

## Measurement of Insulin Sensitivity in Children: Comparison Between the Euglycemic Hyperinsulinemic Clamp and Surrogate Measures

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**Running Title:** Clamp vs. other measures of insulin sensitivity

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## ABSTRACT

*Objective:* This study compared fasting insulin and measures of insulin sensitivity based on fasting insulin and glucose (i.e., HOMA, QUICKI, FGIR) or triglycerides to the insulin clamp in a cohort of children/adolescents.

*Research Design and Methods:* The subjects were Minneapolis 5<sup>th</sup>-8<sup>th</sup> grade students. Euglycemic hyperinsulinemic clamps were performed on 323 at mean age 13 and repeated on 300 at mean age 15. Insulin sensitivity (M) was determined by glucose uptake (mg/kg/min) adjusted for lean body mass ( $M_{LBM}$ ) and steady state insulin ( $M_{LBM}/\ln$  SSI). Comparisons were made for the whole cohort and by body size (BMI <85<sup>th</sup>ile vs. BMI ≥85<sup>th</sup>ile). ROC curves tested whether specific fasting insulin cut-points separated true positive from false positive approximations of insulin resistance.

*Results:* Fasting insulin was significantly correlated with HOMA ( $r=0.99$ ), QUICKI ( $r=0.79$ ), FGIR ( $r=-0.62$ ) and [ $\ln$  fasting insulin +  $\ln$  triglycerides] (0.88). Correlations of the surrogates with  $M_{LBM}$  were significantly lower than M for the total cohort and ≥85<sup>th</sup>ile group. In general, correlations in the ≥85<sup>th</sup>ile group were higher than the <85<sup>th</sup>ile group. Correlations with  $M_{LBM}$  and  $M_{LBM}/\ln$  SSI decreased in the total cohort and ≥85<sup>th</sup>ile group from age 13 to 15. ROC curves showed only a modest capability to separate true from false positive.

*Conclusions:* Surrogate measures are only modestly correlated with the clamp measures of insulin sensitivity and do not offer any advantage over fasting insulin. In general, lower correlations are seen with  $M_{LBM}$  than M and with heavier than thin individuals.

The increasing prevalence of childhood obesity, the strong association between insulin resistance and obesity, and the relation of insulin resistance to the metabolic syndrome have led to an intense clinical and research interest in the measurement of insulin resistance in children (1-3). The “gold standard” method for measuring insulin resistance is the euglycemic-hyperinsulinemic clamp (4), in which a constant intravenous infusion of insulin is balanced by a simultaneous infusion of glucose in a clinical research setting. Because of the invasive, time-consuming nature of the clamp procedure, it is difficult to use in routine clinical practice or large epidemiologic studies, particularly in children.

In an attempt to simplify the measurement of insulin resistance, a number of surrogate measures, based on fasting levels of insulin and glucose, (i.e. the homeostasis model assessment [HOMA], the quantitative insulin-sensitivity check index [QUICKI], and the fasting glucose-to-insulin ratio [FGIR]) have been developed and widely used in adult (5-7) and, subsequently, pediatric studies). Others have used fasting insulin and triglycerides as the surrogate measures (8). However, only two studies have directly compared these surrogate measures to insulin clamp-derived measures of insulin resistance in children and adolescents (9, 10), and most studies have been in relatively small cohorts. Thus, there are ongoing questions about the validity of the surrogate measures and their applicability in the pediatric population.

The purpose of the present study was to compare fasting insulin (FI), HOMA, QUICKI, FGIR and  $[\ln \text{FI} + \ln \text{triglycerides}]$  to euglycemic insulin clamp measures of insulin resistance in a cohort of over 300 randomly selected children studied at mean age 13 and again at mean age 15 years. The results show that the surrogate measures do not offer any advantage over FI, they have

only a moderate correlation to the insulin clamp, their correlation to the insulin clamp is lower in thin than heavy children, and the correlation may change with increasing age.

## **RESEARCH DESIGN AND METHODS**

This study was approved by the University of Minnesota Committee for the Use of Human Subjects in Research. Informed consent was obtained from the parents and informed assent from the children. The subjects were participants in a longitudinal study of the relation between insulin resistance and cardiovascular risk factors in children. The original cohort was randomly recruited after blood pressure screening of Minneapolis 5<sup>th</sup>-8<sup>th</sup> grade public school children, as previously described (11). From this cohort, 323 insulin clamps were completed in pubertal children (Tanner Stage II or greater) at mean age  $13.1 \pm 1.2$  years. A second clamp was performed two years later in 300 of these participants at mean age  $15.0 \pm 1.2$  years.

Prior to each insulin clamp, participants underwent a clinic examination and Tanner staging, as determined by pubic hair development in boys and breast and pubic hair development in girls. The greater of the two values in the girls was used in order to avoid underestimation of pubertal maturation. Height was measured with a wall-mounted stadiometer, and weight was determined using a balance scale. BMI was calculated as the weight (kg) divided by the height (meters) squared. BMI percentiles were determined using the 2000 Centers for Disease Control and Prevention (CDC) BMI-for age percentiles growth charts (12). Triceps and subscapular skinfold thickness were measured twice to the nearest millimeter with Lange calipers, and the mean value was used to predict percentage body fat and lean body mass using the Slaughter regression equation developed specifically for this age group (13).

The euglycemic hyperinsulinemic clamps have previously been described in detail (11). Participants were admitted to the University of Minnesota Clinical Research Center after a 10-hour overnight fast. An arm vein was cannulated for infusion of potassium phosphate, insulin and dextrose, and a contralateral vein was cannulated for blood sampling with the hand placed in a heated box (65°C) to arterialize venous blood. Baseline insulin and glucose levels were determined from samples drawn at 15, 10, and 5 minutes before beginning the insulin and glucose infusions. Baseline triglycerides were determined in samples drawn 15 minutes before beginning the infusions. The insulin infusion was started at time 0 and continued at a rate of 1 mU/kg/min for 3 hours. An infusion of 20% glucose was started at time 0 and adjusted to maintain euglycemia (serum glucose level at 5.6 mmol/l) with plasma glucose determined every 5 minutes.

Plasma glucose was measured immediately at the bedside with a Beckman Glucose Analyzer II (Beckman Instruments Inc., Fullerton, CA). Insulin samples were collected on ice and centrifuged within 20 minutes. Serum insulin levels were determined in the University of Minnesota Hospital laboratory by radioimmunoassay using a double antibody method. Triglyceride levels were determined in the same laboratory as previously described (11). Insulin sensitivity (M) was calculated as the average amount of glucose (milligrams per kilogram per minute) required to maintain euglycemia during the last 40 minutes of the clamp and was expressed as  $M_{LBM}$  [milligrams of glucose infused per kilogram lean body mass (LBM) per minute]. Insulin sensitivity was also expressed as  $M_{LBM}/\ln$  steady state insulin (SSI) with SSI calculated from samples drawn at 160 and 180 minutes after beginning the insulin infusion. Lower M,  $M_{LBM}$  and  $M_{LBM}/\ln$  SSI values represent a greater degree of insulin resistance.

The mean of the three FI and glucose levels and the triglyceride level obtained at baseline were used to calculate FI, HOMA [fasting insulin ( $\mu$ U/ml)  $\times$  fasting glucose (mmol/l)]/22.5], QUICKI [ $1/\ln(\text{fasting insulin } (\mu\text{U/ml}) + \ln(\text{fasting glucose (mg/dl)}))$ ], FGIR, and  $[\ln \text{ FI} + \ln \text{ triglycerides}]$ . FI, HOMA and  $[\ln \text{ FI} + \ln \text{ triglycerides}]$  are inversely related, whereas QUICKI and FGIR are directly related to degree of insulin sensitivity.

Means and standard deviations (SD) were computed for the total cohort and for each BMI category ( $<85^{\text{th}}$ ile and  $\geq 85^{\text{th}}$ ile) at each clamp at each age. Correlation coefficients in 3 forms are presented. The first is for a pair of variables (e.g., the correlation for  $M_{LBM}$  vs. FI) in independent subgroups of people. The difference in this form of correlation was tested in a 2 sample t-test using Fisher's  $Z = \frac{1}{2} \ln((1+r)/(1-r))$ , with variance  $1/(N-3)$ , where N is the number of persons in the analysis. The second form is for two different variables with a third common variable in a constant sample of people (e.g., correlation between M vs. FI and  $M_{LBM}$  vs. FI). The difference in this form of correlation was tested using the method of Meng et al (14). To compare correlations  $r_{13}$  and  $r_{23}$  in a sample of N people, calculate the difference of the Fisher's Z for  $r_{13}$  and  $r_{23}$ . The difference is tested as a t test with variance  $(N-3)/(2*(1-r_{12})^2*h)$ , where  $h = (1-f*r^2_{\text{mean}})/(1-r^2_{\text{mean}})$ ;  $r^2_{\text{mean}}$  is the average of  $r_{13}^2$  and  $r_{23}^2$ ; and f is  $(1-r_{12})/(2*(1-r_{2\text{mean}}))$ , with a maximum value of 1. The third form is for the correlation between two variables measured at one time compared to the correlation between the same two variables measured at another time in a sample that is partially or completely overlapping between the two measurement times (e.g., between M vs. FI at age 13 and M vs. FI at age 15). Here we used the p-value of the regression coefficient for interaction of the first variable with time in a repeated measures regression of

the repeated second variable on an intercept, an indicator for time, the repeated first variable, and the interaction mentioned above.

In an attempt to find an alternative method for assessing insulin resistance, ROC (receiver operating characteristic) curves were developed as previously described in adults (15). The curves describe the ability of a surrogate measure to separate true positive (i.e., sensitivity) insulin resistance from false positive (i.e., specificity) at a series of cutpoints. The test accuracy is determined by the area under the ROC curve (AUC) with a value of 0.5 indicating no significant relation and a value of 1 indicating a perfect relation. In this study ROC curves were used to describe the accuracy with which levels of FI, HOMA or QUICKI can identify individuals with insulin resistance, defined as an  $M_{LBM}$  value below the tenth percentiles of the total  $M_{LBM}$  distribution.

## RESULTS

The clinical characteristics and measures of insulin resistance at mean ages 13 and 15 are provided for the total cohort and by BMI groups in table 1. The mean fasting glucose levels for the whole cohort were  $4.9 \pm 0.4$  mmol/l (range 3.5-6.3 mmol/l) at mean age 13 and  $4.8 \pm 0.4$  mmol/l (range 3.5-6.5 mmol/l) at mean age 15. The levels were not significantly different between the BMI groups at mean age 13; at mean age 15 fasting glucose was slightly, but significantly, greater in the  $\geq 85\%$ ile BMI group. FI levels for the whole cohort were  $70.2 \pm 55.8$  pmol/l (range 9-477.6 pmol/l) at mean age 13 and  $72 \pm 52.8$  pmol/l (range 3.6-413.4 pmol/l) at mean age 15. FI, HOMA and triglyceride levels were significantly higher while QUICKI and FGIR were significantly lower in the  $\geq 85\%$ ile BMI group at both ages. Insulin resistance by all three clamp measurements ( $M$ ,  $M_{LBM}$ ,  $M_{LBM}/\ln$  SSI) was significantly higher in the  $\geq 85\%$ ile group at age 13, but only  $M$  remained significantly higher at mean age 15.

Figure 1 shows the similar relations between FI and  $M_{LBM}$  at mean ages 13 and 15. Of particular note is the considerable degree of scatter of FI levels for any given level of  $M_{LBM}$ .

FI was significantly correlated with HOMA ( $r = 0.99$ ), QUICKI ( $r = -0.79$  and  $-0.78$ ), FGIR ( $r = -0.62$  and  $-0.52$ ) and  $[\ln$  FI +  $\ln$  triglycerides] ( $r = 0.88$  and  $0.87$ ) at age 13 and 15, respectively. The longitudinal correlations between the surrogate values at age 13 and insulin sensitivity at age 15 were modest and varied by group. The correlations for the entire cohort ranged from 0.15 to 0.17 ( $p = 0.006-0.1$ ). The correlations for the  $\geq 85\%$ ile and  $< 85\%$ ile groups were within the same range (0.12-0.18), but they were not significant ( $p = 0.9-0.25$ ). The same pattern was seen for the correlations between the surrogates at age 13 and change in insulin sensitivity from age 13-15. In contrast, the correlations between change in the surrogate values from age 13-15 and change in insulin sensitivity from age 13-15 for the entire cohort ( $r = 0.24-0.25$ ), the  $< 85\%$ ile group ( $r = 0.24-0.26$ ) and the  $\geq 85\%$ ile group ( $r = 0.31-0.35$ ) all were significant ( $p = 0.005-0.0001$ ).

The correlations between the surrogate and clamp measures of insulin resistance are shown in Table 2. With the exception of FGIR (0.11) at mean age 15, the correlations were significantly different from zero ( $< 0.0001$ ) for  $M$ ,  $M_{LBM}$  and  $M_{LBM}/\ln$  SSI at both ages. In general, the correlations were slightly higher for the girls ( $r = 0.45-0.66$ ) than boys ( $r = 0.37-0.51$ ), but the differences were statistically significant ( $p < 0.03$  for all) only at age 13. There were differences in the pattern of the correlations. In the total cohort, correlations between the surrogate measures and  $M_{LBM}$  were significantly lower than for  $M$  and  $M_{LBM}/\ln$  SSI at age 13, with the exception of FGIR; however, at age 15 the correlations for the surrogates with  $M_{LBM}/\ln$  SSI were similar to the correlations with

$M_{LBM}$  and significantly lower than the correlations with  $M$ .

Among the BMI subgroups, there were significantly higher correlations with  $M$  than  $M_{LBM}$  for FI and HOMA and with  $M_{LBM}/\ln$  SSI than  $M_{LBM}$  for all the surrogates in the <85<sup>th</sup> percentile group at age 13. In the ≥85<sup>th</sup> percentile group at age 15 the correlations between the surrogates and  $M$  were significantly greater than with  $M_{LBM}$  or  $M_{LBM}/\ln$  SSI. The correlations between surrogate measures and both  $M_{LBM}$  and  $M_{LBM}/\ln$  SSI also changed with age. The correlations for  $M_{LBM}$  and  $M_{LBM}/\ln$  SSI with FI, HOMA, QUICKI and FGIR in the total cohort and in the ≥85<sup>th</sup> percentile BMI group decreased from mean age 13 to 15. In particular, the change was statistically significant for all the surrogate measures vs.  $M_{LBM}/\ln$  SSI in the total group and ≥85<sup>th</sup> percentile group. In general, the correlations in the ≥85<sup>th</sup> percentile group were higher than in the <85<sup>th</sup> percentile group.

The ROC analysis showed there was no significant difference in the AUC among FI, HOMA and QUICKI in prediction of dichotomous insulin resistance. The AUC values (0.771, 0.770 and 0.771, respectively) indicated only a modest capability to separate true positive insulin resistance from false positive. For instance, a FI cut point of 22  $\mu\text{u/ml}$  (the upper 10% for fasting insulin) identified only 12 of 32 participants in the lower 10% of  $M_{LBM}$  (true positive), but 22 participants with  $M_{LBM}$  above the lower 10% (false positive) also were included. The AUC results were similar when the definition for insulin resistance was increased to the lower 20% for  $M_{LBM}$  and also were similar for both the <85<sup>th</sup> percentile and ≥85<sup>th</sup> percentile BMI groups.

## **CONCLUSIONS**

This large cohort of randomly selected adolescents participating in a longitudinal study of insulin resistance offered the unique opportunity to compare surrogate measures of insulin resistance based on FI and glucose

levels (FI, HOMA, QUICKI, and FGIR) and [ $\ln$  triglycerides +  $\ln$  FI] with the “gold standard” insulin clamp measure of insulin resistance at two separate ages. The results showed that the surrogate measures were only modestly correlated with the euglycemic insulin clamp and do not appear to offer any advantage over FI alone. This study further showed that the correlations vary with BMI, with lower correlations for  $M_{LBM}$  than  $M$  and higher correlations in the ≥85<sup>th</sup> percentile group compared to the <85<sup>th</sup> percentile group. When SSI was added to  $M_{LBM}$ , the correlations were greater than with  $M$  at age 13 but significantly lower than with  $M$  at age 15.

In general, HOMA is the most widely used of the surrogate measures in children. The high correlation between HOMA and FI ( $r = 0.99$ ) in this study is not surprising, considering the HOMA formula ( $\text{FI} \times \text{fasting glucose}/22.5$ ) and the finding in adults of a 24 fold variation in FI compared to a 1.8 fold variation in fasting glucose (16). The same was true in this study with a 1.8 fold variation in fasting glucose and a 53-fold variation in FI. Fasting glucose also is maintained within a narrow range among obese children (3) and children with abnormal glucose tolerance tests (1). Studies in adults have reported comparisons between FI and HOMA similar to the present study (16, 17). The relative influences of FI and glucose would be expected to be the same in the QUICKI and FGIR equations, and both of these also were significantly correlated with FI in this study, although the  $r$  values were lower. [ $\ln$  FI +  $\ln$  triglycerides] also did not appear to offer any advantage over FI, with high correlations with insulin resistance at age 13 but lower correlations at age 15.

The correlations between the surrogate measures and clamp derived insulin resistance unadjusted for fatness ( $M$ ) were approximately 0.5 at both ages. However, after removal of fatness from the estimate of glucose disposal ( $M_{LBM}$ ), the correlations

became lower, particularly at mean age 15. Similar differences were found in a young adult African American cohort (18). Among the BMI subgroups, the greatest differences between M and  $M_{LBM}$  correlations were in the  $\geq 85^{\text{th}}$  percentile group at age 15. Fatness is omitted from the calculation of clamp derived insulin resistance (4), because most glucose uptake is localized to skeletal muscle (19). Thus, using M rather than  $M_{LBM}$  appears to artificially improve the relation between the clamp and surrogate measures, particularly in the fatter adolescents. It has been suggested that  $M_{LBM}$  should be corrected for SSI levels (4). Although  $M_{LBM}/\ln$  SSI in this study increased the correlations with the surrogate measures, the effect was small relative to the correlations with  $M_{LBM}$ .

Previous studies have compared surrogate measures to clamp-derived insulin resistance with varying results. In a cohort of 31 children age 6-11 years, primarily prepubertal and obese, similar correlations to the present study were found for HOMA ( $r = -0.51$ ) and FGIR ( $r = 0.37$ ) but there was a higher correlation for QUICKI ( $r = 0.69$ ) (9). In a cohort of 131 pre-pubertal and pubertal children correlations of 0.91 were found for FI, QUICKI, HOMA, and FGIR in whites and 0.86 in African Americans (10). Others have compared surrogate measures to FSIVGTT, also with disparate results. In a small study of 18 obese children the correlations for FI, HOMA, QUICKI, and FGIR all were approximately 0.9 (20), and in a study of 30 obese and 36 lean children the correlations with HOMA and QUICKI were  $<0.2$  (21). In adults, the European Group for the Study of Insulin Resistance reported a correlation of 0.37 between FI and the insulin clamp in 1140 subjects (4) and correlations of 0.41-0.53 were found between insulin resistance defined by the FSIVGTT and FI, HOMA and QUICKI (22). It is not clear why the correlations differ among the studies, and in particular with regard to the present study, but

they could be related to differences in age, pubertal status, BMI, or cohort size. We believe the results in the present cohort are accurate for pubertal adolescents because of the large cohort, selection of participants across the entire distribution of BMI and use of the "gold standard" insulin clamp.

A new finding in this study is the higher correlations in the heavier (BMI  $\geq 85^{\text{th}}$  percentile) children. This also has been reported in adults where correlations with FI, HOMA, and QUICKI were approximately 0.35 for normal weight, 0.55 for overweight and 0.60 for obese subjects, (16). Although an explanation for this difference between heavy and thin individuals is not readily apparent, it may be related to the fact that an increase in BMI is most commonly related to an increase in fatness, and insulin resistance could increase at a faster than linear rate as adiposity increases. As previously discussed (16), obesity is associated with higher levels of FI than in normal weight individuals, even when the weight groups are matched for glucose intolerance or insulin resistance. This difference in FI also was found between the  $\geq 85^{\text{th}}$  percentile and  $<85^{\text{th}}$  percentile groups in the present study. It seems reasonable to suggest that higher levels of FI, representing altered insulin secretion or clearance, could influence the correlations between the surrogate measures, which are dependent on levels of FI, and the clamp. The low correlations in the  $<85^{\text{th}}$  percentile group suggest that the use of surrogate measures to assess insulin resistance in thin children is particularly unreliable.

The results from this study demonstrate the dilemma faced in assessing the role of insulin resistance during childhood and adolescence. While it generally is not feasible to conduct invasive tests for insulin resistance in large cohort studies, the correlation data, graphs and ROC analyses show that FI and other surrogate measures are imprecise substitutes. This is not surprising since the clamp measures only cellular

glucose uptake, while FI represents the integrated effect of glucose and insulin release and clearance. That is not to say that FI may not be a marker of cardiovascular risk, but only that it is a poor representation of insulin resistance.

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**TABLE 1.** Subject Characteristics (mean  $\pm$  SD)

	Total Cohort	BMI <85 <sup>th</sup> tile	BMI $\geq$ 85 <sup>th</sup> tile	P*
<u>Mean Age 13</u>				
No. of subjects	323	208	115	
Age (years)	13.1 $\pm$ 1.2	13.2 $\pm$ 1.2	12.8 $\pm$ 1.1	0.01
Sex (M/F)	170 / 153	114 / 94	56 / 59	NS
Race (AA/White)	66 / 257	46 / 162	20 / 95	NS
BMI (kg/m <sup>2</sup> )	22.0 $\pm$ 4.4	19.5 $\pm$ 1.8	26.6 $\pm$ 4.0	<0.0001
M (mg/kg/min)	8.9 $\pm$ 3.3	10.0 $\pm$ 3.1	6.9 $\pm$ 2.8	<0.0001
M <sub>LBM</sub> (mg/kg/min)	12.3 $\pm$ 4.1	13.0 $\pm$ 4.0	11.0 $\pm$ 3.9	<0.0001
M <sub>LBM</sub> /ln SSI	2.87 $\pm$ 1.04	3.09 $\pm$ 1.02	2.46 $\pm$ 0.96	<0.0001
Fasting Glucose (mmol/l)	4.87 $\pm$ 0.42	4.88 $\pm$ 0.41	4.86 $\pm$ 0.43	NS
Triglycerides (mmol/l)	1.02 $\pm$ 0.58	0.93 $\pm$ 0.53	1.18 $\pm$ 0.63	0.0004
FI (pmol/l)	70.2 $\pm$ 55.8	57.0 $\pm$ 47.4	93.6 $\pm$ 61.8	<0.0001
SSI (pmol/l)	482 $\pm$ 174	426 $\pm$ 113	582 $\pm$ 215	<0.0001
HOMA	2.56 $\pm$ 2.13	2.09 $\pm$ 1.83	3.41 $\pm$ 2.37	<0.0001
QUICKI	0.15 $\pm$ 0.02	0.16 $\pm$ 0.02	0.14 $\pm$ 0.02	<0.0001
FGIR	12.3 $\pm$ 9.6	14.3 $\pm$ 10.0	8.8 $\pm$ 7.8	<0.0001
<u>Mean Age 15</u>				
No. of subjects	300	192	108	
Age (years)	15.0 $\pm$ 1.2	15.2 $\pm$ 1.2	14.7 $\pm$ 1.2	0.002
Sex (M/F)	167 / 133	109 / 83	58 / 50	NS
Race (AA/White)	59 / 241	36 / 156	23 / 85	NS
BMI (kg/m <sup>2</sup> )	23.5 $\pm$ 5.1	20.7 $\pm$ 2.0	28.6 $\pm$ 5.2	<0.0001
M (mg/kg/min)	8.3 $\pm$ 3.3	9.3 $\pm$ 3.0	6.7 $\pm$ 3.1	<0.0001
M <sub>LBM</sub> (mg/kg/min)	12.3 $\pm$ 4.4	12.4 $\pm$ 3.9	12.1 $\pm$ 5.1	NS
M <sub>LBM</sub> /ln SSI	2.87 $\pm$ 1.18	2.93 $\pm$ 0.90	2.77 $\pm$ 1.57	NS
Fasting Glucose (mmol/l)	4.8 $\pm$ 0.4	4.7 $\pm$ 0.4	4.9 $\pm$ 0.4	<0.0002
Triglycerides (mmol/l)	1.00 $\pm$ 0.54	0.88 $\pm$ 0.39	1.23 $\pm$ 0.67	<0.0001
FI (pmol/l)	72.0 $\pm$ 52.8	54.0 $\pm$ 29.4	103.8 $\pm$ 68.4	<0.0001
SSI (pmol/l)	467 $\pm$ 155	402 $\pm$ 89	576 $\pm$ 183	<0.0001
HOMA	2.60 $\pm$ 2.05	1.91 $\pm$ 1.09	3.83 $\pm$ 2.68	<0.0001
QUICKI	0.15 $\pm$ 0.02	0.16 $\pm$ 0.02	0.14 $\pm$ 0.01	<0.0001
FGIR	11.1 $\pm$ 10.4	13.3 $\pm$ 12.0	7.2 $\pm$ 4.6	<0.0001

\*P values reflect differences between the BMI < 85<sup>th</sup>% and BMI  $\geq$  85<sup>th</sup>% groups.

**TABLE 2.** Pearson partial correlation coefficients (r) between clamp-derived measures (M,  $M_{LBM}$  and  $M_{LBM}/\ln SSI$ ) and surrogate measures of insulin sensitivity (adjusted for sex, race, age and Tanner stage) for the total cohort at each age and by BMI group

	Total			BMI <85 <sup>th</sup> %			BMI ≥85 <sup>th</sup> %		
	M	$M_{LBM}$	$\frac{M_{LBM}}{\ln SSI}$	M	$M_{LBM}$	$\frac{M_{LBM}}{\ln SSI}$	M	$M_{LBM}$	$\frac{M_{LBM}}{\ln SSI}$
Mean Age 13									
FI	-0.48	-0.42‡	-0.49†	-0.36	-0.31§	-0.38	-0.51	-0.48	-0.53†
HOMA	-0.49	-0.43‡	-0.49†	-0.37	-0.32§	-0.38	-0.53	-0.50	-0.55†
QUICKI	0.54	0.50†§	0.57†	0.45	0.41	0.48	0.53	0.57	0.62†
FGIR	0.48	0.45†	0.52†	0.41	0.37	0.44	0.44	0.50	0.56†
[ln FI + ln Trig]	-0.60	-0.52	-0.60†	-0.46	-0.40	-0.48	-0.64	-0.63	-0.68†
Mean Age 15									
FI	-0.52	-0.29‡	-0.34	-0.31	-0.33	-0.38	-0.58*	-0.37‡	-0.38‡
HOMA	-0.53	-0.30‡	-0.35	-0.31	-0.33	-0.38	-0.60*	-0.40‡	-0.40‡
QUICKI	0.43	0.23‡	0.29	0.21	0.21	0.27	0.61*	0.38‡	0.42‡
FGIR	0.25	0.09‡	0.14	0.11	0.10	0.14	0.44*	0.21‡	0.29‡
[ln FI + ln trig]	-0.50	-0.27	-0.32	-0.29	-0.26	-0.30	-0.29	-0.33‡	-0.38‡

\*  $P < 0.01$  vs. M in BMI <85<sup>th</sup>% group†  $P < 0.05$  vs. r at mean age 15‡  $P < 0.01$  vs. M in same group§  $P < 0.05$  vs. M in same group||  $p < 0.05$  vs.  $M_{LBM}$  in same group

## **FIGURE LEGEND**

**Figure 1.** Relation of fasting insulin-to-insulin resistance ( $M_{LBM}$ ) at mean age 13 (graph A) and mean age 15 (graph B). Insulin resistance is inversely related to level of  $M_{LBM}$ .

FIGURE 1

