10-1-2012

Inflammatory Markers in Pediatric Obesity: Health and Physical Activity Implications

Stacy Stolzman
Marquette University

Marie K. Hoeger Bement
Marquette University, mariehoeger.bement@marquette.edu

Accepted version. *Infant, Child, & Adolescent Nutrition,* Vol. 4, No. 5 (October 2012): 297-302. DOI: 10.1177/1941406412459344.

Inflammatory Markers in Pediatric Obesity: Health and Physical Activity Implications

Stacy Stolzman
Marquette University
Milwaukee, WI
Marie Hoeger Bement
College of Health Sciences, Department of Physical Therapy,
Marquette University
Milwaukee, WI

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

Infant, Child, and Adolescent Nutrition (ICAN), Vol 4, No. 5 (October 2012): pg. 297-302. DOI.

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 States[1]. 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 (TNFα) 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 TNFα 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-6[4]. Both types of inflammatory markers

influence insulin sensitivity, glucose metabolism, and atherosclerosis[5]. Accordingly, adipose tissue plays an important role in the complex cross-talk between organs regulating the body's homeostasis[6].

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 thrombosis[7-9]. 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, TNFα, IL-6, and CRP are predictors for type 2 diabetes, metabolic disease, and cardiovascular disease[12-18]. 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, TNFα, and IL-6 levels[20-24] with this relation occurring in children as young as three years of age[25]. 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 obesity[29]. Despite

Infant, Child, and Adolescent Nutrition (ICAN), Vol 4, No. 5 (October 2012): pg. 297-302. DOI.

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 thickness[30].

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 thickness[26]. Similar to CRP, IL-6 and TNFα are elevated in obese children with atherosclerosis risk factors[7]. Even in age- and sex-adjusted models, IL-6 was associated with elevated insulin, insulin resistance, BMI, and waist circumference[22]. Subsequent analysis indicated that the relation between IL-6 and insulin resistance was most likely mediated by obesity[22]. 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 lifespan[25]. 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 diabetes[36]. 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 childhood[38]**.** 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 age[40].

Infant, Child, and Adolescent Nutrition (ICAN), Vol 4, No. 5 (October 2012): pg. 297-302. DOI.

Fitness levels at six years of age strongly predicted risk factors for cardiovascular disease at nine years of age[40]. 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 TNFα 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 adiposity[51]. 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 activity[48]. 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 children[41]. 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

Infant, Child, and Adolescent Nutrition (ICAN), Vol 4, No. 5 (October 2012): pg. 297-302. DOI.

cardiovascular dysfunction[52-54], including obese adults[55,56]. Likewise, exercise in children has been found to be beneficial and may reverse the development of metabolic syndrome[57]. Inflammatory markers, in particular, have been shown to decrease following interventions that incorporate exercise in children and adolescents[57-59]. 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 composition[58]. 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 occur[66].

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 pathways[42]. 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

Infant, Child, and Adolescent Nutrition (ICAN), Vol 4, No. 5 (October 2012): pg. 297-302. DOI.

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.

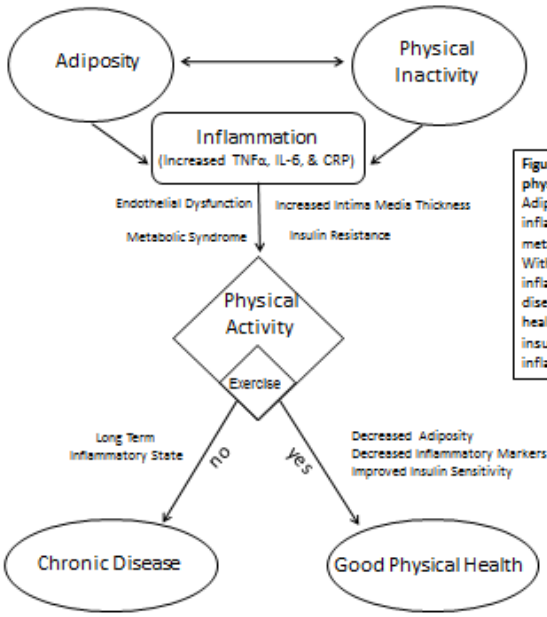

Figure 1: Relation between adiposity and physical activity in health status. Adiposity and physical inactivity lead to an inflammatory state which can impair metabolic and cardiovascular health. Without proper interventions, a long term inflammatory state can lead to chronic disease. Physical activity leads to good health by decreasing adiposity, improving insulin sensitivity, and decreasing inflammatory markers.

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

Infant, Child, and Adolescent Nutrition (ICAN), Vol 4, No. 5 (October 2012): pg. 297-302. DOI.

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
TNFα: tumor necrosis factor alpha

References

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index among US children and adolescents, 1999-2010. *JAMA*. 2012;307(5):483-490.
2. Ferris WF, Crowther NJ. Once fat was fat and that was that: Our changing perspectives on adipose tissue. *Cardiovasc J Afr*. 2011;22(3):147-154.
3. Berggren JR, Hulver MW, Houmard JA. Fat as an endocrine organ: Influence of exercise. *J Appl Physiol*. 2005;99(2):757-764.
4. Nicklas BJ, Ambrosius W, Messier SP, Miller GD. Diet-induced weight loss, exercise, and chronic inflammation in older, obese adults: A randomized controlled clinical trial. *Am J Clin Nutr*. 2004; 2004;79(4):544-544-551.
5. Cancello R, Taleb S, Poitou C, et al. Is obesity an inflammatory disease? *Journ Annu Diabetol Hotel Dieu*. 2006:115-128.
6. Fischer-Posovszky P, Wabitsch M, Hochberg Z. Endocrinology of adipose tissue - an update. *Horm Metab Res*. 2007;39(5):314-321.
7. Arslan N, Erdur B, Aydin A. Hormones and cytokines in childhood obesity. *Indian Pediatr*. 2010;47(10):829-839.
8. Lyon CJ, Law RE, Hsueh WA. Minireview: Adiposity, inflammation, and atherogenesis. *Endocrinology*. 2003;144(6):2195-2200.
9. Verma S, Yeh ET. C-reactive protein and atherothrombosis--beyond a biomarker: An actual partaker of lesion formation. *Am J Physiol Regul Integr Comp Physiol*. 2003;285(5):R1253-6; discussion R1257-8.
10. Keller C, Keller P, Giralt M, Hidalgo J, Pedersen BK. Exercise normalises overexpression of TNF-α in knockout mice. *Biochem Biophys Res Commun*. 2004;321(1):179-182.
11. Umpaichitra V. Roles of adipose tissue-derived factors in obesity. *Pediatr Endocrinol Rev*. 2006;3 Suppl 4:537-543.

Infant, Child, and Adolescent Nutrition (ICAN), Vol 4, No. 5 (October 2012): pg. 297-302. DOI.

12. Hu FB, Meigs JB, Li TY, Rifai N, Manson JE. Inflammatory markers and risk of developing type 2 diabetes in women. *Diabetes*. 2004;53(3):693-700.
13. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*. 2001;286(3):327-334.
14. Rader DJ. Inflammatory markers of coronary risk. *N Engl J Med*. 2000;343(16):1179-1182.
15. Packard CJ, O'Reilly DS, Caslake MJ, et al. Lipoprotein-associated phospholipase A2 as an independent predictor of coronary heart disease. west of scotland coronary prevention study group. *N Engl J Med*. 2000;343(16):1148-1155.
16. Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC study group. fragmin during instability in coronary artery disease. *N Engl J Med*. 2000;343(16):1139-1147.
17. Haddy N, Sass C, Droesch S, et al. IL-6, TNF-alpha and atherosclerosis risk indicators in a healthy family population: The STANISLAS cohort. *Atherosclerosis*. 2003;170(2):277-283.
18. Pai JK, Pischon T, Ma J, et al. Inflammatory markers and the risk of coronary heart disease in men and women. *N Engl J Med*. 2004;351(25):2599-2610.
19. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med*. 2002;347(20):1557-1565.
20. Steene-Johannessen J, Kolle E, Reseland JE, Anderssen SA, Andersen LB. Waist circumference is related to low-grade inflammation in youth. *Int J Pediatr Obes*. 2010;5(4):313-319.
21. Galcheva SV, Iotova VM, Yotov YT, Bernasconi S, Street ME. Circulating proinflammatory peptides related to abdominal adiposity and cardiometabolic risk factors in healthy prepubertal children. *Eur J Endocrinol*. 2011;164(4):553-558.
22. Herder C, Schneitler S, Rathmann W, et al. Low-grade inflammation, obesity, and insulin resistance in adolescents. *J Clin Endocrinol Metab*. 2007;92(12):4569-4574.
23. Alikasifoglu A, Gonc N, Ozon ZA, Sen Y, Kandemir N. The relationship between serum adiponectin, tumor necrosis factor-alpha, leptin levels and insulin sensitivity in childhood and adolescent obesity: Adiponectin is a marker of metabolic syndrome. *J Clin Res Pediatr Endocrinol*. 2009;1(5):233-239.

Infant, Child, and Adolescent Nutrition (ICAN), Vol 4, No. 5 (October 2012): pg. 297-302. DOI.

24. McMurray RG, Zaldivar F, Galassetti P, et al. Cellular immunity and inflammatory mediator responses to intense exercise in overweight children and adolescents. *J Investig Med*. 2007;55(3):120-129.
25. Skinner AC, Steiner MJ, Henderson FW, Perrin EM. Multiple markers of inflammation and weight status: Cross-sectional analyses throughout childhood. *Pediatrics*. 2010;125(4):e801-9.
26. Giannini C, de Giorgis T, Scarinci A, et al. Obese related effects of inflammatory markers and insulin resistance on increased carotid intima media thickness in pre-pubertal children. *Atherosclerosis*. 2008;197(1):448-456.
27. Codoner-Franch P, Tavarez-Alonso S, Murria-Estal R, Megias-Vericat J, Tortajada-Girbes M, Alonso-Iglesias E. Nitric oxide production is increased in severely obese children and related to markers of oxidative stress and inflammation. *Atherosclerosis*. 2011;215(2):475-480.
28. Kim ES, Im JA, Kim KC, et al. Improved insulin sensitivity and adiponectin level after exercise training in obese korean youth. *Obesity (Silver Spring)*. 2007;15(12):3023-3030.
29. Weiss R, Dziura J, Burgert TS, et al. Obesity and the metabolic syndrome in children and adolescents. *N Engl J Med*. 2004;350(23):2362-2374.
30. Woo KS, Chook P, Yu CW, et al. Overweight in children is associated with arterial endothelial dysfunction and intima-media thickening. *Int J Obes Relat Metab Disord*. 2004;28(7):852-857.
31. Tam CS, Garnett SP, Cowell CT, et al. IL-6, IL-8 and IL-10 levels in healthy weight and overweight children. *Horm Res Paediatr*. 2010;73(2):128-134.
32. Petty KH, Li K, Dong Y, et al. Sex dimorphisms in inflammatory markers and adiposity in african-american youth. *Int J Pediatr Obes*. 2010;5(4):327-333.
33. Deckelbaum RJ, Williams CL. Childhood obesity: The health issue. *Obes Res*. 2001;9 Suppl 4:239S-243S.
34. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. The relation of childhood BMI to adult adiposity: The bogalusa heart study. *Pediatrics*. 2005;115(1):22-27.
35. Lebensztejn DM, Kowalczuk D, Tarasow E, Skiba E, Kaczmarski M. Tumor necrosis factor alpha and its soluble receptors in obese children with NAFLD. *Adv Med Sci*. 2010;55(1):74-79.
36. Morrison JA, Friedman LA, Wang P, Glueck CJ. Metabolic syndrome in childhood predicts adult metabolic syndrome and type 2 diabetes mellitus 25 to 30 years later. *J Pediatr*. 2008;152(2):201-206.
37. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: Definitions and distinctions for health-related research. *Public Health Rep*. 1985;100(2):126-131.

38. Kavey RE, Daniels SR, Lauer RM, et al. American heart association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. *J Pediatr*. 2003;142(4):368-372.
39. The president's council on physical fitness and sports - publications http://www.fitness.gov/digest_mar2000.htm. Accessed 4/10/2012, 2012.
40. Andersen LB, Bugge A, Dencker M, Eiberg S, El-Naaman B. The association between physical activity, physical fitness and development of metabolic disorders. *Int J Pediatr Obes*. 2011;6 Suppl 1:29-34.
41. Halle M, Korsten-Reck U, Wolfarth B, Berg A. Low-grade systemic inflammation in overweight children: Impact of physical fitness. *Exerc Immunol Rev*. 2004;10:66-74.
42. Hamer M. The relative influences of fitness and fatness on inflammatory factors. *Prev Med*. 2007;44(1):3-11.
43. Ischander M, Zaldivar F,Jr, Eliakim A, et al. Physical activity, growth, and inflammatory mediators in BMI-matched female adolescents. *Med Sci Sports Exerc*. 2007;39(7):1131-1138.
44. Geffken DF, Cushman M, Burke GL, Polak JF, Sakkinen PA, Tracy RP. Association between physical activity and markers of inflammation in a healthy elderly population. *Am J Epidemiol*. 2001;153(3):242-250.
45. Ford ES. Does exercise reduce inflammation? physical activity and C-reactive protein among U.S. adults. *Epidemiology*. 2002;13(5):561-568.
46. Colbert LH, Visser M, Simonsick EM, et al. Physical activity, exercise, and inflammatory markers in older adults: Findings from the health, aging and body composition study. *J Am Geriatr Soc*. 2004;52(7):1098-1104.
47. Bergstrom G, Behre CJ, Schmidt C. Moderate intensities of leisure-time physical activity are associated with lower levels of high-sensitivity C-reactive protein in healthy middle-aged men. *Angiology*. 2012;63(6):412-415.
48. Esteghamati A, Morteza A, Khalilzadeh O, et al. Physical inactivity is correlated with levels of quantitative C-reactive protein in serum, independent of obesity: Results of the national surveillance of risk factors of non-communicable diseases in iran. *J Health Popul Nutr*. 2012;30(1):66-72.
49. Hawkins M, Belalcazar LM, Schelbert KB, Richardson C, Ballantyne CM, Kriska A. The effect of various intensities of physical activity and chronic inflammation in men and women by diabetes status in a national sample. *Diabetes Res Clin Pract*. 2012.
50. Taaffe DR, Harris TB, Ferrucci L, Rowe J, Seeman TE. Cross-sectional and prospective relationships of interleukin-6 and C-reactive protein with

physical performance in elderly persons: MacArthur studies of successful aging. *J Gerontol A Biol Sci Med Sci*. 2000;55(12):M709-15.

51. Yates T, Khunti K, Wilmot EG, et al. Self-reported sitting time and markers of inflammation, insulin resistance, and adiposity. *Am J Prev Med*. 2012;42(1):1-7.
52. Smith JK, Dykes R, Douglas JE, Krishnaswamy G, Berk S. Long-term exercise and atherogenic activity of blood mononuclear cells in persons at risk of developing ischemic heart disease. *JAMA*. 1999;281(18):1722-1727.
53. Tisi PV, Hulse M, Chulakadabba A, Gosling P, Shearman CP. Exercise training for intermittent claudication: Does it adversely affect biochemical markers of the exercise-induced inflammatory response? *Eur J Vasc Endovasc Surg*. 1997;14(5):344-350.
54. Mattusch F, Dufaux B, Heine O, Mertens I, Rost R. Reduction of the plasma concentration of C-reactive protein following nine months of endurance training. *Int J Sports Med*. 2000;21(1):21-24.
55. Straczkowski M, Kowalska I, Dzienis-Straczkowska S, et al. Changes in tumor necrosis factor-alpha system and insulin sensitivity during an exercise training program in obese women with normal and impaired glucose tolerance. *Eur J Endocrinol*. 2001;145(3):273-280.
56. Bruun JM, Helge JW, Richelsen B, Stallknecht B. Diet and exercise reduce low-grade inflammation and macrophage infiltration in adipose tissue but not in skeletal muscle in severely obese subjects. *Am J Physiol Endocrinol Metab*. 2006;290(5):E961-7.
57. Chen AK, Roberts CK, Barnard RJ. Effect of a short-term diet and exercise intervention on metabolic syndrome in overweight children. *Metabolism*. 2006;55(7):871-878.
58. Balagopal P, George D, Yarandi H, Funanage V, Bayne E. Reversal of obesity-related hypoadiponectinemia by lifestyle intervention: A controlled, randomized study in obese adolescents. *J Clin Endocrinol Metab*. 2005;90(11):6192-6197.
59. Gallistl S, Sudi KM, Aigner R, Borkenstein M. Changes in serum interleukin-6 concentrations in obese children and adolescents during a weight reduction program. *Int J Obes Relat Metab Disord*. 2001;25(11):1640-1643.
60. Dandona P, Aljada A, Mohanty P, et al. Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: Evidence for an anti-inflammatory effect? *J Clin Endocrinol Metab*. 2001;86(7):3257-3265.
61. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: Mechanisms and implications for the prevention and treatment of disease. *Nat Rev Immunol*. 2011;11(9):607-615.

Infant, Child, and Adolescent Nutrition (ICAN), Vol 4, No. 5 (October 2012): pg. 297-302. DOI.

62. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol*. 2005;98(4):1154-1162.
63. Kelly AS, Steinberger J, Olson TP, Dengel DR. In the absence of weight loss, exercise training does not improve adipokines or oxidative stress in overweight children. *Metabolism*. 2007;56(7):1005-1009.
64. Nassis GP, Papantakou K, Skenderi K, et al. Aerobic exercise training improves insulin sensitivity without changes in body weight, body fat, adiponectin, and inflammatory markers in overweight and obese girls. *Metabolism*. 2005;54(11):1472-1479.
65. Kelly AS, Wetzsteon RJ, Kaiser DR, Steinberger J, Bank AJ, Dengel DR. Inflammation, insulin, and endothelial function in overweight children and adolescents: The role of exercise. *J Pediatr*. 2004;145(6):731-736.
66. Tam CS, Clement K, Baur LA, Tordjman J. Obesity and low-grade inflammation: A paediatric perspective. *Obes Rev*. 2010;11(2):118-126.
67. Brage S, Wedderkopp N, Ekelund U, et al. Features of the metabolic syndrome are associated with objectively measured physical activity and fitness in danish children: The european youth heart study (EYHS). *Diabetes Care*. 2004;27(9):2141-2148.