Published in final edited form as:

Exerc Sport Sci Rev. 2015 January ; 43(1): 41–47. doi:10.1249/JES.0000000000000034.

Exercise for Obese Youth: Refocusing attention from weight loss to health gains

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Abstract

Despite evidence to the contrary, exercise interventions for obese youth target weight loss as a means for improving health. Using Exercise is Medicine® as a framework, we present a conceptual model for the beneficial effects of exercise independent of weight loss in obese youth and highlight novel biomarkers of cardiometabolic health that could prove useful as interventional targets for this population.

Keywords

Exercise; obesity; cardiometabolic syndrome; youth; weight management; type 2 diabetes; insulin resistance

INTRODUCTION

Pediatric obesity has reached epidemic proportions in children and adolescents. In parallel with the current pediatric obesity epidemic is an increase in obesity-related health conditions including hypertension, dyslipidemia, and type 2 diabetes. Although still rare in young children, these conditions are becoming increasingly more common in adolescents and may ultimately contribute to a decreased life expectancy for obese youth.

Until population-based, public health strategies are able to shift trends in pediatric obesity, the burden of addressing weight-management among obese children and adolescents has fallen on healthcare practitioners. Using a simplistic biobehavioral model, lifestyle modifications that target decreased energy intake and increased energy expenditure to induce a negative energy balance is the cornerstone approach to weight loss. From a pragmatic perspective, this approach has proven to be of limited success in terms of treating pediatric obesity. In contrast, a growing body of literature suggests that it is plausible for

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Conflict of interest: The Authors have no conflicts of interest.

lifestyle modification, and more specifically exercise, to improve cardiometabolic health even in the absence of weight loss.(21, 31, 34, 36, 40, 41) Given that the majority of obese youth will remain as such for the remainder of their lives, we propose an alternative approach that targets reducing disease risk factors through exercise rather than weight loss.

The purpose of this review is to present recent evidence on the impact of exercise on disease risk factors among obese youth. We will briefly discuss the effects of exercise on ‘traditional’ risk factors for cardiovascular disease (CVD) and type 2 diabetes (T2D), collectively cardiometabolic disease, but will refer readers to several recent systematic review articles that have covered these topics extensively. The remainder of the review will focus on the potential for exercise to improve novel biomarkers of cardiometabolic disease independent of weight loss. Whenever possible, we will present data from exercise interventions in obese youth rather than cross-sectional or longitudinal studies examining associations between habitual physical activity and health across the spectrum of weight-status. Although the latter are important from an epidemiological perspective, their findings may be less-readily translatable than findings from intervention studies. For a more comprehensive overview on the associations between physical activity and cardiometabolic health in youth, we refer readers to an excellent review paper by McMurray and Ondrak.(30) Lastly, we will discuss gaps in the available science that need to be addressed in order to facilitate the translation of pediatric exercise research into clinical practice to support Exercise is Medicine® for obese youth. Figure 1 presents a conceptual framework for this review.

Obesity

Changes in body mass, BMI, and/or BMI percentile are the primary means used to assess ‘success’ of lifestyle interventions for obese youth in clinical practice. However, these indicators are not health-based measures and may misclassify youth in terms of adiposity as well as health status. Current clinical recommendations for obese youth call for a staged approach that takes into account age and the degree of obesity in order to set target treatment goals which do not necessarily call for universal weight loss.(3) Nonetheless, many studies and most clinicians rely primarily on decreases in body mass, BMI, and/or BMI percentile to determine health improvements for obese youth following intervention.(16) Based upon the available evidence, exercise alone should not be considered an effective approach for treating obesity among obese youth.(19) The weight loss observed from exercise is minimal. Further, exercise is unlikely to move an obese youth into the overweight category and the degree to which exercise alone may prevent further weight gain among obese youth is unknown. In contrast, exercise can lead to improvements in overall body composition among obese adolescents.(19) These improvements include increases in lean tissue mass and/or decreases in fat mass that result in a reduction in percent body fat. The reduction in percent body fat may be observed even in the presence of weight gain due to linear growth and development.

Type 2 Diabetes

While still considered rare, T2D is increasingly becoming a clinical problem among sub-groups of adolescents and especially those from minority populations. T2D is clinically

defined as hyperglycemia measured by fasting plasma glucose ≥ 126 mg/dl, 2 hour glucose ≥ 200 mg/dl following an oral glucose tolerance test (OGTT), or by HbA1c $\geq 6.5\%$. These clinical indicators are seldom used as primary intervention targets in pediatric exercise studies of obese youth. In contrast, researchers have historically focused on changes in insulin action (i.e. reductions in insulin resistance and/or increases in insulin sensitivity), which are thought to be central to the pathophysiologic process underlying T2D. Several reviews (26, 37) and a recent meta-analysis (11) have focused on the effects of exercise on insulin action in youth. Collectively, these publications support the efficacy of exercise training (both resistance and aerobic) to improve insulin action in obese youth and suggest that the health improvements are independent of changes in body weight or composition. (26)

Cardiovascular Disease Risk

Traditional CVD risk factors include resting blood pressure and fasting lipids / lipoproteins such as triglycerides (TG), total cholesterol (TC), low-density lipoprotein, (LDL), and high-density lipoprotein (HDL). These markers are useful in the context of clinical practice for stratifying CVD risk and have been shown to track into adulthood.(18) Several recent reviews have examined the utility of exercise to reduce resting blood pressure as well as lipid and lipoprotein profiles in obese youth. These include a meta-analysis of 9 randomized, controlled trials on 410 obese youth (n=205 intervention and n=205 control) which found that the overall effect size (ES) for exercise to reduce systolic blood pressure was modest (ES=-0.46) and only significant in 1/3 of the studies that met inclusion criteria.(13) In contrast, a larger meta-analysis encompassing 12 studies and 1266 youth failed to show significant beneficial effects of exercise on blood pressure.(20) Based upon these reports, the effects of exercise on reducing blood pressure among obese youth appear to be minimal. However, it should be noted that most participants studied were normotensive. An area for future research to explore is the utility of exercise training to reduce blood pressure in obese youth with prehypertension/hypertension, as exercise has been shown to significantly reduce blood pressure in otherwise healthy hypertensive youth independent of weight loss.(15).

In terms of traditional blood markers for CVD, Escalante et al conducted a meta-analysis of 7 studies totaling 356 obese youth and found that the effects of exercise on lipid and lipoproteins are equivocal with the largest effects observed for fasting plasma TG (ES=-0.55).(10) These results are in partial agreement with a previous meta-analysis that reported a trend for exercise to reduce TG by ~12% in children and adolescents. (19) Of note, the reduction in TG was found to be independent of changes in weight and body composition. Collectively, these meta-analyses suggest that the effects of exercise on traditional CVD risk factors are modest, at best, and provide the impetus for researchers to look beyond these traditional markers. To that end, a growing body of literature stemming from data in adults suggests a 'risk factor gap' exists whereby the cardioprotective effects of exercise are beyond what would otherwise be predicted or explained by changes in traditional risk factors.(14) Therefore, it is plausible to assume that the 'risk factor gap' may be even wider in youth as the period between elevated cardiovascular risk and eventual CVD outcome is expanded. In the sections below we will highlight studies that have examined the effects of exercise on novel and emerging cardiometabolic risk markers in

obese youth which may help close the ‘risk factor gap’ in younger populations and extend the science in the field.

Beyond traditional clinical markers

Clinical risk factors for CVD and T2D have their utility for individual risk stratification as well as population-based health assessment; however, their application within the scope of pediatric exercise science may be limited. For the most part, the long latent period between elevations in these risk factors and eventual chronic disease manifestation presents a challenge for understanding whether exercise interventions will have a direct and measureable impact on future health outcomes. An additional confounding factor is the heterogeneity of cardiometabolic risk even among obese youth, as not all youth present with risk factors despite their obesity status. Most intervention studies use BMI or BMI percentile as the cut-off for inclusion/exclusion and fail to take additional steps to classify or stratify the level of risk among participants upon entry. Therefore, even if the cohort is obese they may be otherwise healthy and exhibit little, if any change in non-elevated risk factors. In contrast, examining the impact of exercise on biomarkers that are physiologically related to the chronic disease processes may provide a more sensitive target to appreciate the effects of exercise on cardiometabolic health in obese youth. We will identify several novel markers of CVD and T2D and evaluate their potential utility for determining changes in cardiometabolic health in response to exercise for obese youth.

NOVEL MARKERS OF CARDIOMETABOLIC HEALTH IN OBESE YOUTH

Novel Type 2 Diabetes Risk Markers

Decreased insulin action is a core defect in the pathogenesis of T2D, but it is not sufficient to explain the resultant hyperglycemia that typifies this condition. Ultimately, inadequate insulin secretion relative to the degree of insulin resistance is necessary before overt hyperglycemia manifests. There is a hyperbolic relationship between insulin action and insulin secretion that provides an estimate of β -cell function. Therefore, to fully capture reductions in diabetes risk, a measureable improvement in β -cell function is necessary. To date, very few exercise studies in obese youth report improvements in β -cell function despite observing improvements in insulin action.(4, 35) Of note, a recent study by Davis et al,(9) found that 13 weeks of high-dose 40-min/day, 5 days/week) aerobic exercise training resulted in significant increases in insulin sensitivity as well as β -cell function as measured by the oral disposition index during an oral glucose tolerance test (OGTT). Youth receiving a lower dose of exercise at the same frequency 20-min/day, 5 days/week) exhibited increases in insulin sensitivity but not β -cell function. These findings suggest that higher volumes of exercise may be required for improving β -cell function in obese youth. A technical point of clarification that differentiates the study by Davis et al from previous studies showing exercise-induced improvements in insulin action was the use of an OGTT rather than an intravenous glucose tolerance test (IVGTT) or hyperinsulinemic-euglycemic glucose clamp (clamp) to assess insulin action. This point of clarification is warranted because although insulin action assessed via an OGTT in obese youth is correlated with IVGTT and clamp measures, these assessments reflect different physiological processes whereby OGTT-based measures are more dependent on β -cell function while the IVGTT

and clamp measures are thought to be more reflective of skeletal muscle insulin action.(7, 17) From a clinical perspective, the OGTT offers an appealing alternative to the more invasive procedures (IVGTT and clamp), because the resultant fasting and 2 hour glucose values allow for a complete glycemic risk profile. Physiologically, the OGTT may be a more integrative test of diabetes risk because the gut, which appears to be increasingly important to the pathophysiology of diabetes, is incorporated. More studies are needed in order to examine the utility of exercise to improve β -cell function and hence reduce diabetes risk in obese youth irrespective of weight loss. Moreover, it will be necessary for studies to incorporate robust measures of insulin action as well as insulin secretion in order to advance science in this area.

In addition to β -cell function, two emerging T2D risk markers that may prove useful in determining T2D risk reduction in response to exercise include 1-hour glucose levels during an OGTT and the “shape” of the glucose response curve during an OGTT.(1, 2) Studies in adults have shown that 1-hour glucose is a better prospective predictor of T2D than either fasting or 2-hour glucose.(1) Clinical studies in youth suggest that 1-hour glucose concentration during an OGTT is an emerging biomarker for T2D risk in youth.(25) We have recently observed that 1-hour glucose independently predicts the development of prediabetes and β -cell dysfunction among obese Latino youth.(25) Moreover, the predictive power of 1-hour glucose is stronger than other traditional glycemic indicators including HBA1c, fasting and 2-hour glucose.(24) We are unaware of any exercise training interventions that have specifically examined the ability of exercise to reduce 1-hour glucose concentrations during an OGTT in youth. However, Dr. Kevin Short generously provided data from his recently published study on the acute effects of exercise on postprandial insulin sensitivity following a mixed meal in sedentary adolescents.(38) These data show that a single bout of aerobic exercise (45 minutes at 75% peak heart rate) significantly reduced postprandial glucose concentrations at 60, 90, and 120 minutes but that the largest and most significant reduction was observed at 1-hour (FIGURE 2). Therefore, an area in need of more research is the ability of exercise training to reduce 1-hour glucose during an OGTT in obese youth.

In addition to 1-hour glucose levels, the “shape” created by plotting glucose concentrations during an OGTT, or the “glucose response curve”, provides an integrated assessment of diabetes-related health risk.(39) During a standard 2-hour OGTT, two main glucose responses are observed in non-diabetics: 1) a monophasic response (inverted U shape) and 2) a biphasic response (a second rise of plasma glucose after first decline) (FIGURE 3). In adults, individuals with a monophasic response are more insulin resistant and develop diabetes at a higher rate than those with a biphasic response.(2) Our group recently extended these findings to youth, observing that a monophasic glucose response was associated with a more deleterious metabolic profile including lower insulin sensitivity and decreased β -cell function.(23) These findings were independent of traditional glycemic markers (fasting and 2-hour glucose levels) as well as BMI. Collectively, these data suggest that different glucose response curve phenotypes provide a marker of T2D risk that is present well before the development of hyperglycemia.(23) Similar to 1-hour glucose, no pediatric studies have examined the effects of exercise on glucose response curves during an OGTT. Therefore, we utilized the data graciously provided by Dr. Short and observed that the prevalence of a

biphasic glucose response (healthy response) to a mixed-meal shifted from 33% on a non-exercise control day to 83% when acute aerobic exercise was performed 1-hour prior to mixed-meal consumption. Whether exercise training can shift the shape of the glucose response curve from monophasic to biphasic during an OGTT warrants further examination in overweight and obese youth.

To summarize, the potentially beneficial effects of exercise on novel T2D risk markers include improvements in β -cell function that may be volume dependent, reductions in 1-hour glucose concentrations during an OGTT, and a shift from a monophasic to a biphasic glucose response “shape” during an OGTT. It is important to mention that data supporting the latter two findings were in response to an acute bout of exercise. Given that the effects of a single bout of exercise and the adaptations observed in response to chronic exercise training may impact glucose homeostasis through different physiologic mechanisms,(8) it may be premature to conclude that the observed changes in these novel markers following acute exercise will correspond to long-term T2D risk reduction that occurs with exercise training.

Non-traditional CVD risk factors - Lipoprotein Particle Size and Cholesterol Distribution

Traditional clinical measures of total cholesterol concentrations, particularly LDL and HDL, may not be as useful for predicting CVD risk as the size, density, and/or number of LDL and HDL particles.(28) Due to their heterogeneity, using total LDL and HDL cholesterol concentrations provides only a gross estimate of the phenotype of each lipoprotein particle. Although LDL cholesterol is thought to be an important predictor of CVD risk, small, dense LDL particles are considered to be more atherogenic than larger particles. These particles are more readily oxidized and can easily traverse the arterial wall where they can promote endothelial dysfunction and plaque formation.(29) Therefore, measuring LDL and HDL particles directly may provide better assessment of CVD risk through measures that are more proximally related to the atherosclerotic process. In addition to CVD risk assessment, changes in LDL and HDL particles are important outcomes to measure intervention efficacy. For example, in adults, exercise without weight loss, decreases the concentrations of small LDL and LDL particles and increases the size of LDL particles, without changing total LDL concentrations.(27)

In youth, LDL and HDL particle size and distribution may be better able to differentiate CVD risk in dyslipidemic obese youth compared with a traditional lipid panel.(5) Very little is known about the effects of exercise on LDL or HDL particle size and/or cholesterol distribution in obese youth. Only one study to date has examined the impact of exercise on LDL particle size and distribution and found that 4 months of exercise training in obese youth (4–5 days/week for 40 minutes at HR>150bpm) did not result in significant changes in LDL particle size.(12) However, significant reductions in triglycerides were observed and these changes were inversely correlated with change in LDL particle size ($r=-0.38$, $p=0.02$). These data suggest that those youth who lowered triglycerides the most exhibited the largest increase in LDL particle size. Since very little exercise data exist, we bring attention to our recently completed 12-week lifestyle intervention in obese Latino adolescents.(34) The intervention included an hour of nutrition education along with three, 60-minute moderate to

vigorous (heart rate > 150 BPM) physical activity classes per week.(34, 36). The intervention resulted in increases in mean LDL-particle size and cholesterol in large HDL subfractions along with decreases of cholesterol in small LDL and HDL subfractions. These improvements were accompanied by improvements in traditional CVD risk factors including total and LDL cholesterol as well as triglycerides but without significant weight loss. Given that nutrition education was provided in addition to exercise, we cannot determine the degree to which exercise and/or dietary changes contributed to the observed improvements. More evidence is needed in order to determine if exercise alone can improve lipoprotein particle size and cholesterol distribution, or if the combination of exercise and dietary modification is necessary.

Vascular Markers of Health

Impaired endothelial function (i.e., endothelial dysfunction) is one of the earliest manifestations of the atherosclerotic process. It is characterized by the inability of endothelial cells to produce sufficient amounts of nitric oxide (NO) resulting in lack of vasodilator capacity of the vascular system.(42) Endothelial dysfunction is observed in obese youth and to an even greater extent in obese youth with T2D.(33) Given that endothelial dysfunction precedes and predicts the development of CVD and adverse cardiovascular outcomes in adults, (42) it stands to reason that, improving endothelial function in obese youth represents a potential target for exercise interventions aiming to attenuate or delay the atherosclerotic process.

Growing evidence suggests that exercise can improve endothelial function in obese youth. Kelly et al reported a 23% improvement in endothelial function in obese children and adolescents following a progressive, 8-week cycling program (4 times/week progressing from 50–60% VO₂peak for 30 minutes to 70–80% VO₂peak for 50 minutes) (21). Similarly, Watts et al, showed that 8 weeks of circuit training (three, 60-minute sessions/week of cycling at 65–85% heart rate max and resistance training at 55–70% max) was able to increase endothelial function in obese youth to a level similar to lean peers (40). The authors postulated that endothelial dysfunction in obese youth could be normalized through exercise (FIGURE 4). Neither study resulted in weight loss or changes in BMI, nor were appreciable changes in traditional CVD risk factors noted in response to exercise. In summary, these studies support a powerful effect of short-term exercise on endothelial function in obese youth that is not dependent on weight loss and unrelated to changes in traditional CVD risk factors. An area in need of further research is to better determine the time course and durability of exercise-induced improvements of endothelial function in obese youth. Also, given the technical challenges with assessing endothelial function, more studies examining the impact of exercise on blood-derived biomarkers of vascular health such as vascular adhesion molecules, inflammatory mediators, and markers of oxidative stress are needed. (22)

SUMMARY AND FUTURE DIRECTIONS

Despite recent secular trends suggesting that the prevalence of obesity may be leveling off in youth, the sheer number of obese and severely obese youth remains problematic. Clinicians are faced with a challenge in terms of treating weight-related health issues among obese

youth as the available science on how best to manage this obesity in youth is limited. In this review, it is not our intention to minimize the potential benefits of weight management on long-term health. However, it is clear that sustained weight loss is an increasingly challenging and complex endeavor, which will require a combination of exercise, dietary modification, and behavior modification strategies. In contrast, a growing body of evidence supports the utility of exercise alone to improve the cardiometabolic health of obese youth even in the absence of weight loss. Nonetheless, we believe the evidence-base supporting exercise needs to be further expanded upon by pediatric researchers to facilitate Exercise is Medicine®.

Given the extended timeframe needed to link the beneficial effects of exercise on CVD and T2D in obese youth, we have highlighted several emerging markers that show potential as biomarkers related to the pathophysiology of cardiometabolic disease. In addition to expanding upon markers of cardiometabolic health, pediatric researchers should work towards optimizing exercise parameters (frequency, intensity, duration, and mode) needed to observe health improvements. Current physical activity recommendations for health promotion and disease prevention in youth call for at least 60-minutes of moderate-to-vigorous physical activity daily. However, the majority of exercise intervention studies in obese youth observe health improvements with much lower dosages. An important distinction needs to be made between public health physical activity recommendations and exercise prescriptions where the latter optimizes the dose-response for a specific outcome. In this context, more work on the dose-response effects of exercise on cardiometabolic health in obese youth is needed. This work should move beyond the randomized-controlled clinical trial model to look for more clinically relevant means of assessing the effects of exercise and physical activity on health markers among obese youth. As an example, comparative effectiveness trials could compare the effects of aerobic vs. resistance exercise on traditional and novel cardiometabolic health markers. Approaches should also examine the mechanisms for the biological heterogeneity observed in cardiometabolic risk factor change between individuals in response to the same exercise prescription. As an extreme example, Bouchard and colleagues recently found that almost 7% of adults experience a worsening of cardiometabolic risk factors in response to exercise.(6) Using gene expression profiling in whole-blood, we have observed that distinct molecular signatures differentiate obese youth who respond favorably to lifestyle intervention from those who do not.(32) Collectively, these data suggest that the biological response to exercise may be dependent on innate factors that must be accounted for in exercise studies on health. Lastly, a better understanding of the mechanisms by which exercise can break the link between adiposity and cardiometabolic disease may help propel pediatric exercise research to the forefront. These data will be instrumental for the translation of research into practice and support Exercise is Medicine®.

ACKNOWLEDGMENTS

We wish to thank Dr. Kevin Short for his generosity in sharing his data on glucose response to exercise in sedentary adolescents.

This work was supported, in part, through a grant from the National Institutes of Health, National Center on Minority Health and Health Disparities (P20MD002316). J.R.R. is supported by a training grant from the National Institutes of Diabetes and Digestive and Kidney Disorders (T32DK083250)

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Figure 1.
Conceptual framework for exercise to improve cardiometabolic health in obese youth independent of weight loss.

Figure 2.

Changes in fasting and postprandial glucose concentrations following an acute bout of aerobic exercise in sedentary adolescents (N=12). Black bars are glucose concentrations on the control day (meal only) and grey bars are glucose concentrations when the meal was preceded by exercise. Data are presented as mean $\pm$ SE.

Figure 3.

Representative glucose response curves following a 2 hour oral glucose tolerance test in 2 obese youth with similar fasting and 2 hour glucose levels. Monophasic response is shown in dashed lines and biphasic response is shown in solid lines. Smoothed lines are derived from plasma glucose concentrations at fasting, 30, 60, 90, and 120 minutes.

Figure 4.

Endothelium-dependent flow-mediated dilation (FMD) of the brachial artery in lean control subjects (lined bar) and obese subjects after eight weeks of inactivity (open bar) and eight weeks of circuit training (solid bar). Data are expressed as the mean value $\pm$ SE. Although FMD was significantly impaired in obese subjects relative to matched lean controls at entry ($p < 0.05$), exercise training was associated with normalization of the response ($p < 0.05$).

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