ARTICLE

Exercise and Insulin Resistance in Youth

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SHAIBI, G.Q., C.K. ROBERTS, and M.I. GORAN. Exercise and insulin resistance in youth. *Exerc. Sport Sci. Rev.*, Vol. 36, No. 1, pp. 5–11, 2008. *In parallel with the pediatric obesity epidemic, the incidence of impaired glucose tolerance and type 2 diabetes has increased among youth. Insulin resistance is thought to be central to the pathophysiology of these obesity-related disorders. A growing body of literature suggests that exercise may ameliorate insulin resistance and thus potentially reduce the long-term diabetes risk in overweight youth.* **Key Words:** insulin sensitivity, obesity, fitness, adolescents, diabetes, children, activity

INTRODUCTION

According to the U.S. Centers for Disease Control and Prevention (CDC) overweight in the pediatric population is defined by a body mass index (BMI) at or above 95th percentile for age and gender. This definition takes into account variations in adiposity by age and between sexes and provides a clinical marker that may confer increased risk of metabolic and cardiovascular diseases. In addition to the definition of overweight among youth, a category defined as at-risk for overweight (BMI ≥85th but <95th percentile for age and gender) is described. Controversy exists surrounding the ambiguous nature of the at-risk classification, and there is growing support among the scientific and medical communities to modify these definitions in favor of the terms "overweight" (BMI ≥85th) and "obese" (BMI, ≥95th) to more closely align with international pediatric definitions and adult terminologies. Moreover, the term "obesity" is often used to describe the general population of youth with increased adiposity regardless of BMI percentile. For the purposes of this review, the terms "overweight" and "obesity" will be used interchangeably unless specific BMI criteria are listed.

The prevalence of overweight (BMI ≥95th percentile) among youth has more than tripled in recent years such that approximately 17% of youth are overweight (24). In parallel with the pediatric obesity epidemic, the comorbidities of hypertension, dyslipidemia, and glucose intolerance (collectively referred to as the metabolic syndrome) have become critical public health and research priorities. An estimated 30%–50% of overweight youth exhibit the metabolic syndrome phenotype (14), placing them at high risk for the premature development of cardiovascular disease and type 2 diabetes (11). The core defect linking obesity to chronic disease risk is thought to be peripheral insulin resistance (25). We have recently observed that children with the metabolic syndrome are significantly more insulin resistant compared with those without the disorder even after controlling for adiposity (6). Therefore, we propose that exercise interventions that target insulin resistance have the potential for improving multiple risk factors and ultimately reducing chronic disease risk. However, to date, a relative paucity of data exist examining the effects of exercise on insulin resistance among overweight youth.

Measuring Insulin Resistance in Youth

Insulin resistance is defined as the inability of circulating insulin to exert a normal physiological effect at a target tissue, classically described as impaired insulin-stimulated skeletal muscle glucose uptake. Conceptually, tissues and individuals can be characterized by how sensitive they are to insulin's action, and thus, the terms "insulin sensitivity" and "insulin resistance" are used as interchangeable opposites. In other words, an insulin-resistant individual has low insulin sensitivity, and an insulin-sensitive person is not insulin resistant. Insulin action is quantified using a variety of methodologies with varying levels of complexity. The gold standard for determining insulin resistance *in vivo* is the hyperinsulinemic-euglycemic clamp technique (9). This technique provides

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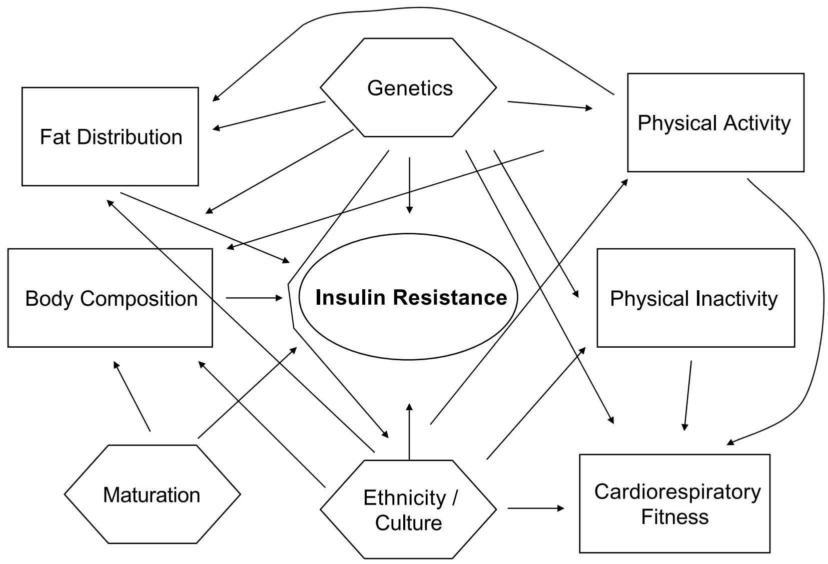

Figure 1. Schematic of the complex multifactorial determinants of insulin resistance in youth.

for a direct measure of glucose uptake under insulin-stimulated conditions. Briefly, insulin is infused intravenously at predetermined supraphysiologic levels, whereas glucose is simultaneously infused at a variable rate to maintain euglycemia. The rate at which glucose is infused under steady-state conditions provides for a measure of insulin resistance with higher rates of glucose infusion equating to lower levels of insulin resistance and *vice versa* (9).

A second measure frequently used in children to quantify insulin sensitivity is the frequently sampled intravenous glucose tolerance test (FSIVGTT) (7). The FSIVGTT requires the administration of an intravenous glucose bolus followed 20 min later by an insulin bolus (dosages determined by body mass). Frequent blood sampling is required for 180 min, and plasma insulin and glucose values are subsequently entered into a mathematical model for determination of insulin sensitivity. Both measures allow for direct quantification of whole-body glucose uptake but are often deemed impractical because of their high cost, labor intensiveness, and invasive natures. Therefore, surrogate measures have been developed to estimate insulin resistance in children. These measures include fasting insulin, the homeostasis model assessment of insulin resistance (HOMA-IR) (21), the quantitative insulin-sensitivity check index (18), and several oral glucose tolerance–derived indices (20). Although these measures have been shown to correlate to varying degrees with either the hyperinsulinemic-euglycemic clamp or the FSIVGTT, they may represent physiologically different metabolic processes with specific limitations compared with either the clamp or FSIVGTT techniques. Readers are referred to a recent review outlining the strengths and weaknesses of various measures of insulin resistance in youth (8).

Regardless of measurement method, insulin resistance in youth is a complex physiological process that is a function of genetics, body composition (total and regional), ethnicity/culture, pubertal status, physical activity, and cardiorespiratory fitness (Fig. 1). Furthermore, the interaction of the individual components such as sex, ethnicity/culture, and physical activity in the background of genetic predisposition presents an even more complicated picture of disease risk. A comprehensive overview of the individual and combined factors contributing to the development of insulin resistance is beyond the scope of this article; thus, readers are referred to a recent review by our group on this topic (5). Instead, this brief review will focus on the relationships between physical activity, cardiorespiratory fitness, and insulin resistance in youth, with a particular emphasis on the improvement of insulin resistance through exercise in overweight youth.

PHYSICAL ACTIVITY, CARDIORESPIRATORY FITNESS, AND INSULIN RESISTANCE

Clear evidence has established that adults who engage in regular physical activity and/or exhibit high cardiorespiratory fitness have a reduced risk of developing type 2 diabetes (19). Furthermore, the beneficial effects of a physically active lifestyle seem to hold true for normal-weight, overweight, and obese individuals alike. It is hypothesized that the mechanisms underlying this protective effect may be due, at least in part, to the insulin-sensitizing properties of physical activity on skeletal muscle. In children, less is known regarding the associations between physical activity or cardiorespiratory fitness and insulin resistance. Further complicating the matter is the fact that habitual physical activity in youth is not strongly associated with cardiorespiratory fitness (22), and thus, each construct may be representative of distinct biological processes that impart separate effects on insulin resistance. As such, we will present associations between insulin resistance and either activity or fitness separately.

Physical Activity

A growing body of literature suggests that children who participate in regular physical activity may have higher insulin sensitivity levels compared with their more sedentary

TABLE 1. Observational studies of associations between physical activity and insulin resistance.

Study	Population	Measures	Major Finding
Andersen *et al.* (2)	Representative sample of European youth aged 9 and 15 yr	PA via 4-d accelerometry; IR via HOMA-IR	Small but significant inverse correlation between physical activity and insulin resistance
Bunt *et al.* (4)	Pima Indian Children aged 5 and 10 yr	PA behavior via questionnaire; PA level via doubly labeled water; body composition via DEXA; IR via fasting insulin and glucose	No independent cross-sectional association between activity and IR Youth with smallest decrease in activity over 5 yr exhibited smallest decreases in IR
Imperatore *et al.* (15)	Representative sample of U.S. adolescents aged 12–19 yr (NHANES 1999–2002)	PA via questionnaire; IR via QUICKI; body composition via BMI percentage	Weak but positive association between physical activity and insulin sensitivity after adjusting for age, ethnicity, and BMI; When sexes were analyzed separately, the association was only significant in boys
Schmitz *et al.* (26)	African American and white youth aged 10–16 yr	PA via questionnaire; IR via clamp; body composition via skin folds	Significant independent association between physical activity and insulin sensitivity

BMI indicates body mass index; DEXA, dual-energy x-ray absorptiometry; HOMA, homeostasis model assessment of insulin resistance; IR, insulin resistance; PA, physical activity; QUICKI, quantitative insulin-sensitivity check index.

counterparts (Table 1). However, most of this work has used self-reported estimates of physical activity that are prone to reporting errors. Furthermore, whether activity is protective against insulin resistance independent of body composition or obesity is still a matter of debate. Bunt and colleagues (4) attempted to shed light on these questions by examining the cross-sectional associations and prospective relations between physical activity and insulin sensitivity in Pima Indian children at high risk for developing type 2 diabetes. They found that both physical activity behavior (measured via questionnaire) and physical activity level (measured via doubly labeled water) were significantly and directly related to insulin sensitivity. Although these associations held true after adjusting for sex ($r = 0.24$; $P = 0.02$ and $r = 0.21$; $P = 0.02$, respectively), when measures of body composition were controlled for in multiple regression analysis physical activity (by either measure) was no longer a significant independent determinant of insulin sensitivity ($\beta = 0.014$; $P = 0.06$ and $\beta = 0.059$; $P = 0.69$, respectively). When the authors analyzed their data over a 5-yr period, they found that both activity and insulin sensitivity significantly decreased in their cohort but noted that youth with the smallest decrease in physical activity behavior exhibited the smallest decrements in insulin sensitivity independent of body mass changes ($r = 0.22$; $P = 0.04$) for change in insulin sensitivity and activity behavior). These results suggested that youth who maintained an active lifestyle over time were somewhat protected from the adiposity-related development of insulin resistance. Given the high levels of adiposity and diabetes in Pima Indians, these findings offers promising information on potentially reducing disease risk in this population through maintenance of activity levels.

In perhaps one of the largest cross-sectional studies to date to examine the associations between objectively measured physical activity and insulin resistance in youth, Andersen and colleagues (2) used accelerometry to objectively quantify moderate-to-vigorous physical activity in 1732 European children aged 9 and 15 yr. They found a weak association ($r = -0.17$; $P < 0.0001$) between physical activity and insulin resistance (HOMA-IR). Unfortunately, the authors did not control for adiposity in their analysis which begs the question of whether physical activity uniquely affected insulin resistance in their population or whether body composition may have moderated this relationship. The independent association between activity and insulin resistance was better delineated in a recent examination of National Health and Nutrition Examination Survey (NHANES) data (15). Imperatore *et al.* (15) examined the relationship between physical activity (by questionnaire) and insulin sensitivity in a representative sample of 1783 adolescents. After controlling for age, ethnicity, and BMI, a weak but positive association between activity and insulin sensitivity was found ($r = 0.11$; $P < 0.001$). Interestingly, when data were examined separately by sex, this relationship remained significant only for boys. The authors concluded that in girls, a physically active lifestyle is not significantly associated with insulin sensitivity but rather may impact insulin metabolism indirectly through effects on adiposity in contrast to boys where a direct and independent effect on insulin sensitivity remained.

Given the limitations in methodologies and lack of compelling data, it is presently unclear whether habitual physical activity is independently protective against insulin resistance in children or adolescents. Clearly, adequate physical activity is important for the normal growth and development of youth. One plausible explanation for the lack of an overwhelming association between physical activity and insulin resistance in youth may be related to a minimum dosage in terms of frequency, intensity, and duration required before metabolic improvements are observed. In other words, habitual physical activity outside a structured exercise program may not impart sufficient stimulus on skeletal muscle to cause physiological adaptations that would lead to improved insulin action. The effects of specific exercise programs on insulin resistance will be further discussed in the section on exercise training.

Although it may be reasonable to assume that patterns and preferences of physical activity in youth lay the framework for activity patterns later in life, more research is warranted to determine the impact of a physically active lifestyle in youth on insulin resistance and diabetes risk. To more definitively answer this question, robust techniques should be used to objectively quantify activity amount, intensity, and duration as well as precise measures of whole-body insulin action. Furthermore, the extent to which sex, pubertal maturation, and body composition impact the association between physical activity and insulin resistance warrants further investigation. These well-designed studies will not only advance the scientific knowledge in the field but may provide some insight on a potential dose-response relationship between physical activity and insulin resistance in the pediatric population.

Cardiorespiratory Fitness

Unlike in adults, cardiorespiratory fitness in youth (as measured by maximal oxygen uptake — $\dot{V}O_{2max}$) is not highly correlated with habitual physical activity patterns (22). As such, fitness may be less variable in response to environmental influences and theoretically more reflective of innate physiological characteristics (*e.g.*, oxidative capacity of skeletal muscle). These characteristics, particularly at the skeletal muscle level, would lead one to believe a strong relationship between fitness and insulin sensitivity in youth. Indeed, several studies have found that cardiorespiratory fitness is inversely related to insulin resistance in youth (Table 2). These findings would imply that highly fit youth are inherently more insulin sensitive. However, the association between fitness and insulin resistance is often difficult to interpret based upon data presentation.

Traditionally, fitness is expressed relative to some index of body size (*e.g.*, per kilogram of body mass). Given that body mass is a strong determinant of insulin sensitivity, when fitness data are presented as a ratio per total body mass, it is challenging to parcel out the independent contribution of fitness on insulin resistance. Therefore, the less fit youth in these studies also tend to be heavier and more insulin resistant. Researchers have attempted to address this issue by expressing fitness relative to fat-free mass (1). However, we have previously demonstrated that even expressing fitness relative to fat-free mass does not sufficiently remove the confounding effects of adiposity on disease risk in youth (27). Thus, to avoid spurious conclusions and appropriately examine the independent impact of fitness on insulin sensitivity, fitness data should be expressed in absolute terms (*e.g.*, milliliters of oxygen per minute), with body composition data adjusted for in a statistical model (31).

Using this approach, Ball *et al.* (3) examined the associations between cardiorespiratory fitness and insulin sensitivity (measured via FSIVGTT) in 95 overweight Latino youth. In univariate models, a significant inverse association was found between $\dot{V}O_{2max}$ and insulin sensitivity, suggesting that the most fit youth paradoxically exhibited the lowest insulin sensitivity ($r = -0.46$; $P < 0.05$). However, in multivariate linear regression analysis, the authors found that body fat was the primary determinant of insulin sensitivity explaining 53% of the variance, whereas fitness was not a significant independent predictor. In contrast, researchers from the CDC examined the association between insulin sensitivity and cardiorespiratory fitness in adolescents participating in NHANES 1999–2002 (15). The authors found that the most fit youth had significantly higher insulin sensitivity levels compared with the least fit youth, a finding

TABLE 2. Observational studies of associations between cardiorespiratory fitness and insulin resistance.

Study	Population	Measures	Major Finding
Allen *et al.* (1)	106 Middle school students aged 12.8 ± 1.4 yr; BMI, >95th percentile	Fitness via $\dot{V}O_{2max}$ (lean, $mL \cdot kg^{-1} \cdot min^{-1}$); IR via HOMA-IR; body composition via DEXA	Both fitness and body fat were significant independent predictors of IR in boys but not in girls
Ball *et al.* (3)	95 Overweight Hispanic youth aged 11.1 ± 1.7 yr; BMI, >85th percentile	Fitness via $\dot{V}O_{2max}$ ($mL \cdot min^{-1}$); IR via FSIVGTT; body composition via DEXA	Body fat explained 53% of the variance in IR, but fitness was not a significant independent predictor
Gutin *et al.* (13)	282 white and African American youth aged 14–18 yr; BMI, >95th percentile	Fitness via submaximal treadmill test; IR via fasting insulin; body composition via DEXA	Fitness and adiposity independently explained significant proportion of the variance in IR in boys but not in girls
Imperatore *et al.* (15)	Representative sample of U.S. adolescents aged 12–19 yr (NHANES 1999–2002)	Fitness via submaximal treadmill test IR via QUICKI; body composition via BMI percentage	Higher fitness was independently associated with higher insulin sensitivity in boys but not in girls
Kasa-Vubu *et al.* (17)	53 Postpubertal female subjects aged 16–21 yr; BMI, 10th–95th percentile	Fitness via $\dot{V}O_{2max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$); IR via HOMA-IR; body composition via DEXA	In multiple regression models, fitness but not percent body fat was significantly and inversely associated with IR

BMI indicates body mass index; DEXA, dual energy x-ray absorptiometry; FSIVGTT, frequently sampled intravenous glucose tolerance test; HOMA, homeostasis model assessment of insulin resistance; IR, insulin resistance; QUICKI, quantitative insulin-sensitivity check index.

that was independent of age, sex, ethnicity, and BMI. However, when youth were examined separately by sex, the relationship between fitness and insulin sensitivity only held true for boys, suggesting a sexual dimorphism in the protective effect of higher fitness on insulin resistance. Interestingly, two other recent reports in overweight adolescents have highlighted similar independent associations between fitness and insulin resistance in boys but not girls (1,13). Collectively, these findings present an intriguing hypothesis that deserves further consideration in future studies related to why the potential protective effects of fitness on insulin resistance seem to hold true for boys and not for girls.

Similar to the body of physical activity research to date, studies examining the associations between fitness and insulin resistance in youth are less conclusive than those in adults. Future studies should build upon previous work by using direct measures of insulin resistance such as the euglycemia-hyperinsulinemic clamp or the FSIVGTT while appropriately controlling for the confounding effects of body composition.

EXERCISE TRAINING INTERVENTIONS AND INSULIN RESISTANCE IN OVERWEIGHT YOUTH

Given the increasing trends in obesity and metabolic disorders in youth, an important line of inquiry relates to whether exercise interventions can improve insulin resistance in this population. Several promising studies in a variety of populations and settings have demonstrated that exercise training can be a potent intervention strategy for improving insulin resistance in overweight youth. Most of these studies have used aerobic exercise modalities; however, we will present some more recent evidence to suggest that resistance training may be a viable alternative for improving insulin resistance in overweight youth.

Ferguson and colleagues (10) recruited 79 overweight African American and white youth aged 7–11 yr who were randomized to either receive 4 months of exercise training or be included for 4 months on a nonexercise waiting list. The program was offered 5 d·wk^{-1}, and youth were encouraged (via incentives) to maintain a heart rate above 150 beats·min^{-1} throughout the semistructured aerobic exercise sessions. The authors found that youth randomized to the exercise group exhibited a 10% decrease in fasting insulin concentrations as a result of the program compared with a negligible increase in the control group. The decrease in fasting insulin was not accompanied by a change in fasting glucose and was interpreted by the authors to suggest an improvement in insulin sensitivity in the trained youth. Another interesting aspect of the study was that the authors used a crossover design, whereby the trained youth were subsequently followed for an additional 4 months after the program to examine the sustainability of the improvements. Not surprisingly, the authors found that 4 months of de-training resulted in a reversal of the exercise effects, suggesting that exercise patterns must be continued to maintain improvements.

In a related follow-up study, Kang *et al.* (16) examined whether comparable exercise-induced improvements in fasting insulin could be observed in 13- to 16-yr-old overweight adolescents who performed exercise for 8 months. In contrast to the earlier findings, the authors did not observe similar improvements in insulin resistance in the adolescents. However, these results should be interpreted cautiously, given some of the differences between the two studies. Although the programs were not comparable in terms of length, the latter being 8 months and the former being 4 months, the lack of an exercise effect probably had more to do with differences in study populations than program duration. In the adolescent study, the exercise effects on fasting insulin may have been confounded by the fact that insulin resistance is a normally occurring biological process observed in all youth during maturation (12). Therefore, adolescents of similar chronological age may be at varying stages of puberty, thus resulting in large variability in measures of insulin resistance. Indeed, larger SE for fasting insulin values were reported in the adolescents compared with the children. This is further complicated by the 8-month duration of the adolescent study that was more than enough time for youth to potentially progress through stages of maturation. Because the authors did not report pubertal status in their population, it is difficult to differentiate whether the lack of significant improvement in insulin resistance was a reflection of the exercise program or pubertal progression. For this reason, it is imperative for investigations examining the effects of exercise on insulin resistance in youth to appropriately ascertain pubertal status at baseline and follow-up to adequately control for maturational changes in insulin resistance in circumpubertal participants.

Two recent studies have established that adolescents can significantly improve insulin resistance in response to exercise training; even more intriguing is that these improvements may be independent of body composition changes. Nassis and colleagues (23) examined the effects of 12 wk of aerobic exercise training on insulin response to an oral glucose challenge in overweight adolescent girls. The program consisted of three 40-min supervised sessions per week at moderate exercise intensity (heart rate > 150 beats·min^{-1}). Compared with baseline values, the girls exhibited a decrease in serum insulin concentrations in response to a 2-h oral glucose tolerance test. Collectively, the lower insulin concentrations resulted in a 23% reduction in insulin area under the curve ($P < 0.05$), an indication of improved whole-body insulin sensitivity. This improvement in insulin sensitivity was not accompanied by changes in body mass or body fat percentage which suggested an independent effect of exercise on insulin metabolism. Similarly, our research group recently examined the effects of a 16-wk resistance training intervention on directly measured insulin sensitivity (FSIVGTT) in overweight adolescent boys at high risk for developing type 2 diabetes (28). Youth were randomized to either a twice-per-week progressive exercise program or a nonexercising wait-list control group. The exercise sessions were delivered at a local community center and were monitored closely by research personal trainers. Each session consisted of single and multijoint exercises for approximately 1 h. Training volume was increased at prescribed intervals within the

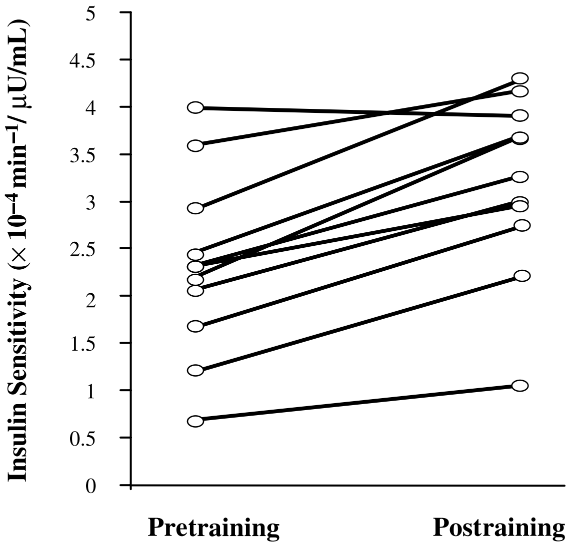

Figure 2. Individual changes in insulin sensitivity in overweight adolescent Latino subjects in response to 16 wk of progressive resistance training. Ten of the 11 youth experienced an increase in insulin sensitivity, whereas one individual exhibited a negligible decrease. Insulin sensitivity was measured 48–72 h after the last training bout to minimize any acute effect of the last exercise session. (Reprinted from Shaibi, G.Q., M.L. Cruz, G.D. Ball, M.J. Weigensberg, G.J. Salem, N.C. Crespo, and M.I. Goran. Effects of resistance training on insulin sensitivity in overweight Latino adolescent males. *Med. Sci. Sports Exerc.* 38:1208–1215, 2006. Copyright © 2006 Lippincott Williams & Wilkins. Used with permission.)

program, and loads were adjusted within a structured protocol. We noted that the exercise group increased insulin sensitivity 45% over baseline values compared with no change in the control youth. Although we did observe large variability in the individual response to exercise training, 90% of participants exhibited an increase in insulin sensitivity (Fig. 2). Furthermore, the collective improvement in insulin sensitivity was independent of body composition changes, confirming the results of Nassis *et al.* (23) that overweight adolescents can improve insulin resistance without necessarily altering adiposity. Perhaps the most telling outcome from our study was that the youth attended nearly 96% of the exercise sessions. Although we did not incorporate objective measures of program satisfaction to explain our high adherence rate, subjective responses suggested that providing the intervention in a community setting and offering an exercise mode in resistance training where early and tangible success was experienced were among the contributing factors.

A growing body of evidence supports the notion that overweight youth who participate in a structured exercise program can significantly improve insulin resistance. Although these proof of concept studies are scientifically important for establishing the efficacy of exercise to improve insulin resistance and decrease diabetes risk, more work is needed to define the optimal acute program variables (*i.e.*, frequency, intensity, duration, and mode) to improve insulin sensitivity in overweight youth. This information is imperative for developing and testing large scale trials in various populations and settings, with the ultimate goal of building upon current evidenced-based physical activity guidelines (29).

CONCLUSIONS AND FUTURE DIRECTIONS

Cross-sectional studies to date have failed to conclusively demonstrate an independent protective effect of either cardiorespiratory fitness or physical activity on insulin resistance in youth. More work is needed in this area and should build upon previous studies by incorporating precise measures of insulin resistance and body composition, appropriately ascertaining pubertal maturation (*e.g.*, Tanner staging), using statistical methodologies that delineate independent contributions, and by more closely examining the potential physiological differences observed between sexes. Given the increased incidence of obesity and type 2 diabetes among youth (30), we would argue that the more pressing research priority relates to the development of intervention strategies that result in meaningful improvements in insulin resistance. Several promising intervention studies in overweight youth suggest that exercise training programs can lead to significant improvements in insulin resistance independent of body composition or weight loss. Unfortunately, the duration of these studies has been relatively short with limited follow-up. Whether improvements in insulin resistance after an exercise intervention can be supported by a less structured maintenance program is an intriguing line of inquiry that deserves further study. Ultimately, the most effective and appropriate interventions will be those that can be readily implemented in a variety of settings and populations that aim to prevent the progression toward type 2 diabetes in overweight youth.

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