these proteins in the Multiethnic Cohort (13), we used stepwise and best subsets (R^2 and C_p criteria) selection to find the set of variables that best explained the variation in IGF-I, IGFBP-3, and IGF-I/IGFBP-3 molar ratio (molar ratio) levels. Variables tested in the previous sex-specific analyses were allowed to compete in these regressions (13), in addition to several new continuous variables. New variables included gender, dietary fiber intake density, percentage of daily calories from carbohydrates, added sugar intake (teaspoons added sugar per day), total fruit and vegetable intake density, regular soda intake density, diet soda intake density, metabolic equivalents of physical activity per day, and energy density of the diet (total calories/total grams food and caloric beverages/day). In the regression analyses, a continuous BMI variable was used. The interaction terms for race/ethnicity × BMI, also as a continuous variable, were allowed to compete in the multivariate regression for each protein. To perform these stepwise regressions, the distributions of the continuous protein values were assessed, and subsequently, the Box-Cox procedure was used to find the optimal power transformations, which produced the best approximate normality. Thus, IGF-I, IGFBP-3, and the molar ratios were transformed by raising values to the powers 0.4, 0.5, and 0.15, respectively.

After assessment of the regression models, adjusted mean plasma IGF-I, IGFBP-3, and molar ratios were calculated. These values were adjusted for the covariates found to be important in the regression models and calculated for each category of BMI, defined according to the WHO guidelines as follows: normal, < 25; overweight, 25.01 to 29.99; and obese, ≥30, among each racial/ethnic group. Means presented are least-squares means, which were calculated using the GLM procedure. Adjusted mean values were transformed back to their original scale for the purpose of presentation. Predicted values of transformed plasma IGF-I at the average age and gender effect were plotted against BMI by race/ethnicity to visually examine the adjusted relationships between these factors. A similar plot was created for molar ratio, adjusted only for gender. All analyses were done in SAS v9 (SAS Institute, Cary, NC).

Results

Table 1 shows characteristics for the 811 healthy subjects selected for this analysis by racial/ethnic group. In our sample, African Americans had the lowest proportion of males. Native Hawaiians had the greatest proportion of males. Japanese Americans had the highest proportion of subjects falling into the greatest age category. African Americans had the highest proportion of subjects in the youngest age category. As previously published (13), body size characteristics (weight and height) also differed significantly across racial/ethnic groups in our sample. African-American, Native Hawaiian, and Latino subjects had a higher proportion of subjects with BMI > 25 than Whites or Japanese Americans.

In a multivariate regression, with both genders combined, of the transformed IGF-I variable [root(IGF-I)], the most parsimonious model for IGF-I levels included gender, age, race/ethnicity, BMI, and the interaction between race/ethnicity and BMI. The interaction term for race/ethnicity × BMI was highly statistically significant ($P = 0.005$). IGF-I levels differed by BMI category in a race-specific manner. Table 2 provides the least-squares mean plasma IGF-I levels (ng/mL) by racial/ethnic group and BMI category. The least-squares mean IGF-I level declined as BMI increased among Latinos ($P_{trend} = 0.0002$), Whites ($P_{trend} = 0.009$), and Japanese ($P_{trend} = 0.04$). Least-squares mean plasma IGF-I remained stable across BMI categories in African Americans ($P_{trend} = 0.97$) and Native Hawaiians ($P_{trend} = 0.35$). We did not find a significant three-way interaction for sex, race/ethnicity, and BMI, and we found that the relationship between IGF-I and BMI was similar for males and females of the same racial/ethnic group (data not shown).

In a multivariate regression, with both genders combined, of the transformed IGFBP-3 variable [root(IGFBP-3)], the most parsimonious model for IGFBP-3 levels included age, race/ethnicity, fat intake from meat, and BMI. In further testing, addition of the interaction between race/ethnicity and BMI in the adjusted model was not significant ($P = 0.22$). Table 2

Table 1. Characteristics of 811 Multiethnic Cohort participants

	Latino	White	Japanese American	African American	Native Hawaiian
Total *N* (%)	171 (21.1)	165 (20.4)	169 (20.8)	147 (18.1)	159 (19.6)
Gender					
Male (%)	52.1	54.6	52.1	47.6	59.8
Age (%)					
<55	28.6	27.9	23.7	32.6	28.3
55-59	18.7	18.2	17.8	21.1	17.6
60-64	20.5	18.8	17.8	10.9	23.9
≥65	32.2	35.1	40.8	35.4	30.2
BMI (%)					
<25	26.9	41.8	63.3	28.6	28.3
25-29	49.1	38.8	31.4	41.5	37.7
≥30	24.0	19.4	5.3	29.9	34.0

Table 2. Least-squares mean (95% confidence limits) plasma IGF-I, IGFBP-3, and IGF-I/IGFBP-3 molar ratio levels (ng/mL) by BMI category (by race/ethnicity)

	BMI (kg/m^2)			
	<25	25-29.99	≥30	P_{trend}
IGF-I*				
Latino	184.6 (164.7-205.7)	147.7 (134.8-161.4)	132.7 (115.2-151.7)	0.0002
White	184.9 (168.4-202.3)	155.2 (139.9-171.4)	151.3 (130.1-174.5)	0.009
Japanese American	173.7 (161.8-186)	166.5 (150.2-183.9)	122.9 (91.3-160.2)	0.04
African American	172.2 (149.5-196.9)	172.3 (153.3-192.5)	172.9 (150.6-197.1)	0.97
Native Hawaiian	166.0 (147.8-185.4)	184.6 (167.9-202.2)	179.4 (162-197.8)	0.35
IGFBP-3 †				
Latino	2,498 (2,252-2,756)	2,488 (2,306-2,676)	2,279 (2,031-2,541)	0.25
White	2,847 (2,635-3,067)	2,881 (2,664-3,106)	2,938 (2,620-3,275)	0.66
Japanese American	2,860 (2,687-3,039)	2,783 (2,542-3,034)	3,112 (2,487-3,806)	0.92
African American	2,609 (2,369-2,861)	2,549 (2,355-2,752)	2,718 (2,476-2,971)	0.55
Native Hawaiian	2,744 (2,488-3,013)	2,971 (2,746-3,205)	2,807 (2,570-3,054)	0.79
IGF molar ratio ‡				
Latino	0.28 (0.25-0.30)	0.22 (0.21-0.24)	0.21 (0.19-0.24)	0.002
White	0.24 (0.22-0.26)	0.20 (0.18-0.22)	0.19 (0.17-0.22)	0.002
Japanese American	0.22 (0.21-0.24)	0.22 (0.20-0.24)	0.17 (0.13-0.21)	0.09
African American	0.24 (0.21-0.27)	0.25 (0.23-0.27)	0.24 (0.22-0.27)	0.80
Native Hawaiian	0.22 (0.20-0.25)	0.23 (0.21-0.25)	0.24 (0.22-0.27)	0.22

*IGF-I is adjusted for covariates found to be significant in a multivariate analysis (gender, age, race/ethnicity, BMI, and the interaction between race/ethnicity and BMI).

† IGFBP-3 is adjusted for covariates found to be significant in a multivariate analysis (age, race/ethnicity, fat intake from meat, and BMI).

‡ IGF molar ratio is adjusted for covariates found to be significant in a multivariate analysis (race/ethnicity, gender, BMI, and the interaction between race/ethnicity and BMI).

provides the least-squares mean plasma IGFBP-3 levels (ng/mL) by BMI category and racial/ethnic group. In no individual racial/ethnic group was the difference across BMI categories statistically significant.

Race/ethnicity, gender, BMI, and the interaction between race/ethnicity and BMI were statistically significantly associated with the molar ratio of IGF-I/IGFBP-3 in a multivariate model. The interaction between race/ethnicity and BMI category was statistically significant for the molar ratio of IGF-I to IGFBP-3 ($P = 0.003$). Table 2 illustrates the pattern of least-squares mean IGF-I/IGFBP-3 molar ratio levels by BMI category and racial/ethnic group. These differences were driven by differences in IGF-I and were statistically significant only in Latinos ($P_{trend} = 0.002$) and Whites ($P_{trend} = 0.002$).

Figure 1 is a plot of the predicted IGF-I values at the average value of age and gender plotted against BMI by race/ethnicity.

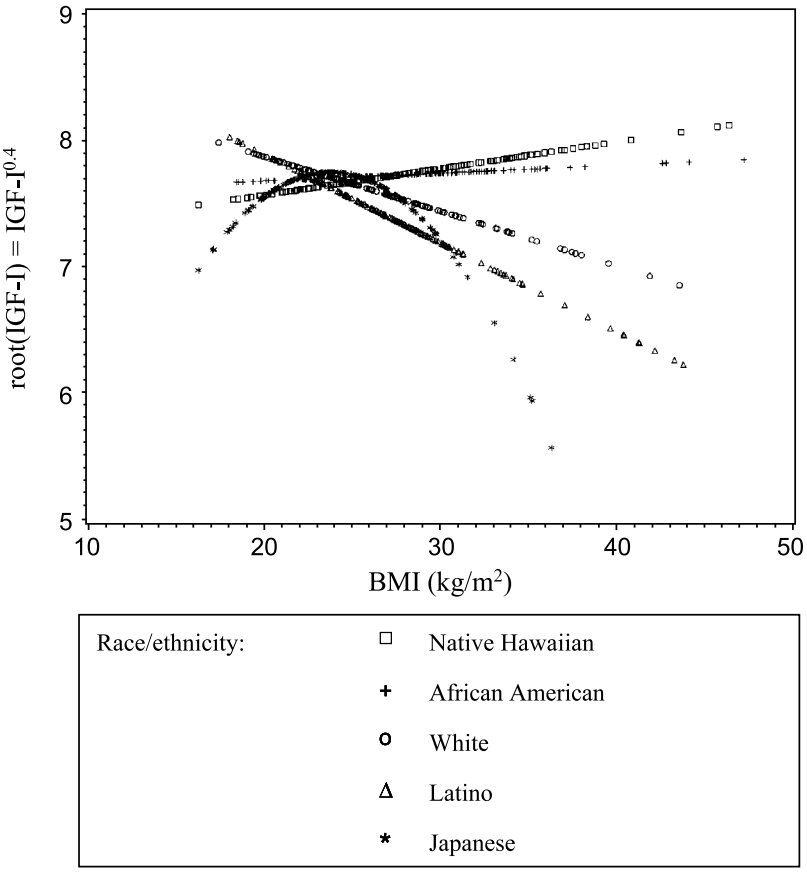

Figure 1. Predicted values for root(IGF-I) for BMI, averaged over gender and age, by race/ethnicity.

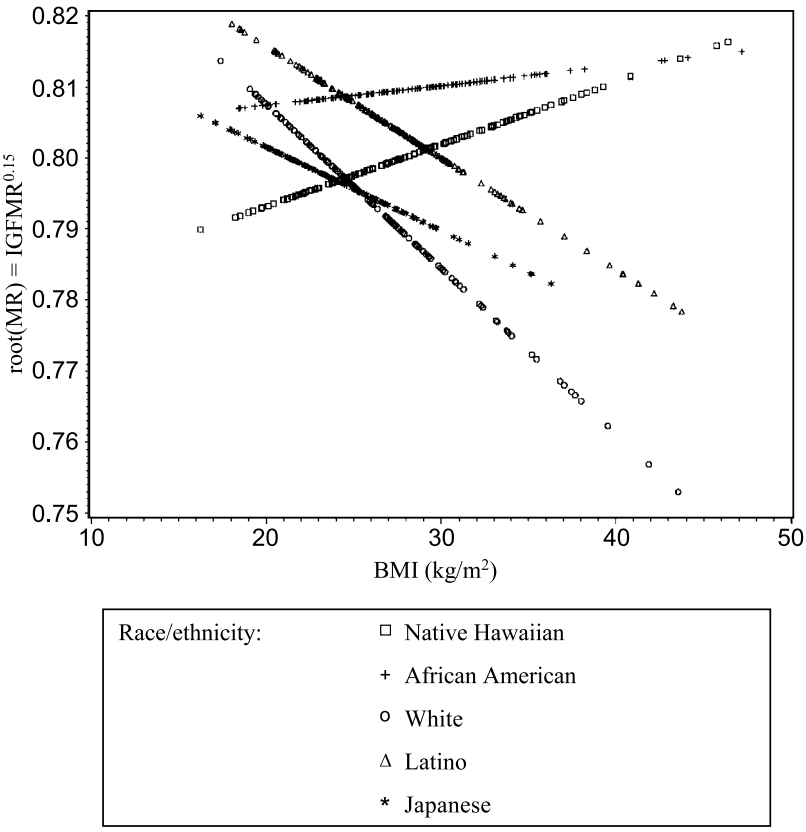

Figure 2. Predicted values for root(MR) for BMI, averaged over gender, by race/ethnicity.

Visual examination of this plot illustrates the difference across racial/ethnic groups in the adjusted relationship between IGF-I and BMI. IGF-I levels declined in a linear manner with increasing BMI most dramatically in Latinos. This decline was less clear in the White subjects and absent or slightly reversed in the African-American and Native Hawaiian subjects. Among Japanese subjects, IGF-I seemed to have an inverse quadratic relationship with BMI. The quadratic term was statistically significant when tested in the multivariate model ($P = 0.002$).

Figure 2 is a plot of the predicted IGF molar ratios at the average value of gender plotted against BMI by race/ethnicity. Visual examination of this plot illustrates the difference across racial/ethnic groups in the adjusted relationship between the molar ratio and BMI. IGF molar ratio levels declined in a linear manner with increasing BMI most dramatically in Latinos, Whites, and Japanese. In contrast, the relationship tended to be in the opposite direction in African-American and Native Hawaiian subjects, with the molar ratio increasing with increasing BMI.

Discussion

This study examined the relationship between circulating levels of two primary proteins in the IGF pathway and obesity, among five racial/ethnic groups, using BMI as an indicator of adiposity. IGF-I levels varied not only by racial/ethnic group but also by BMI category in a race-specific fashion. IGF-I levels declined with increasing obesity status most dramatically in Latinos and Japanese. This decline was attenuated in Whites and absent in African-American and Native Hawaiian subjects. In Japanese, the quadratic term (BMI^2) was statistically significant in a multivariate model ($P = 0.002$). The interaction between race/ethnicity and BMI was not significant for plasma IGFBP-3. With respect to the interaction between race/ethnicity and BMI, differences in the molar ratio reflect those in IGF-I.

Previous studies have reported inconsistent findings with respect to the association between BMI and circulating IGF-I levels. Studies among healthy adults have reported a null association (2-4), a positive association (5), an inverse association (6-9), and a nonlinear association (10, 11) between BMI and IGF-I levels. The nonlinear associations were similar to what we observed in Japanese Americans. A recent study among European women reported a relationship between BMI and serum levels of IGF-I similar to that which we saw in Japanese (15). Studies in children, which are important because they allow examination of potentially underlying biological differences across subgroups in the absence of the potential confounding effects of factors, such as smoking, alcohol, aging, menopausal status, and hormone therapy, have previously reported positive correlations between adiposity and IGF-I concentrations (16, 17); however, the relationships could be physiologically different in children in light of data indicating that IGF-I does begin to decrease after puberty (18).

A possible biological mechanism mediating the association between obesity and IGF-I may be through the effect of growth hormone. In individuals with high BMI, IGFBP1 and IGFBP2 are depressed, leading to an increased negative feedback by free IGF-I on pituitary GH secretion and a decreased IGF-I synthesis (ref. 19; for review, see ref. 20). The current data suggest that the GH-IGF axis may be regulated differently in different racial/ethnic groups. Racial/ethnic differences in the distribution of polymorphisms in genes involved in IGF regulation may be one mechanism mediating such an effect.

One possible explanation for the IGF-I result may be if the age-related decline in IGF-I differed between ethnic groups, and there were also differences in the age distribution of obesity within some groups. In these data, obesity uniformly increased with age, and the age-related decline in IGF-I

seemed to be significant only among African Americans. Therefore, these factors could not account for the findings. However, an alternate explanation that cannot be ruled out is that these differences are due to unmeasured confounding factors.

To ensure that the regressions would not be affected by the choice of cut points, we used a continuous BMI variable in the regressions and when assessing the possible significance of the interaction between race and BMI. However, in the models used to calculate the least-squares means, we used a categorical BMI variable, defined according to WHO guidelines, to facilitate comparison with other populations. These categories may not be appropriate to the same extent for all ethnic/racial groups to characterize obesity, as the correlation of adiposity with BMI may vary, and the complications of obesity may seem at different levels of BMI, across ethnic/racial groups.

One possible limitation of the current study is the reliance on a single time point measurement of plasma IGF-I and IGFBP-3. Although data from the Rancho Bernardo Study reported that the intra-individual variation in plasma IGF-I is minimal (21), suggesting that a single measurement may be adequate to predict long-term circulating levels, it should be noted that these samples were collected only 8 to 54 days apart. Other studies have shown measurable inter-individual variation in IGF-I and IGFBP-3 (3, 22-24).

The present results illustrate the importance of race/ethnicity in the relationship between circulating IGF hormones and BMI, particularly for IGF-I. In addition, these findings, if reproduced, have potentially important implications for understanding the link between obesity and cancer risk. In order for a definitive link between circulating IGF-I levels and cancer risk (for review, see ref. 25) to be established, it may be that this apparent interaction between race/ethnicity and BMI in determination of circulating IGF-I levels must be taken into account. This interaction may aid in explaining certain apparent anomalies in the relationship between obesity and cancer. Despite a similar pattern of obesity, degree of insulin resistance, and high risk for type 2 diabetes across some ethnic groups, such as African Americans and Latinos, there are marked differences in cancer incidence across these racial/ethnic groups. In particular, the Latino population in the Multiethnic Cohort has been shown to have a low risk for postmenopausal breast cancer relative to African Americans despite similarly high BMI values. These results may help to resolve the uncertainty in the relationship between the IGF proteins and obesity and highlight the potential importance of racial/ethnic–specific effects among these factors in explaining ethnic disparities in obesity-related cancers.

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