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Association of IGF Axis Hormones with Waist-to-Hip Ratio Varies by Physical Activity

KATHRYN H. SCHMITZ[1], DAWEI XIE[1], VALERIE TEAL[1],
RACHEL BALLARD-BARBASH[2] and DAVID BERRIGAN[2]

*[1]Center for Clinical Epidemiology and Biostatistics,
University of Pennsylvania School of Medicine, Philadelphia, PA 19104-6021, U.S.A.;
[2]Applied Research Program, Division of Cancer Control and Population Sciences,
National Cancer Institute, Bethesda, MD 20892-7344, U.S.A.*

Abstract. *Background/Aim: Insulin-like growth factor (IGF) axis hormones are associated with multiple chronic diseases. Reports of the relationship between adiposity and IGF-axis hormones vary widely. This study hypothesized that physical activity levels modify the association of IGF axis hormones with adiposity. Patients and Methods: Data from NHANES III were used to assess whether associations of adiposity, namely waist-to-hip ratio (WHR), with IGF axis hormones varied according to physical activity. Results: Among those in the lowest physical activity quintile, WHR had a substantive inverse association: bioavailable IGF-I was 16% lower among those in the highest versus the lowest WHR quintiles among the least active subjects (p<0.001). By comparison, among those in the highest physical activity quintile, IGF-I did not vary by WHR. Conclusion: The association of bioavailable IGF-1 with central adiposity differs among active versus inactive adults in the U.S.A. This has relevance to understanding previously reported benefits of physical activity among overweight individuals.*

The insulin-like growth factor I (IGF-I) is a potent growth factor that has been observed to prevent apoptosis and promote angiogenesis and cell migration (1). A total of six IGF-binding proteins have been identified. Of these six proteins, IGFBP-3 has been the subject of most studies, in part due to its prevalence, but also because the majority of circulating IGF-I is bound to it. IGF-I has multiple roles in development and metabolism. Elevated IGF-I levels are associated with reduced disability with aging (2), reduced risk of cardiovascular disease (3) and improved glucose homeostasis in diabetics (4). Concurrently, IGF-I is also associated with negative health outcomes: serum IGF-I levels are inversely associated with longevity (2) and higher serum levels are associated with increased risk for several forms of cancer (5).

Circulating IGF-I levels are regulated by hepatic growth hormone levels and nutritional status. This implies that serum IGF-I levels will differ according to body size and overall or central adiposity, as measured by body mass index (BMI), waist-to-hip ratio (WHR) or waist circumference, as well as factors that alter adiposity, such as physical activity (5, 6). However, reports of the associations of IGF-I with overall and central adiposity vary widely (7, 8). The relationship between IGF-I and habitual physical activity is similarly unclear (9-11). It is possible that the conflicting findings from prior studies can be explained by modification of the relationship of adiposity and IGF-I by physical activity. Two prior studies have examined associations between adiposity and IGF-axis hormones in the NHANES III (12, 13). Both studies reported that IGF levels decrease with BMI across age, race or ethnicity, and gender groups. One of the studies examined physical activity and IGF-I levels and reported no association (12). Given that IGFBP-3 is thought to influence bioavailable IGF-I, it may be important to examine the interaction of adiposity and physical activity on IGF-I and the molar ratio of IGF-I:IGFBP-3. This study used serum IGF-I and IGFBP-3 data from the National Health and Examination Survey III (NHANES III) to determine whether the association of adiposity with these important circulating growth factors varies according to self-reported physical activity.

Patients and Methods

Data. NHANES III was conducted from 1988-1994 by the National Center for Health Statistics, Centers for Disease Control and Prevention (Atlanta, GA, U.S.A.). Data collected for this survey were representative of U.S.A. non-institutionalized civilians. The study

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Correspondence to: Kathryn H. Schmitz, Associate Professor, Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, 903 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104-6021, U.S.A. Tel: +1 2158986604, Fax: +1 2155732265, e-mail: Schmitz@mail.med.upenn.edu

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was reviewed and approved by Human Subject Ethical Committees for NHANES and all participants provided written informed consent. A stratified multistage probability design was used and African- and Mexican-Americans were oversampled (14). The data were reported on questionnaires and measured during physical examinations, including serum collection in a subset of participants.

Study sample. A subset of 6,226 adults, 20 years of age and older from NHANES III, was selected at random and the participants were asked to fast overnight before attending the morning examination and supplying serum samples. Response rates were ~97% (15). Subjects were required to complete a comprehensive questionnaire in addition to a physical examination at the Mobile Examination Center (MEC). Generally, the questionnaire was completed approximately four to six weeks prior to the MEC exam. Some participants with serum samples were excluded for the following reasons: pregnancy (n=84), lactation (n=42), BMI under 18.5 kg/m^2 (n=66), taking any drugs that may alter growth hormone (n=159), diagnosed with cancer within the past two years (n=43) or unreliable, missing or incomplete physical activity data (n=165).

Sensitivity analyses were conducted to determine whether the results would remain consistent after exclusion of individuals who self-reported a diagnosis of diabetes or who self-reported regular use of non-steroidal anti-inflammatory drugs (NSAIDs), as these variables have been noted to be associated with IGF-pathway hormones (16, 17). Results were unchanged when the 314 participants with diabetes were excluded (results not shown), but a significant modification of some associations was observed when the 417 participants who reported regular NSAID use were excluded. Therefore, results are presented after excluding for NSAID use (N=417). After accounting for overlap from multiple exclusions, the analysis dataset included a total of 5,254 participants.

Variables. Details of serum handling procedures and quality control protocols are provided elsewhere (18). Assays were performed by a single technician at the DSL Labs facility in Webster, TX, U.S.A. For the IGF-I assay, the reagent for the ELISA assay was from a single batch for the entire experiment. The IGFBP-3 IRMA required fresh batches of radioactive tracer during the study. Throughout the study samples were reanalyzed if the coefficient of variation for replicate samples from a single vial was >15%. Blind quality control samples were included into every assay batch, resulting in coefficients of variation of approximately 14% for IGF-I and 11.5% for IGFBP-3. The molar ratio of IGF-I and IGFBP-3 concentration measures was calculated and used as a surrogate for bioavailable IGF-I. The assay performed used non-glycolsylated standards, thus the adjustment in IGF-I and IGFBP-3 from ng/ml to nM was as follows: 1 ng/ml IGF-1=0.130 nM IGF-1, and 1 ng/ml IGFBP-3=0.036 nM IGFBP-3. This ratio was multiplied by 100 for all analyses and, thus, reported as a percentage, for ease of presentation.

Physical activity was assessed by self-report. Questions asked about a list of activities that may have been performed over the prior 30 days, including: walking, jogging, running, bike riding, swimming, aerobics, dancing, calisthenics or exercise, gardening or yard work, lifting weights and an option for up to four other non-listed activities. Each of these activities was coded as moderate or vigorous intensity using commonly accepted MET values (19). The frequency of performing each activity was translated from the data provided for the past 30 days into a 'number of sessions per week' variable for each individual activity. Activities associated with a MET value of less than six were used to sum the number of sessions per week across all moderate intensity activities. The intensity-weighted physical activity variable was calculated by multiplying the MET value associated with each of the activities performed and summing these values for an overall intensity-weighted activity frequency variable.

Other NHANES III variables used in this analysis included respondent's age, gender, race or ethnicity, education, poverty-to-income ratio, smoking status, height, weight and waist and hip circumferences. Details of the questionnaires and methods for collecting each of these variables are available elsewhere (14). All anthropometric variables in this study are obtained from measurement by NHANES staff, not from self-reports. BMI was calculated as the ratio of body mass (expressed in kg) to height squared (expressed in m^2). WHR was calculated as the ratio of the waist circumference to the hip circumference.

Statistical analysis. All analyses were performed using SAS-callable SUDAAN, version 8.0 (RTI International, Research Triangle Park, NC, U.S.A.) (20), which run under the SAS statistical environment (SAS Institute, Cary, NC, U.S.A.). The sampling design of the survey was considered by taking into account the stratification, clustering and appropriate statistical weights for the morning examination (MEC only) subsample (15). The normality of the outcome variables was compared before and after natural logarithm transformation both visually and by comparing the skewness and kurtosis. The log transformation did not appear to improve the normality of the data visually and both skewness and kurtosis were farther from zero after log transformation. Therefore, the original IGFBP-3 and bioavailable IGF-I were used in all models.

Linear regression models were fitted for each outcome variable and each physical activity variable separately, adjusting for age, gender, ethnicity and smoking status. These variables were included as adjustments in models after preliminary analyses revealed significant bivariate associations with both the outcome and predictor variables, but there was no modification of the association of outcomes and predictors. The intensity-weighted physical activity variable was included in models after being categorized by quintiles obtained after accounting for sampling weights. Associations did not change substantively when models were repeated with continuous physical activity variables.

Modification of the association between predictors and outcomes by physical activity was explored in models that included both main effects for adiposity and a multiplicative term for adiposity and physical activity, namely the product of WHR and physical activity. A separate model was developed to explore the modification of bioavailable IGF-I and IGFBP-3. Finally, adjusted means and the associated standard errors were obtained using the appropriate options in SUDAAN for the two outcome variables (bioavailable IGF-I and IGFBP-3) in order to facilitate the interpretation of the results in the final models.

Results

This analysis included a total of 5,254 adults aged 20 to 90 years. As shown in Table I, over half of the subjects were between the ages of 20 and 49 years and approximately 77% of the subjects were non-hispanic white. A majority of the subjects had a BMI that was within the normal to overweight categories, 22% of the subjects were in the

Table I. *Selected characteristics of the 5,254 NHANES III participants included in the analysis.*

	Overall 5,254	Male 2,517 (49.5)	Female 2,737 (50.5)	*p*-Value[a]
Demographics				
Age (years):				
20-29	1,172 (22.7)	573 (24.6)	599 (20.8)	0.0056
30-39	1,173 (25.5)	524 (25.9)	649 (25.1)	
40-49	903 (20.5)	431 (20.2)	472 (20.7)	
50-59	602 (12.4)	273 (12.6)	329 (12.2)	
60-69	636 (9.6)	350 (9.3)	286 (9.8)	
≥70	768 (9.4)	366 (7.4)	402 (11.3)	
Race/ethnicity				
White, non-Hispanic	2,169 (76.7)	1,029 (77.2)	1,140 (76.1)	0.0001
Black, non-Hispanic	1,427 (10.2)	646 (9.1)	781 (11.3)	
Mexican American	1,436 (5.2)	739 (5.7)	697 (4.7)	
Other	222 (8.0)	103 (8)	119 (8)	
Education				
High school	1,978 (22.4)	1,002 (22.9)	976 (22)	0.0032
College	1,652 (33.5)	683 (29.6)	969 (37.4)	
Post-baccalaureate	1,602 (44.0)	819 (47.5)	783 (40.7)	
Poverty-income ratio	3.0 (0.0)	3.1 (0.1)	3.0 (0.0)	0.0004
Physical activity & body size				
Adherence to current physical activity guidelines				
No activity in past 30 days	1,057 (13.2)	376 (9.7)	681 (16.7)	0.0001
Some activity but not adherent	2,179 (42.6)	1,036 (41.4)	1,143 (43.8)	
Adherent to current guidelines	2,017 (44.2)	1,105 (48.9)	912 (39.5)	
Moderate intensity physical activity (sessions/week)	4.7 (0.2)	5.3 (0.2)	4.1 (0.2)	0.0001
Intensity-weighted physical activity (intensity-weighted sessions/week)	116.0 (4.1)	134.0 (5.3)	98.4 (4.6)	0.0001
BMI (kg/m^2)	26.5 (0.2)	26.72 (0.17)	26.3 (0.2)	0.0109
WHR	0.9 (0.0)	1.0 (0.0)	0.9 (0.0)	0.0001
Waist (cm)	91.5 (0.4)	95.1 (0.5)	88.0 (0.5)	0.0001
IGF axis hormones				
IGF-I (ng/ml)	273.1 (3.3)	285.9 (3.1)	260.5 (4.4)	0.0001
IGFBP-3 (ng/ml)	4,468.1 (31.8)	4,402.0 (43.5)	4,532.7 (30.6)	0.0001
Molar ratio IGF-I:IGFBP3 (%)	22.1 (0.3)	23.6 (0.3)	20.6 (0.3)	0.0001

Data are reported as N (%) or mean (standard error of the mean). [a]*p*-Values are derived from the chi-squared and *t*-tests for categorical and continuous variables, respectively, comparing male and female, using survey-weighted data.

obese range (BMI >30). The overall proportion of adults who reported doing sufficient physical activity to meet the current U.S.A. public health guidelines for sufficient physical activity (21) was 44%, while 43% reported some activity and 13% reported not having done any physical activity in the prior 30 days.

IGF axis variables and body size. Table II shows the association of bioavailable IGF-I and IGFBP-3 with body size variables after adjustment for age, ethnicity, gender and smoking status. Additional results are shown for both BMI and WHR after adjustment for the other variable, *i.e.* adjustment for BMI or WHR for the model with WHR or BMI, respectively. IGF axis variables were lower among those who were larger as measured by BMI or WHR.

IGF axis variables and WHR: modification by physical activity. Figures 1A and 1B show the association of intensity-weighted physical activity quintiles with the bioavailable IGF-I and IGFBP-3. Figure 1A shows that bioavailable IGF-I was higher in the lower WHR quintiles for the least active compared to the most active subjects and that the difference in bioavailable IGF by WHR quintile was blunted among those in the highest activity quintile. In a model that included main effects and intensity-weighted physical activity as a continuous variable, the interaction term for WHR and physical activity was statistically significant (p=0.01). For example, among those in the lowest physical activity quintile, bioavailable IGF-1 was 16% lower in the highest compared to the lowest WHR quintile (p<0.001). By comparison,

Table II. *Adjusted[a] means (standard error of the mean, of the molar ratio IGF-I:IGFBP-3 and IGFBP-3 by quintiles of body-size measurements in 5,254 participants of NHANES III.*

	Molar ratio IGF-I:IGFBP-3 (%)	IGFBP-3 (ng/ml)
BMI (kg/m^2)		
<22	23 (0.4)	4,385.2(46.5)
22-24.4	22.4 (0.4)	4,470.8 (51.8)
24.4-26.7	22.3 (0.3)	4,496.6 (47.6)
26.7-30.4	22.1 (0.3)	4,534.2 (61.6)
30.4 +	20.6 (0.3)	4,451.7 (56.7)
p-Value (overall/trend)	0.0001/0.0001	0.2863/0.6095
BMI (kg/m^2)[a]		
<22	22.5 (0.4)	4,429.7 (46.0)
22-24.4	22.1 (0.4)	4,495.4 (54.7)
24.4-26.7	22.3 (0.3)	4,500.4 (47.5)
26.7-30.4	22.2 (0.3)	4,522.7 (63.5)
30.4 +	21.2 (0.3)	4,426.3 (64.2)
p-Value (overall/trend)	0.0091/0.0001	0.4961/0.6459
WHR		
<0.82	24.1 (0.5)	4,368.4 (52.7)
0.82-0.88	23.3 (0.5)	4,395.0 (52.1)
0.88-0.93	21.3 (0.3)	4,505.1 (45.5)
0.93-0.98	21.4 (0.3)	4,513.1 (61.3)
0.98+	20.7 (0.4)	4,566.2 (60.6)
p-Value (overall/trend)	0.0001/0.0001	0.0335/0.0246
WHR[a]		
<0.82	23.6 (0.5)	4,355.3 (63.7)
0.82-0.88	23 (0.5)	4,388.8 (53.2)
0.88-0.93	21.3 (0.3)	4,504.6 (45.5)
0.93-0.98	21.6 (0.4)	4,517.9 (61.8)
0.98+	21.2 (0.4)	4,577.7 (60.9)
p-Value (overall/trend)	0.0024/0.0002	0.0632/0.0346

[a]Adjusted for age, gender, ethnicity and smoking in all models, and BMI and WHR for the models with WHR and BMI, respectively.

bioavailable IGF-1 was only 1% lower in the highest compared to the lowest WHR quintile among subjects in the highest physical activity quintile (p=0.76). Figure 1B shows that IGFBP-3 levels were lower for respondents with low levels of physical activity and lower WHR. In a model that included main effects and intensity-weighted physical activity as a continuous variable, the interaction term for WHR and physical activity was statistically significant (p=0.04).

Discussion

These results suggest that the relationship between adiposity and the serum levels of IGF axis growth hormones may be modified by self-reported physical activity. This is consistent with prior observations that central adiposity, as measured by waist circumference or WHR, is associated with reduced growth hormone secretion (associated with lower IGF-I levels) (22) and that physical activity increases growth hormone secretion (associated with higher IGF-I levels) among obese exercisers (23). Previous studies of the IGF axis hormones have not examined the interaction between adiposity and physical activity (12, 13). The present observation of a significant interaction for adiposity and physical activity with IGF axis hormones may explain prior inconsistent findings regarding relationships with adiposity. As noted earlier, prior studies have noted an inverse association (24, 25), no association (26), or a non-linear association (8) between adiposity and the IGF axis hormones. Furthermore, the occasional, but inconsistently reported association between physical activity and IGF axis hormones (9-11) may also be explained by this interaction, depending on the adiposity distribution of a given study sample.

A particular strength of the present study was its large sample size. The care with which the IGF-I and IGFBP-3 assays were conducted has been reported elsewhere (18) and reflects the high quality of the data. Furthermore the sample was drawn from the NHANES, a representative sample of non-institutionalized U.S.A. adults 20 years of age and older. The cross-sectional nature of this study was a main limitation, since, as a result, it was not possible to comment on the direction of the association observed, consequently limiting the ability to establish temporality and, in turn, causality. Additionally, self-reported physical activity data was used, which may have resulted in greater misclassification than objective measures, such as accelerometry. However, there is evidence that the relationships of adiposity and blood pressure with physical activity are similar when measured objectively or by self-report (27).

The results herein suggest that high levels of physical activity counter the effects of central adiposity on the IGF-axis, consistent with the ‘fit fat’ hypothesis. This hypothesis, originally proposed by Blair’s group (28, 29), posits that physically active, fit individuals who are overweight and obese are at lower risk for chronic diseases than sedentary, unfit, lean individuals. These findings are significant for understanding the independent and interactive contributions of both physical activity and central adiposity to the etiology of chronic diseases associated with IGF-I, such as cardiovascular disease, diabetes and hormonally-related cancer.

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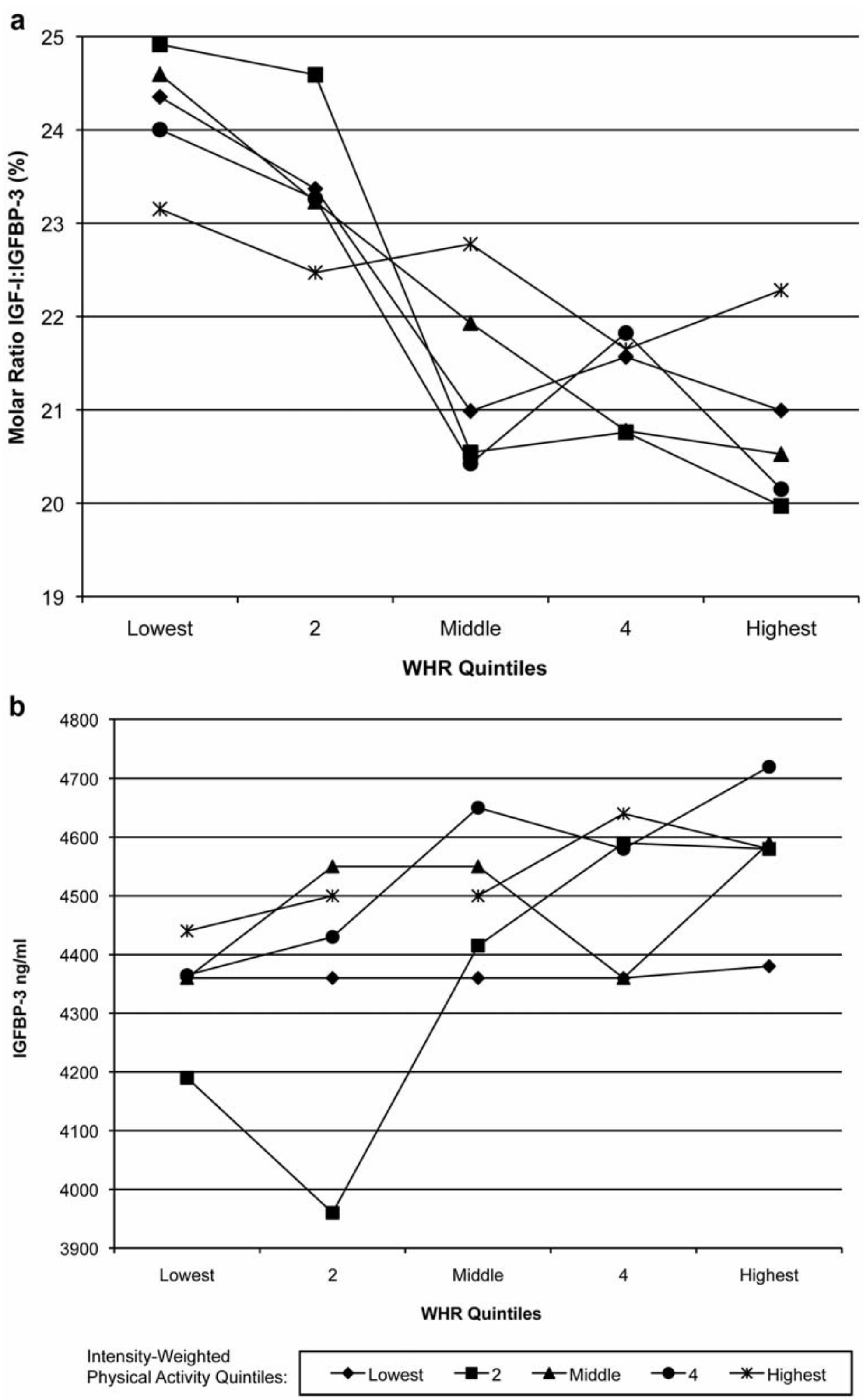

Figure 1. *Adjusted means (for age, gender, ethnicity and smoking) of (a) molar ratio IGF-I:IGFBP-3 (%) and (b) IGFBP-3 (ng/ml) stratified by WHR quintiles and intensity-weighted physical activity quintiles. The p-value for test of modification of the association of WHR and IGF-I:IGFBP-3, IGFBP-3 by intensity weighted physical activity were 0.01 and 0.04, respectively.*

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