Scaling of $\text{VO}_{2\text{max}}$ and Its Relationship With Insulin Resistance in Children

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The relationship between insulin resistance (HOMA-IR), percent body fat, and aerobic fitness ($\text{VO}_{2\text{max}}$ per unit fat free mass; mL/kg$_{FFM}$/min) was examined in 1,710 children. Percent body fat was estimated from sum of skinfolds, and $\text{VO}_{2\text{max}}$ was estimated from submaximal cycle ergometer tests. Overnight fasting blood samples were obtained. $\text{VO}_{2\text{max}}$ (mL/kg$_{FFM}$/min) and percent body fat were correlated with HOMA-IR ($r = -0.076$, $p < .002$; $r = .420$, $p < .001$, respectively); as was $\text{VO}_{2\text{max}}$ in units of mL/kg/min ($r = -0.264$, $p < .001$). When $\text{VO}_{2\text{max}}$ in mL/kg/min was used, a progressive increase in HOMA-IR was found with decreasing fitness ($p < .05$). However, when mL/kg$_{FFM}$/min was used, HOMA-IR scores remained similar between moderate-fit and low-fit group. The stronger association between aerobic fitness (mL/kg/min) and HOMA-IR is partially due to the significant association of fat mass to HOMA-IR. Therefore, our recommendation is to express aerobic fitness in units of mL/kg$_{FFM}$/min to eliminate the confounding factor of adiposity and better understand the influence of muscle on insulin resistance.

In 2006, obesity incidence was 52.1% in 12–19 years old children (16). Obese children have eight times the risk of developing insulin resistance than normal-weight children (17). Furthermore, Narayan et al. (21) have predicted that one in three US children born in 2000 would develop type 2 diabetes at some point of their life. Thus, childhood is a critical period for type 2 diabetes prevention because the pathophysiology starts in early stage of life (22,28).

Existing literature shows that physical inactivity and low cardiorespiratory fitness are predictors for type 2 diabetes mellitus incidence (31) and increased risk ratio for type 2 diabetes-related mortality (32). Furthermore, aerobic fitness is inversely associated with insulin resistance in adult population (26,27). However, fewer children studies have reported the relationship between aerobic fitness and type 2 diabetes.

Aerobic fitness is defined as the ability of skeletal muscle to use oxygen during physical activity (24). It is typically quantified as maximal oxygen uptake ($\text{VO}_{2\text{max}}$) in units of mL $O_2$ per kilogram body mass per minute (mL/kg/min). Body mass includes both fat free mass (FFM) and fat mass. However, the inclusion of fat mass can confound true estimation of physiologic capabilities, because adipose tissue contributes to energy demand, but is minimally involved with
energy production. In support, Goran et al. (11) have shown that when $VO_{2\text{max}}$ is expressed in units of mL/kg/min, $VO_{2\text{max}}$ can increase simply by losing fat mass. Therefore, when comparing physiological ability of tissue to maximally consume oxygen, $VO_{2\text{max}}$ relative to FFM might be a better indicator of aerobic fitness in children (19,23).

The relationship between insulin resistance and $VO_{2\text{max}}$ expressed per kilogram body mass may be directly related to adiposity, such that the relationship becomes stronger as one becomes more overweight (16). In support, Eisenmann et al. (9) reported a stronger relationship between $VO_{2\text{max}}$ (mL/kg/min) and insulin resistance in overweight/obese children compared with normal-weight youth. However, this conclusion may be equivocal because they expressed $VO_{2\text{max}}$ in terms of mL/kg/min. The question remains as to whether the relationship between insulin resistance and $VO_{2\text{max}}$ changes, when fat mass is removed from the measure of aerobic fitness. Therefore, this study examined the relationship between insulin resistance and aerobic fitness when $VO_{2\text{max}}$ was expressed relative to FFM.

**Methods**

**Participants**

Data were obtained from participants in the Cardiovascular Health in Children and Youth (CHIC II and III) studies (J.S. Harrell, PI). A total of 1,710 participants (890 female, 820 male) were included. Mean age was 11.4 ± 2.4 years, and the racial distribution was 49% white, 44% black and 7% other. Participants were categorized into the following three adiposity-groups based on sex-specific BMI references and the recommendation of Barlow et al. (5): Normal-weight (5th to < 85th percentile), Overweight (85th to < 95th percentile) and Obese (≥ 95th percentile).

**Procedures**

Before data collection informed consent and written assent were obtained from the parents and participants, respectively. The Institutional Review Board of the University of North Carolina at Chapel Hill approved all forms and procedures. Data were collected at the participants’ school by teams of research assistants who were trained by the same investigator and met stringent criteria for reliability and precision before gathering any data. Physiological variables of every tenth subject were measured by more than one RA to further control reliability.

Demographic data were collected via self-report. Race was reported as White, African American (Black), and Other. Height and body mass were measured to the nearest 0.1 cm and 0.1 kg using a stadiometer (Perspective Enterprises, Kalamazoo, MI) and electronic scale (Scaletronix, White Plains, NT), respectively. Skinfold measurements were obtained at the triceps and subscapular sites in triplicate based on NHANES III procedures (2). Percent body fat was calculated from the sum of skinfolds using the equations of Slaughter et al. (30) that are sex and pubertal status dependent. Pubertal stage (1–5) was estimated using the Pubertal Development Scale (25). When race was classified as “Others,” the average of the constants for “White” and “Black” was used to calculate body fat.
Blood samples were drawn in the morning (7:00–8:00 a.m.) after an overnight fast; fasting state was confirmed before obtaining the samples. The samples were processed, placed on dry ice and sent to the laboratories for analysis. Plasma glucose levels were measured using a Johnson and Johnson 950 automated chemistry system (UNC Hospital Core Chemistry Laboratory; certified by the College of American Pathologists). Insulin was analyzed by Penn Medical Laboratory, Medstar Reaserch Institute (Washington, DC) using RIA techniques and strict quality control. For determination of insulin resistance, homeostasis model assessment of insulin resistance (HOMA-IR)-was used: HOMA-IR = (fasting insulin [µIU/mL]×fasting glucose [mmol/L])/22.5. The HOMA-IR has been validated in children and adolescents (12).

Maximal oxygen uptake (VO$_{2max}$) was estimated from a multistage submaximal test on the cycle ergometer. The test is based on the Physical Work Capacity test previously described by McMurray et al. (18). Briefly, workloads are increased until the heart rate reaches a range of 150–170 beats/min and the heart rate/workload relationships are used to predict maximal capacity. This test showed good correlations ($r = .807$) with measured maximal values in children. VO$_{2max}$ was estimated in units of mL/min and then scaled relative to fat free mass (mL/kg$_{FFM}$/min) and to total body mass (mL/kg/min). VO$_{2max}$ was then used to compare the effect of fitness unit on insulin resistance. Using tertile values, three fitness groups (Low-, Moderate- and High-fit) were created based on VO$_{2max}$ in mL/kg$_{FFM}$/min and mL/kg/min, respectively. HOMA-IR values were compared between groups. To further understand the effect of sex on HOMA-IR, the participants were divided by fitness level and sex, and then comparisons by sex were made within each fitness group.

**Analytical Methods**

Statistical analyses were conducted using 1-way ANOVAs or a 2 × 3 ANOVA (sex × fitness level) followed by Bonferroni post hoc test. Partial correlations (controlling for sex and puberty) were computed to determine the relationship between HOMA-IR and aerobic fitness in mL/kg$_{FFM}$/min and mL/kg/min. All statistical tests were performed using SPSS software (version 17.0 for Windows; SPSS, Inc., Chicago, IL). Data are shown as mean ± SE. Statistical significance was set at p-value less than 0.05.

**Results**

The characteristics of subjects are presented by adiposity status (Table 1). The three adiposity-groups were similar in age and height. Distributions of pubertal stage were different between adiposity groups. Normal-weight group included more stage 1 children than overweight and obese groups. Children in stage 5 increased with increasing adiposity status. HOMA-IR increased with increasing adiposity group ($p < .05$). The mean aerobic fitness in units of mL/kg$_{FFM}$/min or mL/kg/min was lower in Overweight and Obese groups than the Normal-weight group ($p < .05$). The difference in VO$_{2max}$ between Normal-weight vs. Obese group was greater for mL/kg/min (27.8%) than mL/kg$_{FFM}$/min (15.3%).
Table 1 Characteristics (Mean ± SD) of 1,710 Boys and Girls Presented by BMI-Percentile Category

<table>
<thead>
<tr>
<th></th>
<th>Normal-weight (N = 920)</th>
<th>Overweight (N = 340)</th>
<th>Obese (N = 450)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>11.4 ±2.4</td>
<td>11.5 ±2.4</td>
<td>11.2 ±2.3</td>
</tr>
<tr>
<td>Sex (female/male)</td>
<td>475/445</td>
<td>188/152</td>
<td>227/223</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>149 ±14</td>
<td>152 ±13</td>
<td>152 ±12</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>41 ±12.0</td>
<td>52.5 ±13.2 *</td>
<td>67.4 ±20.3 *†</td>
</tr>
<tr>
<td>BMI percentile</td>
<td>55.9 ±21.0</td>
<td>90.2 ±2.9 *</td>
<td>98.0 ±1.3 *†</td>
</tr>
<tr>
<td>Percent body fat (%)</td>
<td>18.1 ±7.5</td>
<td>25.0 ±7.6 *</td>
<td>33.3 ±7.9 *†</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>7.7 ±4.4</td>
<td>13.3 ±5.9 *</td>
<td>22.9 ±10.8 *†</td>
</tr>
<tr>
<td>Fat free mass (kg)</td>
<td>33.5 ±9.8</td>
<td>39.1 ±10.2 *</td>
<td>43.8 ±11.9 *†</td>
</tr>
<tr>
<td>VO2max (mL/kg/min)</td>
<td>41.0 ±9.4</td>
<td>36.3 ±9.3 *</td>
<td>29.6 ±7.6 *†</td>
</tr>
<tr>
<td>VO2max (mL/kgFFM/min)</td>
<td>48.4 ±13.1</td>
<td>46.9 ±12.4 *</td>
<td>41.0 ±14.8 *†</td>
</tr>
<tr>
<td>Pubertal status stage 1 (%)</td>
<td>19.5</td>
<td>13.3</td>
<td>13.1</td>
</tr>
<tr>
<td>stage 2</td>
<td>23</td>
<td>17.9</td>
<td>16.2</td>
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<tr>
<td>stage 3</td>
<td>28</td>
<td>33.0</td>
<td>34.3</td>
</tr>
<tr>
<td>stage 4</td>
<td>27.2</td>
<td>31.5</td>
<td>29.4</td>
</tr>
<tr>
<td>stage 5</td>
<td>2.2</td>
<td>4.2</td>
<td>7.0</td>
</tr>
</tbody>
</table>

* p < .05: significant difference from normal-weight group
† p < .05: significant difference from overweight group

Pubertal status data are shown as percent of frequency.

The partial correlations, controlling for puberty and sex between insulin resistance and both units of aerobic fitness, as well as percent body fat, fat mass, and BMI are presented in Table 2. For the whole sample analysis, HOMA-IR was correlated with all independent variables: VO2max, percent body fat, fat mass and BMI (p < .01). Percent body fat, fat mass and BMI had stronger relationships with HOMA-IR than either of the two units for VO2max. When VO2max was scaled per kilogram body mass, the relationship between VO2max and HOMA-IR was approximately four times stronger than VO2max scaled per kilogram fat free mass. Within adiposity-group analyses revealed that VO2max (mL/kg/min) was related with HOMA-IR only in the obese group. In contrast, VO2max (mL/kgFFM/min) was not related with HOMA-IR within any adiposity group.

To further examine the effect of VO2max on HOMA-IR, the entire sample was regrouped based on fitness level: mL/kgFFM/min vs. mL/kg/min (Figure 1). When examining the tertiles for VO2max, the low fit group had values less than 32.0 mL/kg/min and 43.4 mL/kgFFM/min. On the other hand, the high fit group had values greater than 40.6 mL/kg/min and 51.5 mL/kgFFM/min. When the unit of mL/kgFFM/min was used, only high-fit group showed a lower HOMA-IR values than moderate- and low-fit groups (p < .05). However, when the unit of mL/kg/min was used, a progressive increase in HOMA-IR values was found with decreasing fitness (p < .05). The influence of sex on the relationship between aerobic fitness
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and insulin resistance was also explored (Figure 2). Boys had significantly lower HOMA-IR values than girls ($p < .05$). In addition, the HOMA-IR values of the high-fit boys were significantly lower than that of low-fit ($p < .01$) or moderate-fit ($p < .01$) boys; but this intergroup difference was not significant for the girls ($p > .05$).

Discussion

The primary purpose of this study was to compare aerobic fitness units on their association with HOMA-IR: mL/kg/min vs. mL/kg$_{FFM}$/min. Our findings show that both units of VO$_{2\text{max}}$ (mL/kg$_{FFM}$/min and mL/kg/min) have significant associations
Aerobic fitness expressed in mL/kgFFM/min decreased with increasing adiposity status. This finding disagrees with a previous study by Goran et al. (11) who found
no significant difference in VO$_{2\text{max}}$ expressed in units of mL/kg FFM/min between lean and obese groups. Discrepancy of the results could be related to sample size; Goran et al. recruited 78 children, whereas 1,710 subjects were recruited in this study. In addition, the subjects from the study by Goran et al. were on average 2.6 years younger than ours. Another possibility is that Goran et al. divided their sample into lean (< 20% body fat) or obese (> 30% body fat) group; whereas the current study separated our participants into BMI categories commonly used clinically and in research studies.

Although VO$_{2\text{max}}$ was reduced with increasing BMI when using either units of VO$_{2\text{max}}$, differences between the two units were evident. When VO$_{2\text{max}}$ was scaled in mL/kg/min, a 27.8% percent difference between Normal-weight and Obese group was evident; however, when expressed in mL/kg FFM/min, the difference was only 15.3%. This smaller percent difference when using mL/kg FFM/min suggests that an impact of fat mass is evident when mL/kg/min is used. In support, a recent report by McMurray et al. (19) also noted that there is a stronger relationship between fat mass and VO$_{2\text{max}}$ expressed in mL/kg/min than mL/kg FFM/min. Therefore, to obtain a better portrayal of the impact of aerobic fitness (and not fatness) on insulin resistance, VO$_{2\text{max}}$ in units of mL/kg FFM/min may be a better choice.

The High-fit boys (mL/kg FFM/min) had a lower HOMA-IR than Low- or Moderate-fit boys. This trend was not evident in the girls. In agreement, Cummins et al. (6) found significantly higher HOMA-IR values in their overweight, low-fit group than high-fit group in boys. Similar to our results, the same trend was not observed in their girls. The reason for these sex-differences could be both physiologic and psychosocial effects. Girls often have a decline in insulin resistance in late puberty, and VO$_{2\text{max}}$ tends to decline in late puberty due to weight gain and reduced activity levels (3,6), while boys tend to increase VO$_{2\text{max}}$ in late puberty and elevated activity levels (20,29).

The current study includes some limitations; first, this study is limited by cross-sectional design. Although we found a significant association between aerobic fitness and insulin resistance, this study does not guarantee causality. In addition, for this age group (9–13 yr old) a clinical standard for measuring insulin resistance is lacking. HOMA-IR was used to estimate insulin resistance. Although not the golden standard, HOMA-IR has been shown to be a valid and reliable method for quantifying insulin resistance in children (8,14). Finally, VO$_{2\text{max}}$ was estimated from a submaximal test and not directly assessed; thus, increasing the possibility of error in our measure.

In conclusion, insulin resistance is inversely associated with aerobic fitness when expressed in units of mL/kg FFM/min. The association is weaker than when aerobic fitness is expressed in the conventional units of mL/kg/min. Kilograms of body mass include fat, muscles, organs, bones, tissues and water. Of these tissues, muscle and fat have a major impact on glucose disposal (e.g., HOMA). Muscle mass directly relates to maximal metabolic rate and glucose disposal, whereas fat mass impedes glucose disposal. So, if the concern is the true effect of metabolism, independent of the negative impact of adipose tissue, expressing VO$_{2\text{max}}$ in units of fat free mass would be a better marker than VO$_{2\text{max}}$ per kilogram body mass. Thus, our recommendation is to express aerobic fitness in mL/kg FFM/min when determining its relationship with insulin resistance.
Acknowledgments

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References