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Wrist Breadth and Homeostasis Model Assessment of Insulin Resistance in Youth: The Fels Longitudinal Study

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Abstract

Objectives—There is biological crosstalk between insulin signaling and bone remodeling pathways, and wrist circumference and bone area were recently found to associate with insulin resistance independent of body mass index (BMI) in overweight/obese children. We aimed to expand on this work by using more specific measures of adiposity for adjustment and examining children with broader range of BMI.

Methods—We used serial data (1,051 total measures) on 313 non-Hispanic white youth (ages 8–18 y) from the Fels Longitudinal Study with homeostasis model assessment of insulin resistance (HOMA-IR) as the outcome. Internal standard deviation score (SDS) for wrist breadth was evaluated as a predictor of HOMA-IR (log-transformed) before and after adjusting for internal-sample SDSs for BMI, waist circumference (WC), and total body fat (TBF) from dual energy X-ray absorptiometry, in addition to age, sex, Tanner stage, and birth year, using generalized estimating equations.

Results—Before additional adiposity adjustment, we found a significant positive association between wrist breadth SDS and log-transformed HOMA-IR ($\beta = 0.13$; 95%CI: 0.09–0.17), which remained significant after adjusting for TBF SDS ($\beta = 0.09$; 95%CI: 0.05–0.13; $P < 0.001$), BMI SDS ($\beta = 0.06$; 95%CI: 0.02–0.10; $P = 0.007$), and WC SDS ($\beta = 0.06$; 95%CI: 0.02–0.09; $P = 0.005$).

Conclusions—Further work is needed to determine whether simple frame size measures such as wrist breadth may be useful markers of metabolic risk.

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The rise in childhood obesity in the US from the 1970s onward paralleled concurrent increases in prevalence and incidence of cardiovascular and metabolic disorders in youth (De Ferranti and Osganian, 2007). There is strong evidence that insulin resistance (IR) is the earliest manifestation and the central driver of cardiometabolic dysfunction in children (Reaven, 1991; Chiarelli and Marcovecchio, 2008), so identifying children at high risk of IR is important for primordial prevention of cardiometabolic diseases later in life (Pereira and Ludwig, 2003).

A recent article by Capizzi et al. (2011) reported that measurement of wrist circumference explained greater variance in measures of IR than did BMI in a sample of overweight and obese children, suggesting that specific anthropometric skeletal frame-size measures may be predictive of IR. However, limiting the investigation to a restricted range of BMI may have biased the study toward alternative markers of IR other than BMI. In addition, BMI is at best an imperfect measure of adiposity during childhood (Maynard et al., 2001; Freedman et al., 2005), suggesting that residual confounding by adiposity may have been responsible for the reported association. Nevertheless, it is possible that measures of skeletal frame size in children are predictive of IR. Insulin concentration correlates with markers of bone formation (Basu et al., 2011), possibly via the effects of elevated insulin-like growth factor (IGF)-1 (Ferron et al., 2010; Fulzele et al., 2010). A recent meta-analysis demonstrated that individuals with type 2 diabetes have higher bone mineral density (Ma et al., 2012). It is unknown if particular frame-size measures are correlated with IR better than others during childhood, and whether associations between bone measures and IR are explained by adiposity.

Thus, the objectives of the current study were to (1) determine if IR has a stronger correlation with wrist breadth than other skeletal frame size measures, and (2) test whether wrist breadth is associated with IR in children independent of BMI, WC, and objectively measured fat mass.

METHODS

Study population

We used serial data (1,051 total measures) on 313 non-Hispanic white youth (ages 8–18 years) (160 males and 153 females) born between 1975 and 2002 in Southwestern Ohio, who were enrolled in the Fels Longitudinal Study. The Fels Longitudinal Study began in 1929 in Yellow Springs, Ohio as a study of normal child growth and development and continues today as a study of the early life antecedents of chronic diseases of aging and has been described in detail elsewhere (Roche, 1992). The 313 individuals in the analysis sample for this study were nondiabetic and selected on the basis of having at least one measurement of each weight, height, wrist breadth, waist circumference, Tanner stage of sexual development (staging 1–5 using pubic hair) (Tanner, 1962), and fasting insulin and glucose between 8 and 18 years of age. Wrist breadth was taken on the left hand, which was the nondominant hand for 89.1% of participants. Wrist breadth was not significantly different for dominant versus nondominant hand ($p = 0.38$). Wrist breadth, birth year, and the proportion of girls to boys were not materially different in the analysis sample than in

the entire data set of individuals born between 1975 and 2002, as determined by an unpaired two-sample *t* test ($p > 0.06$).

The study was conducted according to the guidelines of the Helsinki Declaration. The Wright State University Institutional Review Board approved all protocols and informed consent documents used in the Fels Longitudinal Study. All parents/guardians subjects provided written consent and minors provided verbal assent, as well as written consent. In the case of infants and children under 8 years of age, parents provided written consent for data collected from their offspring at each examination.

Anthropometry

Anthropometric parameters were assessed at each visit. Height was measured to 0.1 cm on a Holtain stadiometer (Seritex, Carlstadt, NJ), and weight was measured to 0.1 kg on an electronic scale. A metric tape measure was used to measure waist circumference (WC) at the level of the anterior-superior iliac crest (National Center for Health Statistics, 1996). Body breadths were measured at the shoulders (biacromial breadth), knee (bicondylar, femur), elbow (bicondylar, humerus), and wrist (bistyloid breadth) to the last completed 0.1 cm with the use of a sliding caliper (Holtain). These data were collected using procedures in the third National Health and Nutrition Examination Survey (Lohman et al., 1988) and the *Anthropometric Standardization Reference Manual* (National Center for Health Statistics, 1996).

Body composition

Total-body bone mineral content (in kg) and total body fat (TBF; in kg) were obtained from dual energy X-ray absorptiometry (DXA) using the DPX system from the Lunar Corporation with DPX software version 3.6z.

Serum biochemical assays

Blood samples were collected following a minimum 8 h of fasting. Serum concentrations of insulin (microunits per milliliter) were measured using the Diagnostic Products Corporation (DPC, Los Angeles, CA) Coat-A-Count Insulin Radioimmunoassay (RIA) kit at the College of American Pathologists (CAP) certified Medical Research Laboratories (Highland Heights, KY) following the Clinical and Laboratory Standards Institute (CLSI) guideline. Glucose concentrations (milligrams per deciliter) were measured using the VITROS GLU DT method (Ortho-Clinical Diagnostics, Raritan, NJ) (coefficient of variation = 1.8%). We calculated homeostasis model assessment of insulin resistance (HOMA-IR) using the following formula:
fasting insulin concentration (IU/L) × fasting glucose concentration (mg/dL) / 405
(Matthews et al., 1985).

Statistical analysis

Individuals in the analytic sample had a median number of 5 (range 1–10) recordings for each aforementioned study variable. All variables were assessed for non-normality by checking skewness (>1). The dependent variable, HOMA-IR, was log-transformed. Internal standard deviation (SD) scores [(observed value – sample mean)/(sample SD)] for each of

the anthropometric indicators and total body fat were calculated using pooled means and SD across all ages so that all variables were on the same scale, thereby allowing comparisons between dimensions. We decided a priori to use the last serial measurement of each subject to evaluate characteristic differences between sexes, using a two-sample t test, and to calculate Spearman correlation coefficients for the frame size measures and bone mineral content with HOMA-IR before (r) and after (partial r) adjustment for age, sex, Tanner stage, and birth year. In a separate model we additionally adjusted Spearman correlations coefficients for total body fat to determine the correlation between the variables and HOMA-IR independent of adiposity. We used the Steiger's z to test the null hypothesis that the (correlated) correlation coefficients for frame size measures were not significantly different from each other (Hardin and Hilbe, 2003).

As serial measures are correlated within each individual over time, and thus violate the assumption of independence necessary for general linear regression, generalized estimating equations (GEE) were fitted using the GENMOD procedure in SAS (Meng et al., 1992). The outcome was log-transformed HOMA_{IR} and the primary exposure variable was wrist breadth SD scores. This approach models the within-individual similarity of residuals, and uses this estimated correlation to re-estimate regression parameters and calculate robust standard errors. We tested a number of matrices, including exchangeable and autoregressive [AR(1)], and found that an AR(1) structure, which specifies that the correlation between two measurements in a series of measurements is an exponential function of their distance from one another, resulted in the best fitting models.

The total variance of HOMA-IR explained by each GEE model was estimated by an extension of R^2 statistics for GEE models (the marginal R^2) proposed by Zheng (2000):

$$R^2_{Marginal} = 1 - \frac{\sum_{t=1}^T \sum_{i=1}^n (Y_{it} - \hat{Y}_{it})^2}{\sum_{t=1}^T \sum_{i=1}^n (Y_{it} - \bar{Y}_{it})^2} \quad (1)$$

using a SAS macro created by Tan et al. to calculate this measure (Tan et al., 2009). Through this approach, we calculated marginal R^2 for each of four separate GEE models. In Model 1 we adjusted for potential confounders: age (continuous), sex, Tanner stage (1–5), and year of birth (continuous). In Model 2, Model 3, and Model 4 we included the variables in Model 1 plus TBF SDS, BMI SDS, and WC SDS, respectively, to determine if the association between wrist breadth SDS and HOMA-IR is confounded or mediated by adiposity. Model fit was assessed using the Quasi likelihood under the Independence model Criterion (QIC), which is analogous to the Akaike's Information Criterion statistic used for comparing models' fit with likelihood based methods, and also the QICu, which adds a penalty for the number of parameters and will approximate the QIC when the GEE is correctly specified.

Finally, we evaluated effect measure modification by stratifying on sex, age (split at median), and BMI (split at median), and by using the Wald chi-square test for interaction

terms in the model. The significance level for all tests was $P < 0.05$, and all analyses were conducted in SAS version 9.1 (SAS Institute, Cary, NC).

RESULTS

Mean and SD for normally distributed, and median and 25th and 75th percentile for non-normally distributed, variables are presented in Table 1. The mean age and median year of birth of the males and females were not significantly different. Males were significantly taller with greater sitting height than females and had significantly broader wrists, shoulders, elbows, and knees than did females. Females had significantly greater total body fat and lower bone mineral content than males. The differences between the sexes in this sample were as expected for normal youth, reflecting the basic sexually dimorphic patterns in body size and composition among males and females.

The Spearman correlation coefficients for frame size measures and bone mineral content with HOMA-IR before (r) and after (partial r) adjustment for total body fat (Model 2) are presented in Table 2. From a descriptive standpoint, the hip circumference and knee breadth appeared to be the frame size measures most strongly correlated with HOMA-IR before and after adjustment for age, sex, Tanner stage, and birth year (Model 1). However, after adjustment for total body fat, measured by DXA, wrist breadth appeared to be the frame size measure most strongly correlated with HOMA-IR (Model 2).

The results of the multivariable (age, sex, Tanner stage, and birth year) GEE regression analyses for wrist breadth SDS and HOMA-IR before and after additional adjustment for total body fat from DXA SDS, BMI SDS, and WC SDS are presented in Table 3. Before adjustment for adiposity measures, the multivariate model with wrist breadth SDS alone accounted for 9% of the variance in HOMA-IR, and the beta-coefficient for log-transformed HOMA-IR ($\beta = 0.13$; 95% CI: 0.09, 0.17) was significant ($P < 0.0001$). The association between wrist breadth SDS and HOMA-IR was attenuated but remained statistically significant after additional adjustment for adiposity measures, including total body fat from DXA SDS, BMI SDS, and WC SDS. The addition of these adiposity measures significantly improved the variance explained (R^2) for each model, and each had a larger standardized β coefficient than wrist breadth. In stratified analyses, observed associations were not modified by sex, age, or BMI (results not shown).

DISCUSSION

In this sample of non-Hispanic white youth aged 8–18 years, wrist breadth was associated with HOMA-IR independent of adiposity measures. Moreover, the correlation between wrist breadth and HOMA-IR appeared to be stronger than other frame size measures after adjusting for objectively measured total body fat.

Our finding that wrist breadth is associated with HOMA-IR independent of adiposity measures is largely consistent with the only previous study, to our knowledge, to test whether skeletal dimensions of the wrist are associated with insulin sensitivity phenotypes in children (Capizzi et al., 2011). In a sample of overweight/obese Italian youth, Capizzi et al. reported that wrist circumference was associated with HOMA-IR independent of BMI and

WC, and that wrist circumference explained a greater portion of the variance in HOMA-IR than BMI (variance explained was not provided in the WC model). In our sample of youth with a wide range of BMI (including normal weight, overweight, and obese children), we found that wrist breadth was associated with HOMA-IR independent of adiposity measures, *yet* wrist breadth explained less variance in HOMA-IR than BMI, WC, or total body fat measured by DXA.

Capizzi et al. used wrist circumference, while in our study only wrist breadth was available for analysis. Wrist breadth, a measure of bone diameter, may be more specific to bone size than wrist circumference because there is less chance for residual confounding by soft tissue included in the wrist circumference. Fortunately, Capizzi et al. were able to account for influence of bone vs. nonbone mass by confirming their findings using axial CT images of the wrist. Imaging data were not available in our study. We believe, however, that wrist breadth is a meaningful proxy for bone size; previous research by Himes and Bouchard (1985) and Chumlea et al. (2002) reported that wrist breadth is the bone measure least correlated with total body fat and weight. Others have also found that wrist breadth is a good anthropometric parameter to evaluate cross-sectional area of long bones in children without being severely confounded by other tissues (Ferrante et al., 1993). Nonetheless, differences in results between this study and previous work (Capizzi et al., 2011) may be due to the different anthropometric indicators used.

The previous finding that wrist circumference had explained more variance in HOMA-IR than did BMI might be the result of restricting the range of data with respect to an explanatory variable (here, BMI). If one restricts a sample on an explanatory variable that is related to the outcome variable (here, HOMA-IR), then the variance in the outcome variable explained by that restricted explanatory variable will be reduced in comparison with an unrestricted explanatory variable. An issue with extrapolating correlation coefficients to the general population from restricted samples is the chance for spurious false-positive associations (Goodwin and Leech, 2006). Due to these concerns, regression in a non-restricted sample is the preferred approach for comparing the association between two explanatory variables and an outcome variable.

Our findings likely reflect the biological interplay of the bone remodeling and insulin signaling pathways. In supplementary analyses, we found that the association between wrist breadth and HOMA-IR was not explained by total bone mineral content (data not shown). Unlike the Italian study (Capizzi et al., 2011), we did not have measures of transversal bone area in the wrist to directly evaluate whether bone mineral status at that specific region explains the observed association. Nevertheless, these findings suggest that insulin may have an anabolic role in bone growth, but not necessarily total bone content. Whereas IGF-1 signaling pathway is a well-established bone anabolic agent, evidence for the role of insulin in bone remodeling is just now emerging (Fulzele et al., 2007; Kawai and Rosen, 2009; Fulzele et al., 2010; Basu et al., 2011). It has been recently shown that insulin has an anabolic effect on bone due to its structural homology with IGF-1, allowing for binding with the IGF-1 receptor in osteoblasts (Kawai and Rosen, 2009). Insulin also binds to insulin receptor/IGF-1 hybrid receptor at physiologically relevant concentrations and this hybrid receptor behaves like IGF-1 receptor (Fulzele et al., 2007). Moreover, insulin, acting

through its own cognate receptor, insulin receptor, acts as an anabolic agent in osteoblasts in vivo and in vitro, providing further support to the notion that the insulin regulatory system is involved in communication between metabolic control and bone remodeling (Fulzele et al., 2010; Basu et al., 2011), and suggesting a possible physiologic mechanism explaining the observed associations.

There are several caveats to consider in the current research. HOMA-IR is not the most sensitive measure of insulin resistance, e.g., it may not detect children with high insulin resistance combined with β -cell failure. Unfortunately, oral glucose tolerance tests or glucose clamps were not performed in our study participants. Our study was also unable to determine temporality in the wrist breadth-insulin resistance association; we examined serial concurrent measures of frame size and HOMA-IR. The current study also did not address the myriad causal factors, e.g., physical activity, that may have led to the differences in wrist breadth. It should also be noted that the vast majority of the children in our study are healthy and not insulin resistant, per se. Thus, while our findings support a positive biologic association between wrist breadth and a measure of insulin resistance, future research is needed to determine if wrist measures add to the prediction of overt insulin resistance. Finally, our study sample was exclusively of non-Hispanic white children born in southwestern Ohio, thus limiting the generalizability of the results to other ethnic groups.

Here, we provide evidence that, in childhood, wrist breadth is associated with a measure of insulin resistance after adjusting for adiposity measures and other potentially confounding variables. These findings lend support to the hypothesis that elevated insulin during childhood may alter bone growth, and they offer insight into the small but growing literature on this topic by suggesting that this association is independent of objectively measured adiposity in children over the full range of BMI. Yet, unlike the previous study on this topic (Capizzi et al., 2011), which measured wrist circumference, in our study wrist breadth explained less variance in HOMA-IR than measures of adiposity. Larger prospective studies are needed to determine if wrist measures during childhood improve prediction of insulin resistance and cardiometabolic disease risk in adulthood.

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TABLE 1

Characteristics of youth aged 8 to 18 years in the Fels Longitudinal Study.

Variable	Males (<i>n</i> = 160)	Females (<i>n</i> = 153)
Birth year (median; 25th, 75th percentile)	1989 (1983 (1994)	1988 (1983 (1994)
Chronological age (years)	11.93 (2.52)	11.65 (2.47)
Tanner stage (median; 25th, 75th percentile)	5.0 (4.0, 5.0)	5.0 (4.0, 5.0)
Wrist breadth (cm)	5.46 (0.50)	4.93 (0.30) ^b
Stature (cm)	152.73 (15.90)	148.73 (12.95) ^c
CDC SDS-Stature ^a	0.41 (0.94)	0.34 (1.11)
Weight (kg)	46.82 (18.00)	43.32 (13.37)
CDC SDS-Weight ^a	0.39 (1.14)	0.29 (1.05)
BMI (kg/m ²)	19.43 (4.48)	19.16 (3.55)
CDC SDS-BMI ^a	0.29 (1.20)	0.20 (1.06)
DXA body fat (kg)	13.37 (10.06)	17.00 (7.68) ^b
DXA bone mineral content (kg)	2.32 (0.70)	1.95 (0.47) ^b
Shoulder breadth (cm)	37.82 (3.94)	35.44 (2.66) ^b
Elbow breadth (cm)	6.82 (0.65)	6.09 (0.42) ^b
Knee breadth flexed (cm)	9.74 (0.80)	9.01 (0.64) ^b
Abdominal circumference (iliac; cm)	79.80 (14.43)	78.17 (11.23)
Hip circumference (cm)	92.35 (12.30)	93.92 (10.86)
Sitting height (cm)	89.02 (7.60)	85.30 (5.92) ^b
HOMA-IR (median; 25th, 75th percentile)	1.7 (1.1, 2.60)	1.9 (1.3, 2.6)
Insulin (Iu/mL; median; 25th, 75th percentile)	8.1 (5.3, 11.9)	9.1 (6.5, 12.0)
Fasting glucose (mg/dL; median; 25th, 75th percentile)	86.0 (81.0, 92.0)	83.0 (79.0, 88.0)

Data are presented as mean (standard deviation) for normally distributed variables and median (25th, 75th percentiles for non-normally distributed variables. Values used are from the last of the serial measures in 313 participants. Overweight and obesity are based on the CDC growth charts age- and-sex-specific 85th and 95th percentiles, respectively, for BMI.

^a Stature-SDS, BMI-SDS, and weight-SDS are based on the CDC growth charts age-and-sex-specific percentiles.

^b Means were significantly different between sexes at the alpha = 0.01 level.

^c Means were significantly different between sexes at the alpha = 0.05 level.

Spearman univariate correlations and multivariate adjusted partial correlations of frame size variables and bone mineral content with HOMA-IR in youth from the Fels Longitudinal Study

TABLE 2

Variable	R	P	Model 1 Partial r	P	Model 2 Partial r	P
Bone mineral content	0.155	0.006	0.141	0.014	0.036 ^a	0.534
Wrist breadth (cm)	0.200	<0.001	0.294	<0.001	0.220 ^a	<.001
Knee breadth (cm)	0.292	<0.001	0.361	<0.001	0.160 ^a	0.005
Elbow breadth (cm)	0.189	<0.001	0.251	<0.001	0.108 ^a	0.060
Biacromial breadth (cm)	0.202	<0.001	0.293	<0.001	0.190 ^a	0.001
Hip circumference (cm)	0.385	<0.001	0.388	<0.001	0.130 ^a	0.023
Sitting height (cm)	0.172	0.002	0.211	<0.001	0.153 ^a	0.007
Height (cm)	0.124	0.028	0.174	0.002	0.124 ^a	0.030

All correlations use last of the serial measurements from children in the study.

Correlations with the same letter (*a/b*) are *not* significantly different from each other.

Model 1, partial correlations were adjusted for age, sex, Tanner stage, and year of birth.

Model 2, partial correlations were adjusted for age, sex, Tanner stage, year of birth, and total body fat from DXA.

TABLE 3

Generalized estimating equations for explaining the variance in HOMA-IR in youth from the Fels Longitudinal Study

Variable	β^b (95% CI)	<i>p</i>	Model 1 + DXA fat SDS ($R^2 = 0.20$)	Model 1 + BMI SDS ($R^2 = 0.22$)	Model 1 + WC SDS ($R^2 = 0.23$)
HOMA-IR					
WB SDS	0.13 (0.09–0.17)	<0.0001	0.09 (0.05–0.13)	<0.007	0.06 (0.02–0.09)
DXA fat SDS			0.14 (0.11–0.18)		
BMI SDS				0.18 (0.14–0.22)	
WC SDS					0.18 (0.15–0.22)

All GEE models use 1,051 serial measurements from 313 youth in the study.

Abbreviations: WB, wrist breadth; WC, waist circumference; BMI, body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; CI, confidence interval

HOMA-IR was log₁₀ transformed to normalize its distribution.

To compare all parameters on the same scale, we standardized wrist breadth (WB), DXA fat, BMI, and waist circumference (WC) using a standard deviation score (SDS) for each variable.

All models were adjusted for wrist breadth, age, sex, Tanner stage, and birth year.

All models were fit with Gaussian generalized estimating equations with identity link and AR(1) correlation structure.

^a R^2 corresponds to the percentage of the variance explained when each variable is added to the model.

^b β corresponds to a one standard deviation change in the parameter.