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Inflammatory Markers in Pediatric Obesity: Health and Physical Activity Implications

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Abstract: The prevalence of childhood obesity has recently peaked in the USA with ~17% of children considered obese. With the increase in adiposity that occurs with weight gain, a persistent low-grade inflammatory state is created. The most commonly studied inflammatory markers associated with obesity are the cytokines tumor necrosis factor α and interleukin-6 and the acute phase reactant C-reactive protein. Understanding the relation between adiposity and inflammation is an important concept because these inflammatory markers influence insulin sensitivity, glucose metabolism, and atherosclerosis ultimately leading to impaired health. In addition to obesity, physical inactivity is associated with elevated inflammatory markers. The literature, however, is inconsistent as to whether the association between physical activity and inflammation is independent of adiposity. In some obese children, physical fitness appears to circumvent the increase in inflammatory markers that are associated with obesity. The purpose of this review is to examine the relation between adiposity and inflammatory markers including potential health implications and the impact of physical activity. We exposed a

dearth of literature in understanding the interaction between obesity and physical activity on inflammatory markers, especially in children as their anthropometrics change. This review highlights the necessity for further research to better understand the complexity of the chronic inflammatory state associated with obesity.

Key Words: overweight; comorbidities; cytokines; exercise; children

Introduction

The prevalence of childhood and adolescent obesity has tripled since 1980 with recent estimates to be ~17% in the United States¹. One important issue with pediatric obesity is to understand that obesity is not just an imbalance of energy intake and expenditure. In particular, adipose tissue while once thought to be a passive energy store is now considered a major endocrine organ^{2,3}. Adipose cells produce numerous chemical signals which act on a variety of physiological processes throughout the body. In particular, inflammatory markers are released creating a persistent low-grade inflammatory state that impairs metabolic and cardiovascular health. Understanding how interventions, such as physical activity, impact inflammatory markers is important in preventing or minimizing obesity-related health problems. The purpose of this review is to examine the relation between adiposity and inflammatory markers including potential health implications and the impact of physical activity.

Inflammatory Markers: Cytokines and Acute Phase Reactants

The most commonly studied inflammatory markers associated with obesity are the cytokines tumor necrosis factor α (TNF α) and interleukin-6 (IL-6) and the acute phase reactant C-reactive protein (CRP). Cytokines are proteins and peptides that are secreted by cells which then act as cell messengers, including pro-inflammatory mediators. Acute phase reactants are plasma proteins that fluctuate with inflammation; CRP increases with inflammation. Unlike the cytokines TNF α and IL-6, CRP is not directly released from adipose tissue, but is secreted by the liver in response to factors released by adipose tissue such as IL-6⁴. Both types of inflammatory markers

influence insulin sensitivity, glucose metabolism, and atherosclerosis⁵. Accordingly, adipose tissue plays an important role in the complex cross-talk between organs regulating the body's homeostasis⁶.

Inflammatory Markers and Disease

Increased levels of inflammatory markers lead to physiological mechanisms that negatively impact health. Inflammatory markers have been shown to damage the innermost layers (intima media) and lining (endothelium) of blood vessels through the stimulation of atherosclerotic lesions that also cause hypertension and thrombosis⁷⁻⁹. In addition to cardiovascular dysfunction, inflammatory markers impact metabolic control by negatively influencing insulin sensitivity and glucose transport^{7,10,11}. Thus, obese individuals with elevated levels of inflammatory markers may experience physiological adaptations that negatively impact metabolic and cardiovascular health.

Research in adult populations has established the link between elevated inflammatory markers and impaired health. For example, TNF α , IL-6, and CRP are predictors for type 2 diabetes, metabolic disease, and cardiovascular disease¹²⁻¹⁸. Two prospective studies of large national cohorts with healthy women have shown that inflammatory markers are predictors for the development of type 2 diabetes^{12,13}. Specific to cardiovascular dysfunction, elevations in inflammatory markers presage coronary events and heart disease in both men and women^{14-16,18}. Early identification of inflammatory markers may provide another component to identifying those at risk of cardiovascular events and may even be stronger predictors of these events than traditional risk factors (e.g., plasma total cholesterol, triglycerides, low-density lipoprotein, and high-density lipoprotein)^{14,15,19}.

Waist circumference and BMI are strongly related to elevated CRP, TNF α , and IL-6 levels²⁰⁻²⁴ with this relation occurring in children as young as three years of age²⁵. Likewise, the increase in inflammatory markers is linked to impaired health including metabolic and cardiovascular dysfunction^{22,25-28}. For example, the prevalence of metabolic syndrome and elevated inflammatory markers are highest among obese children when compared with normal and overweight children; this prevalence increases with worsening obesity²⁹. Despite

the direct association between the development of metabolic syndrome and obesity, it is important to note that children with even a mild-to-moderate degree of obesity demonstrate arterial endothelial dysfunction and increased intima media thickness³⁰.

The elevated inflammatory markers that occur with childhood obesity are likely influencing the child's health status. In obese children (8 ± 2 yrs), CRP is correlated with insulin resistance and carotid intima media thickness²⁶. Similar to CRP, IL-6 and TNF α are elevated in obese children with atherosclerosis risk factors⁷. Even in age- and sex-adjusted models, IL-6 was associated with elevated insulin, insulin resistance, BMI, and waist circumference²². Subsequent analysis indicated that the relation between IL-6 and insulin resistance was most likely mediated by obesity²². Overall, these studies demonstrate that inflammatory markers are increased in obese children leading to the development of risk factors for chronic diseases that are typically associated with adults^{20,21,23,24,31,32}.

Due to the high incidence of obese children becoming obese adults,^{33,34} obese children are at a high risk of experiencing systemic low-grade inflammation throughout their lifespan²⁵. This prolonged exposure to inflammatory markers may exponentially increase their risk in the development of vascular damage, type 2 diabetes, and premature morbidity^{22,25,35}. Metabolic syndrome and increases in body mass index (BMI) in childhood are predictive of adult metabolic syndrome and type 2 diabetes³⁶. In obese children, early identification of elevated inflammatory markers and development of physical activity interventions are important in attenuating the negative health consequences that are likely facilitated as they mature into adults.

Impact of Physical Activity on Inflammatory Levels

Physical activity is "bodily movement produced by skeletal muscles that result in energy expenditure"³⁷. Promotion of physical activity is a hallmark of weight management and recommended by the American Heart Association to prevent atherosclerosis in childhood³⁸. Similarly, physical fitness is a state of well-being that reflects a person's ability to perform physical activity,³⁹ and reflects health status. The significance of physical fitness is highlighted in a mini-longitudinal study following children from six to nine years of age⁴⁰.

Fitness levels at six years of age strongly predicted risk factors for cardiovascular disease at nine years of age⁴⁰. Thus, low fitness levels may be one of the first indicators for the development of metabolic syndrome and cardiovascular disease.

Poor fitness and low activity levels may impair health due to their impact on inflammatory markers^{41,42}. Physical activity is inversely related to IL-6, CRP, and TNF α levels across the lifespan; this relation remains even after adjusting for BMI, waist-to-hip ratio, or body fat^{41,43-50}. In adults, the intensity of physical activity appears to be important in that moderate to vigorous physical activity is inversely related to CRP^{48,49}. Recent evidence has shown that addressing sedentary behavior is also important. Women with higher levels of sitting time had higher levels of inflammatory markers (CRP and IL-6); this relation was independent of physical activity and most likely mediated through adiposity⁵¹. A similar relation between sedentary behaviors and inflammatory markers (CRP) was demonstrated in a large population based study; although this relation was independent of obesity in addition to physical activity⁴⁸. Overall, there is strong evidence showing that physical activity, including the lack of physical activity (e.g., sedentary behaviors), influences inflammatory markers, and the exact role of adiposity continues to evolve.

Similar to adults, fitness levels in children are associated with inflammatory levels. In obese and non-obese children with different fitness levels, obese unfit children had the highest levels of IL-6 levels of all the groups. The obese fit children had comparable IL-6 levels to lean and fit children⁴¹. Consequently, physical fitness in some obese children appears to circumvent the increase in inflammatory markers that are associated with obesity. The importance of physical fitness provides additional insight into the obesity research that was previously discussed because physical activity levels influence obesity-related increases in inflammatory markers. Therefore, the concept that the elevated inflammatory markers that occur with obesity are only due to increases in adiposity is overly simplified.

Due to the beneficial effects of physical activity on inflammatory markers and health status, several studies have assessed whether regular bouts of exercise (a subset of physical activity with specific mode, intensity, and duration)³⁷ provides similar improvements. Numerous adult studies have shown that long-term exercise decreases inflammatory markers for individuals that are healthy and those with

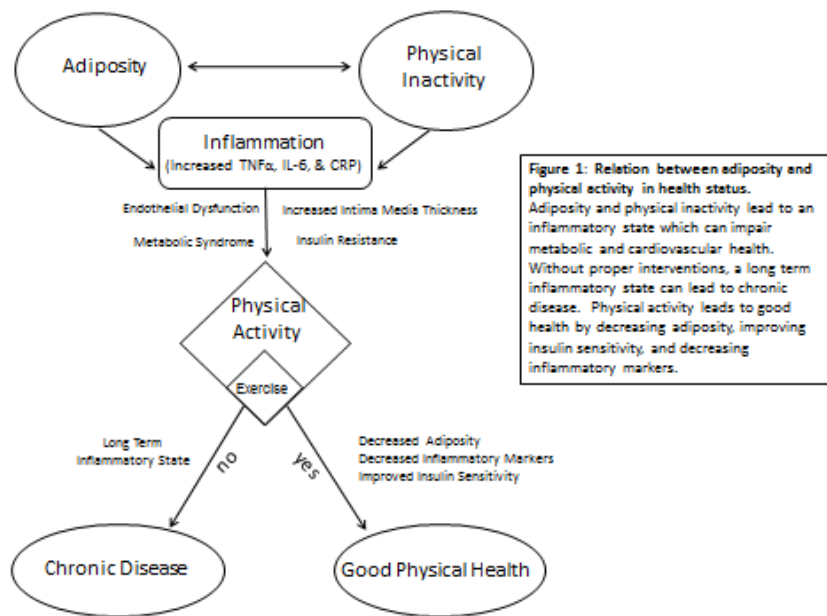
cardiovascular dysfunction⁵²⁻⁵⁴, including obese adults^{55,56}. Likewise, exercise in children has been found to be beneficial and may reverse the development of metabolic syndrome⁵⁷. Inflammatory markers, in particular, have been shown to decrease following interventions that incorporate exercise in children and adolescents⁵⁷⁻⁵⁹. The exact mechanisms regarding the anti-inflammatory effects of exercise are speculative and include changes in fat mass, increase levels of anti-inflammatory cytokines [e.g., interleukin-10 (IL-10)], and increases in insulin sensitivity^{42,60-62}.

Despite evidence showing the beneficial effects of exercise on inflammatory markers, the exercise studies involving children are more equivocal since children do not always exhibit an exercise-induced decrease in inflammatory markers^{28,63,64}. This ambiguity is likely related to the changing anthropometrics of children due to normal growth. With regular participation in physical activity, children will increase in stature while maintaining weight resulting in reduced fat mass. Because adipose tissue secretes inflammatory markers, there may be a parallel reduction in inflammatory markers with the improvement in body composition⁵⁸. Several of the exercise studies that did not show a decrease in inflammatory markers also have unchanged body composition^{31,63-65}. Consequently, a change in body composition rather than just weight loss may be more important for the anti-inflammatory effects of exercise to occur⁶⁶.

Relation between Obesity, Physical Activity, and Inflammation

Both obesity and physical inactivity are positively associated with inflammation but the contribution of each is uncertain (Fig. 1)^{22,25-28,41,42}. The literature is inconsistent as to whether the association between physical activity and inflammation is independent of fat mass. Increasing physical activity through exercise may decrease fat mass resulting in less secretion of inflammatory markers, or the anti-inflammatory effects from exercise and reduction in fat mass may have separate causal pathways⁴². Another reason for the inconclusive nature of the literature is because the majority of pediatric studies showing the association between obesity and inflammation did not measure physical activity or fitness levels^{20-22,25-27,29,31}. Despite these discrepancies, there is strong evidence that regular participation in

physical activity improves the health status of obese children^{38,67}. Children and adults should be encouraged to increase physical activity and not become discouraged if weight loss is negligible because increasing physical activity, independent of weight loss, still provides significant health benefits.



Conclusion

Pediatric obesity is a complex epidemic that leads to impaired metabolic and cardiovascular health. Elevated inflammatory markers that typically occur with obesity are likely an instigating factor for impaired health due to their influence on insulin sensitivity, glucose metabolism, and atherosclerosis. Due to the high incidence of obese children becoming obese adults, these individuals may have an even greater risk of developing health problems due to exposure of elevated inflammatory markers across their lifespan. Early identification of these markers and the incorporation of interventions that can offset this chronic inflammatory state may be an important aspect to rehabilitation. One such intervention is exercise due to the relation between physical activity and inflammatory markers. Whether the beneficial effects of physical activity in decreasing the inflammatory state is dependent on fat mass is not known. This review is an exciting

platform to highlight the necessity for further pediatric research to identify the interaction between obesity and physical activity levels in the modulation of inflammatory markers.

Conflict of Interest: None for either author

Glossary:

BMI: body mass index

CRP: C-reactive protein

IL-6: interleukin-6

IL-10: interleukin-10

TNF α : tumor necrosis factor alpha

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