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The Influence of Exercise on Metabolic Syndrome in Youth: A Review

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Abstract

The metabolic syndrome (MetS) is a clustering of, dyslipidemia, hypertension, glucose intolerance, and central obesity, or waist circumference that places individuals at high risk for developing cardiovascular or heart disease. Although first characterized in adults, it has been found in children; however, the definition of MetS in children is still controversial. Although MetS is most closely associated with obesity in children, two factors believed to impact MetS are physical activity (PA) and aerobic power or fitness. Studies using accelerometry to estimate PA of children have shown that low levels are associated with increased risk of developing MetS. Conversely, high levels of moderate to vigorous intensities reduce the risk. Similarly, low levels of aerobic fitness increases the likelihood of developing MetS. These effects appear to be independent of obesity. Studies have also shown that interventions that increase PA levels and improve aerobic fitness cause a reduction in MetS risk; however, an exact prescription for exercise cannot be presently provided. This review will provide an in-depth analysis of what is presently know about the relationship between MetS and PA and aerobic fitness in children. In addition, information will be presented regarding potential mechanisms for exercise to impact the major markers of MetS.

KEY WORDS: Physical Activity, Fitness, Aerobic power, Children

The metabolic syndrome (MetS) was first described in the mid-1990 by Reaven[1] as "Syndrome X" and recently has also referred to as the "Insulin Resistant Syndrome".[2-4] It consisted of dyslipidemia, hypertension, glucose intolerance, and obesity which, when all factors are present, leads to the greatest risk for developing cardiovascular or coronary disease. Since this initial description, the definition has been refined to include low HDL cholesterol, high circulating triglycerides, hypertension, glucose intolerance and central obesity or waist circumference.[5] Although MetS was first described in adults, a retrospective evaluation of pediatric data as far back as the NHANES I study (1988-1994) conducted in the USA suggests that the MetS characteristics exist in 3-14% of all youth (children & adolescents) and in 13-37% of obese youth.[6]

MetS is based on the fact that these risk factors are not independently distributed in the population, but clustered in some individuals. This concept of clustering is somewhat controversial as some researchers have suggested that there is no single etiology.[2,7] Pladevall et al. (2006), however, using single-factor modeling, has shown that all components of the MetS can be linked by a common factor.[8] Not only is the concept of MetS controversial, but the exact cut-points for each of these characteristics and the number of them that need to be evident to identify MetS has been the focus of numerous manuscripts.[5,9]

Although there appears to be consensus regarding the risk factors for MetS in adults, there appears to be no consensus for the definition in children and adolescents. The reason for the lack of consensus lies in the fact that children do not routinely exhibit cardiovascular disease; thus it is difficult to relate the criteria to a health outcome. For example, Weiss et al.[10] suggested that a blood pressure >95th percentile for age, height, and sex, is the cut-point, whereas Cook and associates[11] suggested the 90th percentile. Similarly, Weiss et al.[10]recommended HDL <5th

percentile, while Cook et al.[11] proposed HDLs below 40 mg/dL. Recently, Jollifee and Janssen[12] used growth curve modeling to develop age and sex-specific criteria for MetS in youth based on the accepted criteria for adults. This approach is logical because the risk factors have a propensity to track from childhood through adulthood and the adult risk factor cut-points are clearly associated with the development of cardiovascular disease.[13] The most biologically meaningful approach may be to select the children where risk factors were not independently distributed, as done by Andersen et al. in 2003.[14]

Another approach used in publication from the European Youth Heart Study (EYHS) is to develop an age and sex-specific metabolic risk score based on z-scores for each of the MetS characteristics.[15--17] The authors argue that since there is no accepted definition of MetS in children, the z-score provide a continuous score which may be more appropriate for investigating associations. Dichotomization of each variable causes reduction in the information and therefore the diagnostic value. One system used a standardized score developed as a sum each of seven criteria (insulin, glucose, triglyceride, HDL-cholesterol, skinfolds, diastolic and systolic blood pressure). The standardized score used the subjects value minus sample mean, divided by standard deviation to produce a continuous overall MetS risk score.[17] The lower the standard score the more favorable the overall profile. However, this score has the problem because it lacks a cut-point above which to identify MetS. An identifying cut-point was found through another analysis where upper quartile in each risk factor was defined to be at risk, and the number of risk factors was then summed in each child. By using this approach the authors were able to calculate when risk factors were not independently distributed. An independent distribution of the risk factors would follow a binominal distribution, and the authors calculated for each number of risk factors if there were more children than expected from the binominal

distribution. This approach selected between 10-15% of the children to have clustered risk, and the cut point in the continuous z-score could now be defined. [19] Since this approach was study-specific comparisons with other studies could be difficult. However, data were available from three different countries, and it turned out that almost the same z-score defined clustered risk in the different populations, which may indicate that cut points may not be population specific. Because the number of children which could be defined with clustered CVD risk was close to 15%, the authors suggested that the youth with z-scores > one SD were considered at risk. This approach does allow for the MetS score to be continuous and possibly makes it easier to compare scores between populations of children. However, when Ekelund et al. calculated how many of these children were diagnosed with MetS using the International Diabetes Foundation definition[9] they only found 0.2% among 10 yr olds and 1.4% among 15 yr olds in the same subjects. Thus, the controversy remains, but the low numbers with MetS using the International Diabetes Foundation definition suggests that this definition is problematic, because we know that risk factors cluster in many more children.

The use of MetS risk factors as continuous variables could improve our categorization because available information is not lost. Equations for summing z-scores from reference data could be made available on the internet so it would be possible to calculate the mean z-score above which risk factors cluster. This approach could improve diagnostic capabilities. The approach could also be used to quantify the improvement the odds ratio for having MetS comparing the lowest quartile compared to the upper quartile of fitness. This may be appropriate for measures of aerobic fitness and physical activity. For example, using data from the EYHS Wedderkopp and associates[20] noted that the lowest quartile of fitness had approximately 6 times the risk for MetS compared to the upper quartile, but when the association was calculated using

continuous z-scores, which was dichotomized to select the same number of children at risk, an odds ratio of 15 was found.[21] Last, the selection of risk factors included in MetS may be of concern. For example, low fitness was not included in the definition when MetS was first introduced, but it is now accepted as an independent risk factor, which makes sense considering the role of muscle tissue in metabolism.

Regardless of the definition of MetS, early risk factor management in youth may have the potential to reduce premature death by cardiovascular disease.[22] Obesity appears to be a key factor related to the development of the MetS[5] and obesity is linked to all the components of the MetS.[2,13,23-25] For many individuals, obesity has its roots in childhood and tracks into adulthood;[13,26] thus prevention or reducing weight gain is of primary importance. Two factors linked to obesity are diet and exercise. A lack of exercise, or physical inactivity, causes poor aerobic fitness and both of these exercise attributes have been linked to increased risk of cardiovascular disease[27,28] and insulin resistance.[29] Thus, physical activity may have a role in the prevention of or ameliorating MetS.

This review will focus on the potential role of exercise to reduce the risk of developing MetS in children. The impact of exercise on MetS is important because McMurray et al. has shown that low levels of physical activity and poor aerobic fitness during childhood are associated with the development of MetS during adolescence.[30] Also, since physical activity and aerobic fitness have independent effect on the components of MetS in adults,[31] and in children[15,16] these behaviors and traits and their relationship to MetS in children will be examined separately. The review will first examine the relationship of MetS with habitual levels of physical activity. This will be followed by a discussion of intervention studies focused on reducing the risk factors of MetS. These interventions typically increase physical activity level

over and above habitual levels of PA and also include some dietary constraints. The focus then turns toward the association between of aerobic power or fitness and MetS. The final section will provide some insights into potential mechanisms regarding the role of exercise in protection from MetS.

Habitual Physical Activity

Studies in adults have found associations between the prevalence of MetS and low levels of energy expenditure,[31] low levels of moderate intensity exercise,[32,33] or lack of vigorous intensity exercise.[33] The relationship between the MetS and PA levels is appropriate when one considers the well-established dose-response relationship of PA and cardiovascular disease risk factors.[34] Physical activity can influence weight status by increasing energy expenditure, as Abbott et al. found that individuals with the most vigorous PA had the lowest percentages of body fat and BMIs.[35] In addition, participation in regular PA, especially if vigorous, has the potential to increase aerobic power or fitness in children.[36] Thus, there is indirect support for a positive influence of physical activity on the development of the MetS.

Studies in children and adolescents regarding the influence of PA levels on the MetS are sparse and inconsistent. One problem with assessing PA in youth is the methodology. Some studies have used survey or questionnaires. These instruments rely on the ability of youth to recall what they did on previous days or weeks, and this ability appears limited in young children and even adolescents as there is a limited relationship between actual PA levels and stated PA on the questionnaire.[37] This could lead to inconsistent conclusions regarding PA and MetS. For example, Pan et al.[38] used the PA section of the NHANES 1999-2002 questionnaire and found no significant relationship between PA and MetS in 4450, 12-19 yr old adolescents. Andersen and associates also reported no association between self-reported PA and MetS in 305 youth

participating in the Danish Youth and Sport Study.[39] Conversely, Moore et al. using the Youth Risk Behavior Surveillance found that after adjusting for sex, race and age, those youth reporting low PA had three times the risk of MetS compared to youth with high PA levels.[40] Unfortunately, the authors did not report the number of their 116 youth that had the MetS, so it is difficult to interpret their risk ratios. McMurray et al. also using a validated questionnaire, found that children who developed the MetS as adolescents had 22% lower PA scores than those youth who did not develop the MetS (18 of 389 youth were characterized as having MetS).[30] Interestingly, the same authors reported that 8-10 year olds with low levels of PA had four-to-five times the risk of having the MetS seven years later as adolescents. Finally, Kelishadi and associates, also using a PA questionnaire in 4811, 6 to 18 yr olds, found the overall rate of MetS was ~13% in the highest tertile of PA and ~15% in the lowest tertile of PA.[41] Furthermore, those youth with low PA levels were 1.6 to 1.8 times more likely to have MetS. This association was independent of age or sex. Thus, although statistically significant, the clinical significance of a 2% (~32 cases) difference is uncertain.

The findings of a relationship between PA and MetS have been more consistent when accelerometry was used to estimate PA. Accelerometers measure acceleration and deceleration, such that more accelerometer counts mean more movement; thus, more PA. Brage et al. determined the relationship between 3-6 days of accelerometer measured PA and the MetS z-score in 389 Danish children.[16] They found that as PA decreased, MetS z-score increased. A study of 529, nine and fifteen year old Swedish youth also found an inverse relationship between PA and MetS, particularly in their fifteen yr old girls.[17] They suggested that the relationship was strongest because the 15 yr old girls had the lowest levels of PA. Other studies from the European Youth Heart Study measured PA levels with accelerometry in 1730 to 2800, nine and

fifteen yr old youth and used a z-score classification for MetS.[15,19] They found that all youth in the second through fifth quintiles[19] or the lower three quartiles[15] of PA had increased risk of MetS compared to those in the first or highest quintile (O.R.~ 1.81 to 3.29). Furthermore, their accelerometry data suggests that moderate-to-vigorous PA must increase to about 90 min/day to reduce the risk of insulin resistance and thus, MetS.[19] Holmes et al. developed a MetS risk z-score based on blood pressure, HDL-C, hemoglobin A1c, and waist circumference in 37 boys.[42] PA was estimated from 4-days of accelerometry. The correlations between total, moderate, vigorous PA and the MetS score were low (r~-0.09 to -0.13), but in a favorable direction. The low correlations may have been a result of the small sample size and large variability in the PA measurements. Although in general, the data on the association between MetS and PA measured by accelerometry are not completely convincing, the associations are in the expected direction.

Intervention Studies

Studies of habitual physical activity should not be confused with intervention studies. Habitual PA refers to the child's normal participation in physical activity, whereas intervention studies typically introduce activity levels *above* habitual levels. Most attempts to intervene with children at high risk for MetS have included a combination of diet and behavior modification, as well as exercise. Thus, determining the extent of the influence of exercise is difficult. For example, Chen et al. examined the influence of two-weeks of a high fiber /low fat diet and daily aerobic exercise on MetS.[43] They found that after two weeks there was no significant weight loss, but 7 of the 16 subjects with MetS had reversed their categorization. Similarly, Monzavi and associates used a 12-week nutrition education (45 min) and exercise (45 min) program to reduce the risk factor for MetS in 59 overweight early adolescents.[44] The exercise program consisted most of games and activities to promote moderate-to-vigorous PA. Although weight

did not significantly change, MetS risk profile improved. These two studies suggest that although obesity is related to MetS, the risk of MetS can be reduced without weight loss.

The interpretation of the importance of exercise in intervention studies is compounded by the fact that some studies also included medications, diet and behavior modification, as well as exercise. For example, a study of Chinese obese youth found that Metformin, in combination with a low-fat diet and 30 min of moderate-intensity aerobics, improved clinical symptoms of MetS.[45] Therefore, the significance of each part of the intervention cannot be determined. Another problem related to the independent effect of training and fitness on MetS is that it may be very difficult to train without changing body composition. Loss of weight can improve the ability to exercise. Also, loss of weight can result in improvements in aerobic power expressed per unit of body weight, even though no biochemical or cardiovascular improvements occurred in the muscle's ability to obtain or and utilize oxygen. Further, adjustment for body fat may be the same as removing part of the effect of exercise, because the changed body composition is a result of training.

Three studies of MetS in youth have focused on exercise training. Kang et al. (2002) completed an 8-month intervention with 80 obese youth comparing lifestyle changes with moderate (55-60% of maximal capacity) and high-intensity (75-80%) exercise programs; both programs expending the same amount of energy.[46] Although both exercise programs improved the markers of MetS, the high intensity exercise had a somewhat greater influence. Kelly et al. randomly assigned 20 overweight adolescents to a 30 min exercise session (50-60% of maximal capacity) or a control group.[36] They found that after eight weeks, those in the exercise group had improved their MetS profile, especially their HDL cholesterol and endothelial function. Ferguson et al. using a randomized, modified cross-over study design, assigned obese children to

one of two conditions: four-months of exercise training followed by four-months of no-exercise training, or the reverse.[47] Measurements were made at three time points: 0, 4 and 8 months. Significant ($P<0.05$) group-by-time interactions were found for plasma triglyceride and insulin concentrations and percent fat. The average change for both groups when they exercised was -0.24 mmol/L for triglyceride, -25.4 pmol/L for insulin, and -1.6 percent for bodyfat. These benefits were lost when the children become less active. Thus, the evidence supports the contention that an exercise intervention, over and above habitual levels of PA, improves MetS profile of youth.

Aerobic Power or Fitness and MetS

Aerobic power, also known as aerobic fitness or cardiorespiratory fitness, is a measure of the maximal amount of energy muscle can produce by aerobic catabolism. It is typically obtained by measuring oxygen uptake during a graded exercise test and is consequently also referred to as VO_2max. The results are expressed in units of milliliters or liters of oxygen, 1) per minute (mL/min or L/min), 2) per kilogram body mass (ml/kg/min or ml/$kg^{0.67}$/min) or 3) per kilogram of fat-free mass per minute (ml/kg_{FFM}/min). Each of these units can be problematic when describing aerobic fitness for the general population. Expressing aerobic power in terms of mL/min (or L/min) favors heavier over lighter weight children (or adults) at comparable heights, or taller over shorter individuals, because the heavier or taller have more metabolically-active muscle tissue than a normal weight or shorter individual at the same height. Although taller and heavier persons have higher absolute VO_2, if they have to carry their own weight (walking or running) they are at a disadvantage. For example, it is not uncommon for an adolescent American football player who is 1.88 m tall, weighs over 91 kg, with 25% body fat and ~68 kg of fat free mass, to have an absolute maximal aerobic power (VO_2max) of 4 L/min, whereas a 1.7

m tall, 55 kg adolescent runner with 5% body fat and a fat free mass of approximately 52 kg may have a lower, but still fairly high absolute aerobic power of ~3.5 L/min.

Expressing oxygen uptake in terms of mL/kg/min can also be problematic because this unit includes not only fat-free but fat and bone mass. Thus, larger individuals (including obese) usually have lower aerobic power expressed per kilogram body mass. From the example above, the football player would have an aerobic power of ~44 mL/kg/min and the runner would have a value of ~63 mL/kg/min. However, if both individuals are walking at the same speed their energy expenditure relative to body mass (METs) would probably be similar, but the runner would be working at a lower relative percentage of maximal power.

To reduce confusion and to obtain information on the metabolic process in the muscle, the best way to express aerobic power may be in terms of fat-free mass, which eliminates fat from the equation. Estimating fitness on what the muscle can actually accomplish may also be optimal, since Wells et al. have shown that there is some skeletal muscle dysfunction associated with MetS.[48] Further, since obesity is highly related to MetS, removing fat mass from the equation allow aerobic power to become a truly independent factor.[5] Thus, still using the above example, the aerobic power of our football player would be ~59 mL/kg_{FFM}/min whereas the runner would be ~67 mL/kg_{FFM}/min; indicating that the muscle of the runner has a greater capability to produce and utilize energy than the football player.

Another technique is to report data in terms of mL/kg/min, but then adjust for body fat statistically. Such an approach may be problematic because of the collinearity between body mass in the unit for aerobic power and body fat, but the approach has been used (Torok 2001). To avoid the collinearity problem, Andersen and associates suggest the use waist circumference or sum of skinfolds rather than body fat.[15] To circumvent the problem of units all together, an

alternative approach may be to use "time on task" during a standardized progressive exercise test protocol. The longer the walk/run time the better the aerobic power/fitness. However, an argument could be made that the metabolic cost of ambulation on a treadmill is still weight-dependent; thus, lighter individuals have an advantage. Conversely, if two individual are approximately the same weight, the one with the longer time on task is most likely to have a higher fitness. In addition, if a heavier individual walks longer than a lighter individual, the heavier individual would have a better aerobic fitness level. Since there appear to be problems with most measures of aerobic power or fitness, the reader needs to be aware of the units used to interpret correctly the results of the study.

Several studies of MetS in adults suggest that aerobic power is lower in individuals with MetS than those without MetS.[31,32,49,50] Three of the studies reported aerobic power in units of mL/kg/min which may be problematic, because the unit of measure includes body fat, which is part of the characteristics of MetS. Liu et al. reported that adult aboriginal Canadians with MetS had lower aerobic power than those without MetS.[49] Since the subjects with MetS had higher percentages of body fat and since body mass was not reported, the interpretation of the results is difficult because estimates of differences in the metabolic capacity of the muscle cannot be clarified. Similarly, Lakka et al. found that adults with MetS had lower aerobic power than those without MetS, but did not provide any estimate of body mass or body fat.[32] Conversely, Whaley et al. reported on aerobic power and also treadmill time for over 19,000 adults.[50] Not only was aerobic power less in those with MetS compared to those without MetS clustering, but the treadmill time appeared to be less for those with MetS. Treadmill time is best related to ml/kg/min because subjects carry their own weight including their body fat while walking or running. Wareham and associates also reported an inverse relationship between aerobic power

and MetS.[31] Since their subjects with and without MetS had similar BMI and body fat, the results are indicative of a lower metabolic capacity of the muscle in adults with MetS.

More studies have examined the relationship between MetS and aerobic power in youth than have examined the relationship between MetS and physical activity. The majority of evidence suggests a strong inverse relationship between MetS and aerobic power in children, when aerobic power is expressed per kilogram of body mass. Anderssen et al. studied approximately 2000, nine- and 15-year old youth and found a 13 times increased risk of MetS for those youth the lowest quartile of fitness compared to those in the top quartile.[21] The association remained strong even after adjustment for fatness.[15] Rizzo et al. examined over 200 nine-year old and a similar number of 15-yr old youth and found that those with the lowest aerobic power, expressed in units of mL/kg/min, had the highest risk for MetS.[17] When the relationship between MetS and aerobic power was adjusted for fat mass, the association was weakened, but still evident. Another study compared the aerobic power of 22 obese adolescent boys with MetS to 17 obese adolescents without MetS and 29 normal weight adolescents.[51] The researchers found that there were no differences in absolute aerobic power (L/min) between the three groups, but when normalized for body mass (mL/kg/min), all the *obese* boys (with or without MetS) had lower aerobic power than the *normal weight* boys. Of most importance, when aerobic power was normalized for body weight, the obese boys exhibiting MetS had lower power than the obese boys without MetS. However, the mass of the obese boys with MetS was approximately 15 kg greater than the obese non-MetS boys. Thus, when peak aerobic power was recomputed based on fat-free mass, the differences between the two obese groups was almost eliminated. However, the normal weight boys still had higher values than either of the obese groups of boys.

This suggests that the metabolic capacity of muscle was diminished in their obese boys, but the presence of MetS did not further reduce the metabolic capacity of the muscle.

In a study of 589 Danish Children, Brage and Associates measured aerobic fitness using a progressive cycle ergometry test, but instead of measuring oxygen uptake they measured power output (watts).[16] The authors provided their fitness data in terms of watts/kilogram body weight which is similar to oxygen uptake expressed in units of mL/kg/min. They found an inverse relationship between MetS z-score and their measure of aerobic fitness. Further they reported significant inverse relationships between fitness and insulin, triglycerides, blood pressure and skinfolds, as well as a positive relationship between fitness and HDL cholesterol. Anderssen et al. followed a similar exercise protocol to Brage and reported that low cardiorespiratory fitness was a strong predictor of MetS in nine and 15 yr old children.[21] Since both of these studies reported their results with respect to body mass; one cannot determine whether fitness or fatness is the most salient factor. In an attempt to unravel the fitness-fatness controversy, Andersen et al. re-analyzed the EYHS data for the relationship between fitness and MetS by adjusting the analyses for sum of skinfolds or waist circumference.[15] Both of these analyses resulted in maximal aerobic power being inversely and independently related to Mets z-score.

A study of 484 adolescents participating in the Aerobics Center Longitudinal Study found that those adolescents with low aerobic power, regardless of BMI, had higher MetS risk scores.[53] Moreover, those adolescents with the highest BMI and lowest aerobic power had the highest MetS scores. In this study aerobic power was based on treadmill time to exhaustion using a standardized protocol. Although when walking on a treadmill the person carries their own weight, longer walk times suggest higher aerobic powers, regardless of weight.

DuBose et al. examined the relationship between MetS and aerobic power in 375 normal and overweight 7-9 year old children.[53] The authors chose to estimate aerobic power from the PWC_{170} cycle ergometry test and used watts/kilogram body weight in their analyses. The PWC_{170} test estimates maximal aerobic power from the heart rate-work rate relationship obtained from three submaximal workloads.[54] They found and inverse relationship between MetS scores and aerobic power, with the lowest fitness and highest BMI group having the highest MetS score. The authors suggested that fitness contributed to MetS, independent of weight status.

Two studies have also resulted in similar findings. Ruiz et al.[55] added the data from Estonian children to the previously reported Swedish children's data[17] and using a cross-sectional design of the 873 children found an inverse relationship between MetS z-score and aerobic power. Aerobic power was obtained from a maximal cycle ergometer test and expressed per kilogram body mass. Data from McMurray et al. also suggest that adolescents with MetS have lower aerobic power expressed in mL O_2/kg/min.[30] Interestingly, for both studies girls with aerobic power values <37 mL/kg/min and boys with <42 ml/kg/min were at highest risk for MetS. Like other studies, when aerobic power was expressed per unit of fat-free mass, differences between the groups did not persist. An interesting aspect of the McMurray study was that those youth with low aerobic power as children were eight-times more likely to develop MetS compared to those with higher aerobic power.[30] This relationship was weaker, but persisted when aerobic power was expressed in units of fat-free mass. These results support the previous works of Wells et al.[48] suggesting differences in the metabolism of muscle between MetS and non-MetS youth. An interesting observation was made by Eiberg et al.[56]. They measured VO_2max directly during maximal running on a treadmill, and found only a doubled risk of MetS in the lowest quartile of fitness in 6-7 year old children. However, when they

examined these children three years later the strength of the association had increased (OR>10). The results of the Eiberg and McMurray studies suggest that either MetS takes time to develop, or that children become more sedentary when once in school.

Lin and associates used a novel approach to study MetS and aerobic fitness, using heart rates obtained during and 1-3 min after a standardized treadmill protocol to predict aerobic power. [57] A higher heart rate, or a slower return of heart rate toward baseline after exercise typically signifies a lower level of aerobic fitness. In their sample of 993 youth, a slower rate of heart rate recovery from the exercise protocol, as indicated by the 3-min post-exercise heart rate, was directly related to MetS score. This approach removes weight status from their estimate of fitness. Ironically, the authors chose to report aerobic power, but did not present their MetS results with respect to aerobic power. However, these results based in the heart rates points to an independent effect of aerobic power/fitness on MetS.

Two studies have examined the relationship between MetS and aerobic power as children age. One study followed a cohort of 389 youth aged 8-10 years for seven years.[30] Aerobic power was estimated from a cycle ergometry test and was expressed per kilogram body mass, or per kilogram fat free mass. Using either units, aerobic power was lower in those that developed MetS than those without MetS. The other longitudinal data comes from the Danish Youth and Sport Study in which they tracked adolescents through early adulthood.[39] They obtained aerobic power by maximal testing and expressed power in units of L/min and mL/kg/min. Regardless of the units, the authors reported stability (persistence) in the relationship between MetS and aerobic fitness from the initial to final testing. These two studies suggest that low aerobic power during childhood is predictive and consistent with increased risk for later development of MetS.

The aforementioned studies, as well as many others, have shown that aerobic power has been independently associated with the risk factors of the MetS; blood pressure, cholesterol, and insulin.[34,36,58-61] Since aerobic power was related to each of the major factors of MetS, a relationship between MetS and aerobic power is appropriate. Genetics strongly influences aerobic power, accounting for 25-60% of the total phenotype variability.[62] Genetics also appears to influence fat metabolism, fat deposition, and BMI, important factors for the development of the MetS.[62] However, a one-leg training studies that included both type 2 diabetics and healthy individuals have shown a doubling of the glucose uptake in the muscle of the trained leg compared to the untrained after a few months of training, and the two legs share genes and the rest of the body which emphasizes the importance of lifestyle.[63] Regardless of the reason for the association of the MetS and aerobic power, the presence of the MetS during childhood and adolescence is strongly related to low aerobic power.

Potential mechanisms for the Influence of Exercise on MetS

Exercise has the potential to impact the major markers of MetS through a number of metabolic pathways. Some of these pathways are better supported in the literature than others and some of the pathways are still controversial. Although most of the evidence for these mechanisms has been derived from animal and adult human research, the evidence is accruing in children that many of these pathways and components are active. This short section will summarize these proposed mechanisms and is not designed to be a complete review. Such a review, although needed in the literature, is beyond the scope of this presentation.

<u>General Effects</u>

Exercise has been shown to help with weight control and if sufficient can result in weight loss. Weight loss via exercise results in less loss of fat-free body mass (muscle) than weight loss

through diet.[64] The maintenance of lean body mass is important for improving glucose transport and also for improving metabolism of fat. The loss of fat mass is important for reducing leptin, increasing adiponectin and improving cytokine profile, all of which have been linked to the MetS. However, 80-90% of the ingested carbohydrate is stored or metabolized in muscle cells, and insulin sensitivity and insulin levels are known to be key factors in the development of MetS, which emphasize the importance of exercise.

Regular participation in exercise has been shown to improve blood pressure in individuals with elevated pressures. This has also been shown in a randomized trial in children.[65] The mechanism is not fully elucidated but is in some way related to a reduction in total peripheral resistance, possible by lower sympathetic tone,[66] or a reduction in inflammatory responses.[97-69] Exercise also increases nitric oxide which is a natural vasodilator. Also, if the exercise is chronic and results in a reduction in body fat, blood pressure can be lowered.

Metabolic Effects

Acute and chronic light and moderate intensity exercise increases fat metabolism.[70] This occurs through activation of hormone sensitive lipase and the catecholamines. In addition, chronic exercise causes enzymatic and mitochondrial changes that shift the substrate utilization during exercise away from carbohydrate sources toward greater use of fats. Oxidative enzymes including Hydroxyacyl-CoA dehydrogenase, or HAD, (degradation of fatty acids to acetyl-CoA) are increased 30-40% during two months of training in previously untrained subjects.[71,72] The greater use of fats during exercise can impact weight, the endocrine system and inflammation.

Exercise has been shown to improve blood lipid levels.[73] Elevated triglycerides have been linked to increased reactive oxygen species, which in turn, is linked to endothelial dysfunction. Regular exercise increases lipoprotein lipase activity which lowers circulating

triglycerides. Furthermore, chronic exercise increases LCAT (lecithin-cholesterol acyltransferase) which transfers free fatty acids to HDL. Concomitantly exercise can decrease CEPT (cholesterol ester transfer protein) decreasing the removal of cholesterol from HDL and preserving the HDL. The combination of increased LCAT and decreased CEPT increases circulating HDL-cholesterol levels; therefore, protective from the development of atherosclerosis and coronary disease. In addition, the ratio of HDL:LDL is strongly associated with capillarization, because LPL (lipoprotein lipase) is on the inner wall of the capillary.[74,75] Further, insulin sensitivity is related to the content of unsaturated fats in the cell membrane, and more active subjects burn saturated fat first, which gradually may change the cell membranes to include more unsaturated fat.[76] Finally, glucose can enter the muscle cell independently of insulin when the muscle contracts. Glucose is still transported by GLUT4, but GLUT4 translocate to the inside of the cell membrane without insulin connecting to the receptor.[77].

Anti-Inflammatory Effects

Evidence is accruing that chronic exercise, if not over-done reduces platelet adhesion and fibrolytic activity. The reduction in fibrolytc activity could be a result of changes in fibrinogen (although controversial) or a decrease in plasminogen activator inhibitor-1; PAI-1.[61] Regular exercise lowers C-reactive protein (CRP) which is associated with increased vascular adhesion and lower inflammation.[61] Chronic exercise appears to lower the pro-inflammatory cytokines IL-1β, IL-2, IL-6, and TNF-α[67] and these have been associated with increased atherosclerosis and decreased insulin sensitivity.[78,79] The enzyme eNOS increases nitric oxide production and nitric oxide is a vasodilator. TNF-α and CRP are known to inhibit the activity of eNOS, which would decrease nitric oxide production, reducing vasodilatation. Thus, an exercise program that lowers circulating TNF-α and CRP would allow for greater nitric oxide production, improved

vasodilatation, and potentially lower blood pressure. Chronic exercise has the capacity to increase the anti-inflammatory cytokines IL-4 & 10, which appear to be athero-protective, by inhibiting cell-mediated immune atherogenic reactions. Chronic exercise improves endothelial function by reducing oxidative stress.[80,61] The reduction in oxidative stress reduces the risk of CVD lesions via increases in shear stress (less leukocyte adhesion).

Endocrine Effects

Chronic exercise has an influence on the hormonal milieu. Exercise lowers the resting catecholamine and sympathetic nervous system activity.[81] Furthermore, increased catecholamine sensitivity has been found after training, which results in lower catecholamine levels during exercise.[82]. Since both lower sympathetic nervous activity and lower catecholamine levels have been linked to elevated blood pressure,[66] lowering their activity has the potential to lower blood pressure. Exercise had been shown to increase insulin sensitivity. Not only does it increase the biochemical response to a given amount of insulin, but the number of GLUT-4 insulin receptors is increased in response to exercise.[83] Therefore, glucose uptake in the cell is improved. Chronic exercise appears to reduce the adipocyte hormone leptin, independent of weight loss.[84] The reduction in leptin would reduce the effect of leptin on the sympathetic nervous system and the production of reactive oxygen species; therefore diminishing the influence of the blood pressure. At the same time lower leptin levels would result in less stimulation of TNF-α & IL-6; thus less detrimental effect on pancreatic B-cell and insulin sensitivity. Chronic exercise and weight loss increases the adiponectin secretion from the adipocyte. Adiponectin could potentially block the NF-κB metabolic pathway in endothelial cells, so ICAM and VCAM adhesion molecules are not activated, reducing risk of atherosclerosis.[85]

Conclusions

The MetS was first observed in adults, but over a decade of studies have shown that MetS risk factors are evident in youth. Although the definition of MetS in children and adolescents is controversial, the markers or risk factors for MetS are clear; blood pressure, dyslipidemia, glucose intolerance and obesity. However, based on the evidence it would have made sense to include low fitness as part of the definition. Evidence is also accumulating that these risk factors track from childhood through adulthood. Furthermore, the prevalence of MetS appears to be increasing in children and adolescents. Thus, we are compelled to develop early prevention programs.

Obesity prevention and treatment has a profound impact on reducing MetS risk in youth. Diet and exercise are two key components of any weight reduction program. Data is accruing in children and adolescents that exercise can impact MetS risk factors, but the amount and intensity of exercise needed is presently unknown. Studies of the relationship between habitual physical activity and MetS are equivocal, with some studies suggesting no effect on MetS, while other studies, particularly those using accelerometry to estimate PA, are suggestive of an independent effect. Furthermore, intervention studies suggest that possibly, in our sedentary world, habitual levels of PA for many youth may not be sufficient to be cardio-protective and increases over and above habitual levels of PA may be needed to provide protection.

Presently, we do not have a specific exercise prescription. With regard to intensity of exercise, a few studies suggest that moderate-to-vigorous PA (MVPA) appears to facilitate the reduction in MetS as well as weight loss. MVPA also has been shown to improve muscle metabolism of fats, improve insulin sensitivity, improve lipid profile, reduce elevated blood pressure, and improve immune function of children and adolescents. We know little about the duration of exercise needed to affect MetS; however, the American College of Sports Medicine

and the American Heart Association have recently recommended that 60 minutes of daily MVPA is needed.[86] MVPA of this duration also has the potential to increase aerobic power and the majority of research has shown an inverse relationship between aerobic power and MetS prevalence, or risk score, independent of weight loss. However the relationship between fitness (a trait) and physical activity (a behavior) is far from perfect.[87] As is often the case, in order to develop a more precise exercise program, more longitudinal research on MetS and youth are needed.

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