Wrist Circumference Is a Clinical Marker of Insulin Resistance in Overweight and Obese Children and Adolescents

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Background—Excess fat is one of the main determinants of insulin resistance, representing the metabolic basis for developing future cardiovascular disease. The aim of the current study was to find an easy-to-detect clinical marker of insulin resistance which can be used to identify young subjects at increased risk of cardiovascular disease.

Methods and Results—Four-hundred and seventy-seven overweight/obese children and adolescents (mean age 10.31±2.80 years) were consecutively enrolled. Standard deviation score body mass index, fasting biochemical parameters, and homeostasis model assessment of insulin resistance were evaluated. Statistical differences were investigated using multiple linear regression analysis. Manual measure of wrist circumference was evaluated in all children and adolescents. Fifty-one subjects, randomly selected, underwent nuclear magnetic resonance imaging of the wrist to evaluate transversal wrist area at the Lister tubercle level. A statistically significant association was found between manual measure of wrist circumference and insulin levels or homeostasis model assessment of insulin resistance (β=0.34 and 0.35, respectively; $P<10^{-5}$ for both comparisons). These associations were more significant than those between SD score body mass index and insulin levels or homeostasis model assessment of insulin resistance (β=0.12 and 0.10, respectively; P≤0.02 for both comparisons). Nuclear magnetic resonance imaging acquisition clarified that the association between wrist circumference and insulin levels or homeostasis model assessment of insulin resistance reflected the association with bone tissue-related areas (P≤0.01 for both) but not with the adipose tissue ones ($P>0.05$), explaining 20% and 17% of the variances of the 2 parameters.

Conclusions—Our findings suggest a close relationship among wrist circumference, its bone component, and insulin resistance in overweight/obese children and adolescents, opening new perspectives in the prediction of cardiovascular disease. **(*Circulation*. 2011;123:1757-1762.)**

Key Words: obesity ■ overweight ■ cardiovascular disease ■ insulin resistance ■ anthropometry

Atherosclerotic cardiovascular (CV) disease is the number one killer in the adult population of Western societies,[1] but the pathological processes and risk factors associated with its development have been shown to begin during childhood.[2]

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Evidence shows that excess of fat is one of the most frequent determinants of early comorbidities in children, including hypertension, dyslipidemia, and insulin resistance[3] that is primarily associated with CV risk factors when interacting with body fatness.[4] Today, one of the major priorities of clinical practice is the identification of young people at increased risk for obesity- and insulin resistance–related complications because in children anthropometric measures, based on adipose tissue distribution, present some limitations relative to the prediction of insulin resistance and CV risk.[5,6]

Several studies show that hyperinsulinemia is associated with increased bone mass.[7,8] The mechanism, by which insulin acts as a growth factor, has become clearer with the discovery of insulin-like growth factor 1 (IGF-1), a regulator of osteoblastic proliferation, differentiation, and bone matrix apposition, which shows 40% similarity in amino acid structure with insulin.[9] Recent studies from independent laboratories[10,11] showed that the insulin regulatory system mediates communication between metabolic control and bone remodeling.

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The circumference of the wrist could be a good parameter to analyze bone metabolism in relation to hyperinsulinemia, because (1) IGF-1 levels are major determinants of bone geometry, as demonstrated by their direct relationship with cross-sectional area of bone[12] and (2) wrist circumference is an easy-to-detect measure of skeletal frame size[13–15] without being severely confounded by body fat variation.[16] In view of these considerations, the aim of our study was to demonstrate a correlation between wrist circumference (an easy-to-detect bone anthropometric marker) and insulin resistance, opening new perspectives in the prediction of CV disease.

Methods

Study Population

Two independent data sets of 492 overweight/obese children and adolescents (241 boys and 251 girls; mean age 10.31±2.80 years, recruited from September 2008 to September 2009) and of 165 overweight/obese children and adolescents (78 boys and 87 girls; mean age 9.9±2.8 years, recruited from August 2010 to November 2010) were consecutively enrolled by the Center for Nutrition and Dietetics at the Department of Pediatrics, "Sapienza" University of Rome. Exclusion criteria were previous diagnosis of diabetes mellitus and/or endocrine diseases. The study protocol was approved by the ethical committee of the "Sapienza" University of Rome, and parents gave written consent for their children to participate in the study after being informed of its nature for 477 children (235 boys and 242 girls) of the first data set and 160 of the second data set (75 boys and 85 girls).

Anthropometric Measurements

In all children and adolescents, body weight, height, wrist circumference, and body mass index (BMI) were evaluated at entry. In the second data set of 160 children and adolescents, waist circumference was also evaluated.

Body weight, expressed in 0.1-kg intervals, was measured at fasting state in the morning. Harpenden stadiometers were used for body height, and every child was measured 3 times to the nearest millimeter according to the technique described by Cameron et al.[17] In brief, the subject stood straight, with feet placed together and flat on the ground, heels, buttocks and scapulae against the vertical backboard, and arms loose and relaxed with the palms facing medially. His head was carefully positioned in the Frankfurt plane, with the lower margins of the orbit in the same horizontal plane as the upper margin of the external auditory meatus.

Dominant wrist circumference was measured with subjects in a seated position using a tension-gated tape measure positioned over the Lister tubercle of the distal radius and over the distal ulna.[18] The Lister tubercle, a dorsal tubercle of the radius, can be easily palpated[19] at the dorsal aspect of the radius around the level of the ulna head,[20] about 1 cm proximal to the radiocarpal joint space.[21] A tension-gated tape measure was used to ensure equivalent tape pressure between subjects.

Body mass index was calculated as body weight divided by height squared (kg/m^2). The BMI of each individual was converted by smooth age-specific curves called L, M, and S to an SD score (SDS)[22] for the child's age, using Italian reference tables.[23] The M and S curves correspond to the median and coefficient of variation of the auxometric trait at each age, whereas the L curve allows for the age-dependent skewedness of the distribution of the same trait. The children were classified as overweight or obese on the basis of SDS-BMI using the cut-off proposed by Cacciari et al.[23] Waist circumference was measured with a flexible tape at the level of the umbilicus, and was recorded to the nearest millimeter.

The collection of anthropometric measurement data was performed by 2 health technicians, one being the examiner and the other the recorder. The 2 operators were trained for both roles. It was the recorder's role to assist the examiner in obtaining correct measurements, to recognize the potential errors in measurements performed by the observer, and to ensure that correct data were entered into the automated system.

Subjects were evaluated by a doctor for the pubertal stages. Tanner stage I was defined as prepuberty, Tanner stage II to IV as midpuberty, and Tanner stage V as postpuberty.[24]

Clinical and Biochemical Parameters

In all children and adolescents, fasting glucose, fasting insulin levels, and lipid profiles were evaluated at entry. Serum total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were determined by a Technicon RA-1000 Autoanalyzer. Glucose levels were determined by the glucose oxidase method (Autoanalyzer, Beckman Coulter, Brea, CA). Serum insulin was measured by radioimmunoassay (Adaltis Insulin Kit, Bologna, Italy). Insulin resistance was estimated according to the homeostasis model assessment of insulin resistance (HOMA-IR).[25]

Magnetic Resonance Imaging Acquisition

Fifty-one subjects randomly selected from the 477 overweight/obese children and adolescents gave their consent to undergo nuclear magnetic resonance imaging (NMR). All examinations were performed on a commercially available open magnetic resonance imaging scanner with a permanent magnet (E-scan Opera, Esaote SpA, Genoa, Italy) equipped with a hand/wrist coil (Esaote SpA). This is a low-field 0.2 Tesla magnetic resonance imaging opened system that allows dedicated imaging of extremities and small body parts such as the wrist joint. Children were placed in a supine (decubitus) position, and the wrist was placed into the magnetic resonance dedicated coil for assessment of circumference. Use of positioning pads inside the magnetic resonance coil was minimized to avoid subcutaneous fat compression and deformation.

Images After Processing and Measurements

Magnetic resonance images were analyzed by a radiologist. Measurements were performed on the first slice in which there was the best evidence of the Lister tubercle (qualitative method). The choice to perform these measurements at the Lister tubercle level was made to provide a standard landmark for the axial images. This finding is consistent with the known lower morphological variability of the tubercle during skeletal growth in childhood and adolescence.[19,26]

The following parameters were assessed:

- Transversal wrist internal (TWI) bone tissue area measured by manual drawing of internal subcutaneous tissue profile on the bony and ligamentous side (square millimeter value is provided by measurement software).
- Transversal wrist external (TWE) adipose tissue area is computed by subtracting TWI area from the total transversal wrist (TTW) area: TWE=TTW−TWI.

An example of the measurement is displayed in the Figure.

Statistical Analysis

Statistical analysis was performed using SPSS statistical software (version 15; SPSS, Chicago, IL). Data are expressed as means±SD. Data for fasting insulin, HOMA-IR, and triglyceride levels were transformed using log base 10 to normalize their distributions for all analyses. The dependent variables for this study were fasting insulin, HOMA-IR, and triglycerides. Independent variables were SDS-BMI, wrist circumference, TWI bone tissue area, and TWE adipose tissue area. Multiple linear regression analyses were used to investigate the influence of independent variables on the variance of insulin resistance parameters and levels of triglycerides. The unstandardized (β) coefficients are the coefficients of the estimated regression model. (The standardized coefficients are an attempt to make the regression coefficients more comparable.) Stepwise model building was used to estimate the relative contribution of the independent variables and the variability of the dependent variable.

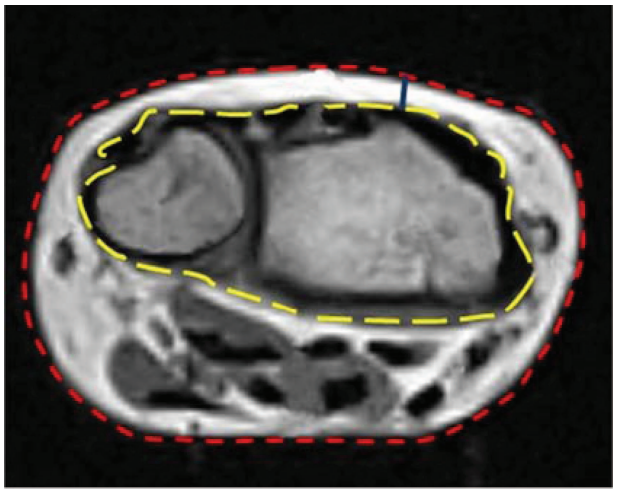

Figure. An example of NMR (nuclear magnetic resonance imaging). Dashed small red line: total transversal wrist (TTW) area. Dashed large yellow line: transversal wrist internal (TWI) bone tissue area.

The change in R^2 is the increased percentage of the variation explained when each variable was added to the model. The test collinearity diagnostics indicated that wrist circumference and SDS-BMI could be used in the same regression model.

Multiple linear regression analysis was performed using fasting insulin and HOMA-IR as dependent variables and TWI bone tissue area and TWE adipose tissue area as independent variables. We included the pubertal stage and gender in the regression analysis. Data with a P value <0.05 were considered statistically significant.

Results

Results of the multiple regression analysis performed on the first data set of 477 children and adolescents, using fasting insulin, HOMA-IR, and triglycerides as the dependent variables, are reported in Table 1. Fasting insulin and HOMA-IR were significantly associated with wrist circumference (β=0.34 and 0.35, respectively; $P<10^{-5}$ for both comparisons) and SDS-BMI (β=0.12 and 0.10, respectively; P≤0.02 for both comparisons) whereas triglyceride levels were associated only with wrist circumference ($P<10^{-5}$). After performing the same analysis without wrist circumference, an association between triglyceride levels and SDS-BMI was obtained (P=0.017; data not shown).

Table 1. Multiple Regression Analysis Models for Explaining the Variance of Biochemical Parameters and Derived Index of 477 Overweight/Obese Children and Adolescents

Variable	β	β±SE	P*	R^2 Change
Fasting insulin, mU/mL				
Wrist circumference	0.34	0.07±0.009	$<10^{-5}$	0.12
SDS-BMI	0.12	0.06±0.02	0.01	0.007
HOMA-IR, AU				
Wrist circumference	0.35	0.08±0.009	$<10^{-5}$	0.123
SDS-BMI	0.10	0.06±0.02	0.02	0.01
Triglycerides, mmol/L				
Wrist circumference	0.22	0.04±0.008	$<10^{-5}$	0.05
SDS-BMI	0.06	0.03±0.02	0.2	

All biochemical parameters were $\log_{10}$ transformed to normalize their distributions. Independent variables were SDS-BMI and wrist circumference.

R^2 change indicates the increased percentage of the variation explained when each variable is added to the model; SDS-BMI, SD score body mass index; HOMA-IR, homeostasis model assessment of insulin resistance; and AU, arbitrary units.

*All data were adjusted for Tanner stage and sex.

Table 2. Multiple Regression Analysis Examining Independent Contributions of Different Sections of Transversal Areas in 51 Children and Adolescents by NMR

Variable	β	P*	R^2 Change
Fasting insulin, mU/mL			
TWI bone tissue area, mm^2	0.45	0.007	0.20
TWE adipose tissue area, mm^2	−0.10	0.49	
HOMA-IR, AU			
TWI bone tissue area, mm^2	0.41	0.01	0.17
TWE adipose tissue area, mm^2	−0.12	0.52	

All biochemical parameters were $\log_{10}$ transformed to normalize their distributions.

NMR indicates nuclear magnetic resonance imaging; R^2 change, the increased percentage of the variation explained when each variable is added to the model; TWI, transversal wrist internal; TWE, transversal wrist external; HOMA-IR, homeostasis model assessment of insulin resistance; and AU, arbitrary units.

*All data were adjusted for Tanner stage and sex.

Wrist circumference and SDS-BMI together explained ≈13% of the variance of fasting insulin levels and 13.3% of the variance of the HOMA-IR index. To evaluate the contribution of wrist circumference and SDS-BMI, respectively, to explained variance (R^2) of insulin levels and the HOMA-IR index, we used the stepwise method (Table 1). The first step, which incorporated only wrist circumference, explained 12% of the total variance of fasting insulin levels and 12.3% of the total variance of HOMA-IR; the second step, which include wrist circumferences and BMI, produced an increase of the variance of only ≈1% for both dependent variables. Wrist circumference explained 5% of the variability in triglyceride levels and was the only significant contributor to the triglyceride levels.

Table 2 shows the results of 51 children and adolescents who underwent an NMR scan to evaluate the independent contributions of different sections of transversal wrist areas. The NMR acquisition clarified that the association between insulin levels and wrist circumference or HOMA-IR reflected the association between insulin levels or HOMA IR with TWI bone tissue area (P≤0.01 for both), but not with the TWE adipose tissue area (P=0.49 and P=0.52, respectively), explaining 20% and 17% of the variances of the 2 metabolic parameters, respectively. Moreover, we found that TWI bone tissue area and TWE adipose tissue area were not significant determinants for triglyceride levels ($P>0.05$ for both comparisons; data not shown).

In order to evaluate the contribution of wrist circumference and waist circumference respectively to the explained variance (R^2) of insulin levels and HOMA-IR index, we recruited a second data set of 160 overweight/obese children and adolescents. Before performing the linear regression analysis, using fasting insulin as the dependent variable and wrist circumference and waist circumference as independent vari-

ables, we demonstrated the presence of a severe collinearity (ill conditioning) and a strong correlation ($r=0.75$) between the 2 parameters, obtaining a condition index of 39.[27] The presence of high collinearity between waist and wrist circumference prevents any attempt to compare the effect of the variables in the same regression model. Therefore the 2 variables were analyzed separately by multiple regression analysis. We observed that both were significantly associated with insulin resistance parameters: $P=0.039$ and $P<0.01$, respectively (data not shown).

Discussion

The present study provides the first evidence that the measurement of wrist circumference, reflecting the TWI bone tissue area, is highly correlated with measures of insulin resistance in a population of overweight/obese children and adolescents. Insulin resistance is believed to play a central role in the pathogenesis of the metabolic syndrome, and its prevalence in the pediatric population is increasing, particularly among obese children and adolescents.[28] Current recommendations for the management of childhood metabolic syndrome suggest testing any child classified as obese on the basis of BMI for metabolic/CV risk factors.[29,30] Nevertheless, BMI in adulthood and SDS-BMI in childhood are not a measure of fatness, but an index of adiposity. Thus, there may be a risk of underestimating the excess of fat in children classified as overweight.[31] On the other hand, not all obese children are at increased risk for metabolic/CV diseases. Therefore, BMI per se has a limited predictive value.

Waist-to-height ratio is a more sensitive and specific index for detecting a higher likelihood of developing metabolic and CV risk among overweight/obese children,[32] being more closely associated with central body fat distribution than with total adiposity.[33] However, waist circumference is subject to significant interoperator variability, is influenced by sex, race, or ethnicity, and in children explains only 25% to 50% of the variation in intra-abdominal adipose tissue,[34,35] the adipose tissue most closely associated with CV risk factors.[36] Thus, waist circumference could potentially lead to misclassifying patients as having obesity-related comorbidities.[37] Because commonly used anthropometric measures, based on adipose tissue distribution, present these difficulties, we sought, in our study, another tissue marker of insulin resistance in children by exploring the relation between bone tissue and hyperinsulinemiasulinism.

In vitro studies have demonstrated that insulin may have anabolic effects on bone formation by stimulating osteoblastic proliferation and inhibiting osteoclastic proliferation.[9] Insulin and IGF-1 are similar in amino acid structure, allowing low-affinity binding between insulin and IGF-1 cell-membrane receptors and vice versa,[9] and IGF-1 is a well known regulator of childhood bone mass growth.[12]

The circumference of the wrist is a good anthropometric parameter to evaluate cross-sectional area of long bones without being severely confounded by other tissues,[16] and it is an easy and well known index of skeletal frame size. Our findings show that wrist circumference explained a greater variance in insulin resistance compared to SDS-BMI in a population of overweight/obese children and adolescents, although SDS-BMI and wrist circumference were both significantly associated with fasting insulin and HOMA-IR index.

We also observed an association between SDS-BMI and triglyceride levels. These results are in line with other studies, which found a significant association between BMI and triglyceride levels.[38,39] Nevertheless, after performing the stepwise multiple regression analysis with SDS-BMI and wrist circumference as independent variables to explain the variance of triglyceride levels, only wrist circumference was a significant predictor. These results showed that wrist circumference is a better predictor than SDS-BMI of insulin resistance measures and of triglyceride levels in overweight/obese children and adolescents. We have tested the conclusions of our study in more detail by examining a further sample of 160 overweight/obese children and adolescents. In this second data set, we evaluated the contribution of wrist circumference and waist circumference, respectively, to the explained variance (R^2) of insulin levels and HOMA-IR index. Before performing the linear regression analysis, we demonstrated the presence of a severe collinearity between the 2 parameters. When 2 variables are highly correlated, they both convey essentially the same information. In this case, neither may contribute significantly to the model after the other one is included.[40] Wrist and waist circumference were then analyzed separately by multiple regression analysis, and we observed that both were significantly associated with insulin resistance. The second original finding of our study is that the association of wrist circumference with insulin resistance is explained only by the bone tissue of the wrist, not by the adipose tissue of the wrist, reflecting the anabolic role of insulin on transversal bone growth.

Because the process of aging is related to impairment of insulin action on target cells, we decided to analyze subjects during their growth, when bone tissues are necessarily sensitive to the anabolic action of insulin.[41] With respect to obesity, we decided to examine a population of obese children because the effect of insulin resistance on tissue growth may be dependent on BMI in children. In fact, it has been determined that insulin resistance in childhood is associated with increased left ventricular mass if it interacts with body fatness.[42]

The interaction between childhood insulin resistance and BMI is expressed even when obese children reach adulthood, because CV risk factors are maintained during adult life for those children and adolescents who remained in the highest categories of obesity.[43] This evidence suggests that interventions directed at identifying and treating insulin resistance, in addition to weight loss, may be required to alter early development of CV risk.

The wrist circumference parameter is easily accessible and measurable by the doctor, minimizing the collaboration needed by the obese patient; furthermore, its reproducibility is higher compared with waist circumference. In fact, despite the widespread use of waist circumference measurements, there remains no uniformly accepted measurement protocol, resulting in a variety of techniques employed throughout the published literature.[44] Therefore, taking into account the high collinearity between the 2 parameters, the wrist circumfer-

ence could be considered in the classification of obesity for the prediction of insulin resistance and, potentially, CV risk. These observations, suggesting the presence of a close relationship among wrist circumference, TWI bone tissue area, and insulin resistance in overweight/obese children and adolescents, open new perspectives in the prediction of CV risk.

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Disclosures

None.

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CLINICAL PERSPECTIVE

One of the major priorities of clinical practice is to identify young people at increased risk for obesity and insulin resistance, representing the metabolic basis for future cardiovascular disease. This study introduces a new clinical marker of insulin resistance in overweight/obese children and adolescents: the wrist circumference. This measurement has been historically included in the calculation of frame size, which is a parameter in evaluating the free fat mass to correct misclassification introduced by the use of body mass index. We produce the first evidence that wrist circumference is highly correlated with insulin resistance parameters (fasting insulin and homeostasis model assessment of insulin resistance index) in a population of overweight/obese children and adolescents. The association of wrist circumference with insulin resistance is explained only by the transversal wrist bone tissue–related areas and not by the wrist adipose tissue ones, reflecting the anabolic role of insulin on transversal bone growth. Wrist circumference is easily accessible and measurable by the doctor, minimizing the collaboration required of the patient, and its reproducibility is higher than that of waist circumference. Therefore, taking into account the high collinearity between the 2 parameters, wrist circumference could be considered in the classification of obesity for the prediction of insulin resistance and cardiovascular risk. The identification of youths with increased risk for insulin resistance–related complications could be achieved with minimal effort by measuring wrist circumference, thus avoiding testing the entire population of overweight/obese children for insulin resistance. Our findings open new perspectives in the prediction of cardiovascular risk.

Wrist Circumference Is a Clinical Marker of Insulin Resistance in Overweight and Obese Children and Adolescents

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