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INFLUENCE OF WAIST ON ADIPONECTIN AND INSULIN SENSITIVITY IN ADOLESCENCE

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Abstract

It has been hypothesized that abdominal obesity leads to insulin resistance partly through decreased adiponectin. However, the cross-sectional and longitudinal associations among waist, adiponectin, and insulin sensitivity have not been examined in older adolescents. Non-Hispanic white and black children were recruited from the Minneapolis school district and underwent three examinations at mean ages 13, 15, and 19. Insulin sensitivity (measured with the gold-standard euglycemic clamp) and waist circumference were measured at all exams. Adiponectin was only measured at mean ages 15 and 19. Partial correlations were used to examine associations among waist, adiponectin, and insulin sensitivity at mean age 15 ($n = 308$) and mean age 19 ($n = 218$). A regression model was used to predict age 19 adiponectin, and age 19 insulin sensitivity, from age 13 waist and change in waist. At age 15, waist and adiponectin were significantly negatively correlated ($r = -0.32$). At age 19, waist and adiponectin were significantly correlated ($r = -0.36$), as were waist and insulin ($r = -0.16$). Both baseline waist and change in waist were significantly associated with age 19 adiponectin but with age 19 insulin sensitivity only in men. Therefore, in adolescents, the association between waist and adiponectin appears to develop several years before the association between waist and insulin sensitivity. These results support the hypothesis that adiponectin may contribute to the association of waist and insulin sensitivity.

Keywords

Adiponectin; abdominal obesity; insulin sensitivity

Introduction

Insulin resistance is an important risk factor for type 2 diabetes (1-4) and is significantly associated with elevated systolic blood pressure, hypertriglyceridemia, and decreased HDL (5-7). The mechanisms mediating these associations are incompletely defined. However, it appears they are related to adiposity, and, in particular, increased central adiposity, possibly through the increased production of inflammatory cytokines (e.g., IL-6 and TNF- α) (8,9) and the reduced production of adiponectin (10).

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Adiponectin, has homology to both TNF- α and complement protein C1q (11) and is the most abundant protein in the adipocyte (12). It has been found to have an insulin sensitizing effect when administered intravenously to rats (13) and to have decreased transcription in the visceral fat of obese, as compared to lean, humans (14). Adiponectin has been associated with waist size, visceral adiposity (15-17), and euglycemic-clamp derived insulin sensitivity (18-21) and it has been shown to increase after significant weight loss (22,23). Only a few cross-sectional studies of the associations among waist, adiponectin, and insulin sensitivity have been conducted in children using the insulin clamp (24-27) and several of these studies have drawn from a similar study population (24,25,27). Few longitudinal studies involving these variables have been undertaken in adults, and none have been conducted in children.

The present study was designed to help elucidate the temporal relationship among central adiposity, adiponectin, and insulin sensitivity measured by the euglycemic clamp in a cohort of adolescents followed longitudinally from age 13 to 19. The results show that the association between waist and adiponectin develops before the association between waist and insulin sensitivity, lending support to the theory that the relation between waist and insulin sensitivity is driven, in part, by adiponectin.

Research Methods and Procedures

Subjects

Subjects were drawn from a longitudinal study of cardiovascular risk factors in adolescents. The Human Subjects Committee of the University of Minnesota approved this study and details of the recruitment have been published previously (28).

Briefly, after a screening of 5th-8th grade Minneapolis school children in 1995, participants were randomly selected with stratification according to sex, race (black and white), and systolic blood pressure (half from the upper quartile and half from the lower 3 quartiles to enrich the study population with potentially higher risk children). Of 2915 students who received a recruitment letter, 537 attended an informational meeting (held in groups of 20 to 30 children and their parents), and informed consent was obtained from 401 children (probands) and their parents. The screening blood pressure, height and weight measurements did not differ between this group and the children choosing not to participate.

Probands were seen at mean ages 13 (baseline), 15 and 19. Adiponectin was measured at ages 15 and 19. Individuals with outlying or implausible waist, adiponectin, or insulin sensitivity values were excluded from analyses ($n = 3$). Probands with waist, adiponectin, and insulin sensitivity measured at mean age 15 were included in age 15 cross-sectional analyses ($n = 308$), probands with waist, adiponectin, and insulin sensitivity measured at mean age 19 were included in age 19 cross-sectional analyses ($n=218$), and probands with waist and insulin sensitivity measured at mean ages 13, 15, and 19, and with adiponectin measured at ages 15 and 19 were included in longitudinal analyses ($n= 195$). There were no significant differences in age, waist, insulin sensitivity, race, or Tanner stage at the baseline visit between those who participated in all three visits ($n = 195$) and those not participating in all three visits ($n = 160$) although the latter group were more likely to be female.

Parents of the probands were recruited into the study at the time of the probands mean age 19 visit and underwent the same measurements as the children (including the insulin clamp) except measurements of serum adiponectin. A total of 276 parents who underwent the clamp were included in analyses in this study.

Phenotypic Measurements

Abdominal adiposity was estimated by measuring waist circumference to the closest .5 cm (29). The measurement was made around the waist at the level of the greatest lateral indentation or smallest part of the midsection. For subjects without any indentation of the waist, measurements were made 1 cm above the umbilicus. Tanner stage was assessed in children during a physical exam by a pediatrician according to pubic hair in boys and pubic hair and breast development in girls.

Blood for adiponectin analysis was drawn in the morning, after an overnight fast and before beginning the insulin infusion for the euglycemic clamp. All serum samples were stored frozen at -70°C until analysis at the cytokine reference laboratory at the University of Minnesota. Age 19 adiponectin was measured with the Quantikine ELISA kit (R and D systems, Minneapolis, MN). Age 15 adiponectin was measured with an ELISA assay developed by the cytokine laboratory prior to the availability of the kit. A statistical model was used to examine growth curves across ages 13-20 (PROC MIXED model; all repeated adiponectin measurements were regressed on age at adiponectin measurement, sex, and ethnicity, and a dichotomous term for examination time). Although there were no cross-sectional associations between age and adiponectin within exams, the $\ln(\text{adiponectin})$ values at the age 15 exam were 0.7983 higher than those at age 19 exam, corresponding to about 6 $\mu\text{g/ml}$ on the natural adiponectin scale. Therefore 0.7983 was subtracted from the $\ln(\text{adiponectin})$ value at age 15 for these data analyses.

Euglycemic clamp studies were conducted in the University of Minnesota Clinical Research Center after a 12 hour fast as previously described (28). Plasma glucose was measured at baseline and every five minutes during the clamp. The insulin infusion was started at time 0 and continued at 1 mU/kg/min for 3 hours. An infusion of 20% glucose was started at time 0 and adjusted, based on plasma glucose levels, to maintain plasma glucose at 5.6 mol/l (100 mg/dl). Insulin sensitivity, M , was determined from the amount of glucose administered over the final 40 minutes of the euglycemic clamp and was expressed as M_{LBM} (i.e., glucose utilization/ kg lean body mass/ minute). Percentag of body fat and lean body mass (LBM), or fat-free mass, was calculated by the skinfold formula method of Slaughter (30) at ages 13 and 15, and by DEXA at age 19 in children and in parents. The LBM values from ages 13 and 15 were adjusted to the DEXA values according to equations derived from studies in siblings of the present cohort, and within the same age range, as previously published (31).

Statistical Methods

All statistical analyses were performed in PC SAS v 9.1 (SAS Institute Inc., Cary, NC). For all analyses, adiponectin was natural log transformed due a skewed distribution. Cross-sectional associations at ages 15 and 19 of waist, $\ln(\text{adiponectin})$ and M_{LBM} were assessed using Pearson correlations and linear regression. Correlations were adjusted for age, sex, race, height, and Tanner stage (for analyses involving data from ages 13 and 15). The Meng test (32) was used to assess statistical significance of differences between correlated correlations (e.g. the correlation of waist with adiponectin compared to the correlation of waist with insulin sensitivity). Effect modification of cross-sectional associations by sex, race, height, and Tanner stage (1-4 vs. 5) was assessed by the inclusion of interaction terms between these variables and waist in linear regression models.

To examine longitudinal associations between waist and adiponectin or insulin sensitivity, linear regression was used to regress age 19 and age 15 adiponectin, age 19 and age 15 insulin sensitivity, and change in adiponectin and insulin sensitivity from age 15 to age 19 on both baseline waist and change in waist. The models were adjusted for age at baseline, sex, race, height at baseline, and Tanner stage at baseline. Effect modification of these associations by

sex, race, Tanner stage at baseline, and height at baseline was examined by including interaction terms with both baseline waist and change in waist variables in the regression models.

Results

Cohort Characteristics

Table 1 lists the characteristics of individuals in the study. On average, waist circumference increased as the children aged while insulin sensitivity decreased over time. Waist circumference was highly correlated across visits ($r = 0.69 - 0.74$). The repeated measurements of adiponectin across visits (mean ages 15 and 19) were also highly correlated ($r = 0.66$). Measurements of insulin sensitivity were less highly correlated across visits ($r = 0.31 - 0.44$).

Cross-sectional Associations

Table 2 shows correlations among waist, adiponectin, and insulin sensitivity from cross-sectional analyses in children at ages 15 and 19 and in parents. Although all correlations presented were adjusted for age, race, Tanner stage (1-4 vs. 5) and height, adjustment for these variables modified the correlations only slightly.

The adjusted correlation between waist and insulin sensitivity was weakest at age 15 ($p=0.14$), stronger at age 19 ($p=0.02$), and strongest in the parents ($p<0.001$). Similarly, the magnitude of the correlation between adiponectin and insulin sensitivity increased between ages 15 ($p=0.40$) and 19 ($p=0.001$). By contrast, the correlation between waist and adiponectin was already relatively strong at age 15 ($p<0.001$) and remained so at age 19 ($p<0.001$). The correlation between waist and adiponectin was significantly greater than the correlation between waist and insulin sensitivity ($p=0.01$ at mean age 15 and $p = 0.002$ at mean age 19).

There was no statistically significant effect modification of the associations between waist, adiponectin, and insulin sensitivity at ages 15 or 19 by gender, race, Tanner stage (1-4 vs. 5), or sex. When analyses were repeated substituting BMI or percent body fat for waist, similar results were obtained (not shown). This was likely due to the high correlations of waist with percentage body fat and BMI, ranging from .83 to .90, in this study population.

Longitudinal associations of waist with adiponectin and insulin sensitivity

Table 3 presents results from longitudinal regression analyses of $\ln(\text{adiponectin})$ and insulin sensitivity on baseline (age 13) waist and change in waist from age 13 to either age 15 or 19. After adjustment for sex, race, age, Tanner stage, and height at mean age 13, baseline waist, but not change in waist, was predictive of age 15 adiponectin; neither was predictive of age 15 insulin sensitivity. In a second set of regression models, both baseline waist and change in waist were significant predictors of adiponectin at age 19, but again neither age 13 waist nor change in waist between ages 13 and 19 were predictive of age 19 insulin sensitivity. Change in waist predicted change in adiponectin (age 15 to age 19: $-0.45 \mu\text{g/ml}$ per SD change in waist, $p = 0.01$), but baseline waist did not. Neither predicted change in insulin sensitivity (age 13 to age 19) (results not shown). Sex was found to be an effect modifier of the association between baseline waist and age 19 insulin sensitivity (p interaction = .04). In females, neither baseline waist nor change in waist was predictive of age 19 insulin sensitivity; in males baseline waist (but not change in waist) was significantly predictive of age 19 insulin sensitivity ($p = .001$).

Discussion

In this study in adolescents, waist was found to be significantly associated with adiponectin, both cross-sectionally at ages 15 and 19 and longitudinally between ages 13 and 19. In contrast,

waist was not associated with insulin sensitivity at age 15, was weakly associated with insulin sensitivity at age 19 and predicted insulin sensitivity in longitudinal analyses only in males. The dynamics of waist and adiponectin and also waist and insulin sensitivity during adolescence generally agreed with these cross-sectional observations: adiponectin changes from age 15 to 19 followed the pattern of waist changes, while changes in insulin sensitivity were not significantly related to changes in waist. Whereas the association between waist and adiponectin appears to be established and remain constant over adolescence (and into adulthood, based on results published in adult populations (15-17,33)), the results from this study suggest that the magnitude of the association between waist and insulin sensitivity increases during adolescence and into adulthood. This suggests that the strong cross-sectional association between waist and insulin sensitivity seen in adults takes years to develop and reflects not only the current adult effect of abdominal obesity, but also represents the cumulative effect of years of exposure to excess abdominal adiposity. The fact that the association between waist and adiponectin develops before the association of waist and insulin sensitivity (as seen in the adult population (15-17,33-36)) lends support to the hypothesis that abdominal obesity leads to insulin resistance, at least in part, through decreased adiponectin or a correlate of adiponectin.

The cross-sectional correlations between waist and adiponectin reported in this paper are largely consistent with other published estimates of the correlation between abdominal adiposity and adiponectin in both adolescents and adults. A study in 12 year olds ($n = 150$) found a correlation of -0.33 between intra-abdominal fat and adiponectin (37) while another study (mean age 12, $n = 83$) found the correlation of adiponectin and visceral fat area to be -0.37 in African Americans (27). Published estimates in adults of the correlation between abdominal adiposity and adiponectin range from -0.24 to -0.46 (15-17,33). No previous estimates of longitudinal associations between waist and adiponectin have been published in adolescents.

In contrast, the cross-sectional correlations between adiponectin and clamp-derived insulin sensitivity and abdominal obesity and insulin sensitivity in this paper are smaller than those previously reported in adolescents. A study in African American and white children (mean age 13, $n = 145$) found a correlation of -0.71 between waist circumference and insulin sensitivity (24) while another study in fourteen obese adolescent females (mean age 13) found the correlation of total abdominal fat and insulin sensitivity to be -0.30 (26). A study in African American and white children (mean age 12, $n = 161$) found the correlation of adiponectin and insulin sensitivity to be 0.51 in African Americans and $.61$ in Caucasians (27). Finally, a study in 49 normal and overweight white adolescents (mean age 13) found a correlation of 0.67 between adiponectin and clamp-derived insulin sensitivity (25). No previous estimates of the longitudinal association of waist and insulin sensitivity have been published in adolescents. It is unlikely that the differences between this study and others are due to measurement or analysis errors, because the correlation between waist and insulin sensitivity in the parents (-0.50) is consistent with other published correlations (-0.35 to -0.55) between abdominal adiposity and clamp-derived insulin sensitivity in adults (34-36). It seems more likely the differences may be due to population heterogeneity, differing ages of the study populations, restriction of studies to obese individuals, inclusion of outliers in other study samples, or small sample sizes.

Strengths and limitations

There were several strengths to this study. It examined serial cross-sectional associations and presents, for the first time, longitudinal associations between waist, adiponectin, and insulin sensitivity from mean age 13 to mean age 19, spanning late childhood to early young adulthood. The study population was larger than previous studies in children and thus afforded adequate power to detect associations. Finally, the study used the gold-standard measure of insulin

resistance, the euglycemic clamp. The use of the insulin clamp appears to be particularly important because surrogate measures of insulin sensitivity such as fasting insulin and HOMA have been shown to be more highly correlated with adiposity and are only modestly correlated with the euglycemic clamp (38,39), possibly leading to overestimates of the correlation between measures of adiposity and insulin sensitivity.

There were also limitations to this analysis. Abdominal adiposity was measured using waist rather than a more specific measure of visceral or total abdominal fat. However, waist is considered a good measurement of abdominal adiposity in many populations and has been shown to be a good measure of truncal fat in children 3-19 years of age (29). The study population was over eighty percent Caucasian with no representation of Hispanic or Asian individuals and all study participants came from the greater Minneapolis area. Finally, we did not have power to determine if associations between waist, insulin sensitivity and adiponectin differed between white and black adolescents.

In conclusion, findings from this study show that the relation between waist and adiponectin is evident before the relation between waist and insulin sensitivity. This lends support to the theory that decreased adiponectin or a correlate of adiponectin contributes to the association between adiposity and insulin sensitivity.

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Table 1

Characteristics of individuals, by visit

	Children Mean age 13 (n= 355)	Children Mean age 15 (n= 308)	Children Mean age 19 (n=218)	Parents (n=276)
Age (years)	12.9 (1.2)	15.0 (1.2)	18.6 (0.9)	48.0 (5.7)
Age range (years)	10-16	12-18	17-22	32-64
Waist circumference (cm)	77.1 (11.1)	79.7 (12.3)	82.4 (13.6)	92.8 (16.0)
Insulin sensitivity (M _{LBM})(mg/kg/min)	12.8 (4.2)	12.7 (4.3)	10.9 (3.7)	11.3 (4.1)
Adiponectin (ug/ml) *	Not measured	5.9 (4.3-7.6)	6.1 (4.1-8.3)	Not measured
Race (%)				
White	80.0	80.2	82.1	87.6
African American	20.0	19.8	17.9	12.4
Male (%)	55.5	56.8	59.5	40.8
Tanner Stage (%)				
<5	82.0	32.1	0.9	NA
5	18.0	67.9	99.1	NA

Mean (SD)

* Median (IQR)

Table 2

Adjusted cross-sectional correlations* of waist, adiponectin, and insulin sensitivity

	Age 15		Age 19		Parents	
	adiponectin	insulin sensitivity	adiponectin	insulin sensitivity	adiponectin	insulin sensitivity
waist	−0.32 (<.0001)	−0.09 (.14)	−0.36 (<.0001)	−0.16 (.02)	NA	−0.50 (<.0001)
adiponectin		0.05 (.40)		.22 (.0012)		NA

Values are Pearson correlation coefficients (p-value)

* Adjusted for age, race, Tanner stage (age 15 only), height, and sex

Table 3

Predicted differences in adiponectin and insulin sensitivity according to baseline waist and change in waist[‡]

Independent variable	Dependent variable			
	<u>Adiponectin (ug/ml) [†]</u>		<u>Insulin Sensitivity (M_{LBM}) (mg/kg/min)</u>	
	Age 15	Age 19	Age 15	Age 19
Mean age 13 waist (cm)	-.11 (.0006)	-.11 (.0012)	-.44 (.21)	-.43 (.15)
Change in waist (cm)*	-.032 (.27)	-.113 (.0005)	-.29 (.35)	-.35 (.18)

Values are β estimates (p-value) for dependent variable corresponding to 1 SD change in independent variable

^{*} [age 19-age 13] for age 19 dependent variables, [age 15-age 13] for age 15 dependent variables

[†] ln-transformed, slopes presented on the ln scale (therefore β s presented for adiponectin approximate percent change in adiponectin values per unit of the predictor variable)

[‡] each column represents a separate multiple linear regression analysis; additional covariates were race, sex, age at baseline, height at baseline, tanner at baseline