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## NOTES FOR FITNESS AND HEALTH PROFESSIONALS

### What is the role of exercise in inflammatory disease prevention and management?

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#### Abstract

*Background:* The average contemporary lifestyle is largely comprised of inactivity and poor nutrition, which has been suggested as a generator of low-grade chronic inflammation. This type of persistent inflammation has become closely associated with numerous non-communicable diseases such as atherosclerosis and type 2 diabetes. *Purpose:* The primary purpose of this article is to examine the role inactivity plays in low-grade chronic inflammation and the optimal exercise program for reducing inflammation. *Findings:* A growing body of evidence suggests that the associated pro-inflammatory cytokine signaling is disrupting normal biological processes producing diseases at an alarming rate. In order to stave off or manage these ailments, physical activity has been identified as a viable option for mitigation. However, inappropriate intensities or durations may not mitigate and in some instances, may promote inflammation. *Conclusions:* In order to be beneficial, patients and healthcare professionals may be well served by using light to moderate exercise routines and modest progressions. **Health & Fitness Journal of Canada 2013;6(2):91-100.**

*Keywords:* Chronic inflammation; Physical inactivity; Cytokines; C-reactive protein; Disease; Adipose tissue

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#### Introduction

Global urbanization has altered the human way of life. Fast paced occupations encourage physical inactivity and include high levels of stress, while leisure activities have become increasingly sedentary. Moreover, the global aspiration for inexpensive food has shaped the complex of agri-business to provide calorically dense foods in impressive proportions. Unfortunately, it

is the combination of physical inactivity and poor diet that has been highlighted as possible co-contributors to various chronic noncommunicable diseases (CNCD) (Bloom et al., 2011; Mathur and Pedersen, 2008). CNCDs are slow developing diseases that are typically of long duration and consist of cardiovascular disease (including heart disease and stroke), type 2 diabetes mellitus, certain cancers, and some chronic respiratory diseases (Bloom et al., 2011). Combined, these CNCDs cause 63% of all deaths worldwide and economists project that they will cost over \$47 trillion globally over the next two decades (Bloom et al., 2011). Once considered “affluent” diseases, CNCDs are now spanning across all socio-economic levels. The global spread of CNCD’s conceivably correlates with a relatively smaller world that promotes sedentary occupations, recreation, and poor nutrition.

As the roles of inactivity and nutrition continue to be debated as to the extent of their influence on the etiology of CNCD’s, researchers are focusing on another common theme - low-grade chronic inflammation (LGCI) (Mathur and Pedersen, 2008). What is traditionally thought of as an acute physiological response to injury or irritant appears to chronically thrive unmitigated and

unresolved in millions of people. Research over the last two decades has connected LGCI to atherosclerosis, type 2 diabetes mellitus, Alzheimer's, obesity, liver disease, and some cancers such as breast and colon (D'Mello and Swain, 2011). Furthermore, other ailments have been associated with LGCI: fibromyalgia, sarcopenia, hypertension, insulin resistance, neurodegeneration, mood disorders, cognitive dysfunction and hyperlipidemia (Eisenberger et al., 2010; Lotrich et al., 2011; Mathur and Pedersen, 2008; Ortega et al., 2009; Walsh et al., 2011)

More noteworthy is the affect that physical activity has on the same pro-inflammatory pathways. Just as physical inactivity is inversely associated with elevated inflammatory cytokines and disease promotion, physical activity is inversely related with less cytokine movement and directly associated with health. Earlier studies established that the role of physical activity minimizes fat mass accumulation and positively affects insulin sensitivity, all independent of dietary manipulation and regardless of sexual characteristics (Aoi et al., 2011). Specifically, in 1991, Helmrich and colleagues reported that "physical activity is inversely related to type 2 diabetes mellitus development. Furthermore, incidence decreases by 6% per 500 kcals of energy expenditure up to 3500 kcals." (Helmrich et al., 1991). Since that study, mounting data has associated inflammatory signaling in disease etiology. In addition, evidence indicating physical activity can positively influence inflammatory signaling and subsequently positively impact disease is accumulating. It is this evolution in understanding of diseases that enables comprehension and

how exercise prescription affects and potentially alleviates inflammatory harm.

Current therapies for many of these hypokinetic chronic conditions often start with medications that treat the symptoms but rarely the underlying cause. Unfortunately, prescription medication may adequately treat the symptoms, but also mask serious health risks such as the signs and symptoms of chronic inflammation. For example, medications prescribed for rheumatoid arthritis can relieve the pain, increase daily function, reduce joint deformity, and alleviate the local manifestations of inflammation, but may not alter systemic inflammation. Left untreated, chronic inflammation can result in continued disease progression and the development of comorbidities, i.e. the individual with type 2 diabetes and cardiovascular disease. However, it is possible that the application of evidence-based first line therapies might mitigate the underlying causes, the resultant inflammation, and the symptoms. First line therapy for virtually all CNCD's is to increase physical activity, eat a sound diet, and maintain a healthy body weight (Aoi et al., 2011). In other words, the treatment for inflammation parallels current prescriptions for maintaining health from the American Medical Association, American Heart Association, American College of Sports Medicine, Academy of Nutrition and Dietetics, American Diabetes Association, and American Obesity Treatment Association (Academy of Nutrition and Dietetics, 2012; American Obesity Treatment Association, 2012; American Heart Association, 2012; Eckel et al., 2006; Garber et al., 2011).

Inflammation is defined as a physiological response to tissue damaging irritants that have altered local or

systemic homeostasis (Gruys et al., 2005; Mathur and Pedersen, 2008). Common irritants are “friction, x-rays, fire, extreme temperature, wounds, corrosive chemicals and allergens” (Cohen and Taylor, 2009, p.367). At the onset of irritation, infection or tissue disruption, the affected cells release histamine in conjunction with pro-inflammatory cytokines and other chemicals to invoke blood vessel dilation, increase membrane permeability, and attract white blood cells (Cohen and Taylor, 2009; Harvard Medical School, 2012). White blood cells further encourage inflammation by producing and releasing pro-inflammatory cytokines, such as Interleukin (IL)-1, IL-6 and Tumor Necrosis Factor (TNF)- $\alpha$  (Kaiser, 2012). These inflammatory agents diffuse into the blood and directly activate the hypothalamic-pituitary-adrenal axis, thus stimulating a hormonal cascade that results in the production of cortisol by the adrenal glands. Cortisol amplifies IL-6 sensitivity by promoting IL-6 receptors in the liver (Cohen and Taylor, 2009). The liver then produces acute phase proteins, one of which is C-reactive protein. Systemic presence of C-reactive protein alerts the body to a non-site specific inflammatory response. LGCI results in a release of cytokines IL-1ra, IL-6, TNF- $\alpha$ , and C-reactive protein that is indistinguishable from an acute irritation and their lingering presence has been implicated in various CNCs.

C-reactive protein is a part of the innate immune system and has a continuous presence in the human blood with a concentration of 0.8 mg/L in healthy individuals. Levels of C-reactive protein climb exponentially as a result of infection or injury and serve to assist macrophages in phagocytosis by linking

to undesirable microbes or cellular debris. Researchers investigating disease mechanisms have focused on C-reactive protein and its contribution to obesity, atherosclerosis pathology, and type 2 diabetes mellitus. C-reactive protein might be a viable co-predictor of disease in conjunction with traditional risk factors such as hyperlipidemia and hypertension and used to evaluate the presence of LGCI; thus allowing physicians to monitor dysfunction (Mathur and Pedersen, 2008; Teixeira et al., 2011). Risk stratification for heart disease is: low with circulating levels of C-reactive protein below 1.0 mg/L, moderate from 1.0-3.0 mg/L and high risk is above 3.0 mg/L (Harvard Medical School, 2012). Furthermore, testing for C-reactive protein levels may enhance the assessment of disease severity in atherosclerosis and rheumatoid arthritis (Goldhammer et al., 2005). Knowing C-reactive protein levels is important in gauging inflammatory and/or disease progression as well as indicating the need for an acute intervention. However, a caveat to these recommendations should be coupled when assessing test results. No single blood test provides a definitive diagnosis, but in conjunction with additional data, C-reactive protein monitoring aids analysis of an individual's health status. In general, because of wide fluctuations in C-reactive protein levels, it is recommended by the Center for Disease Control and American Heart Association that persons provide two blood samples separated by 14 days. Results that are greater than 10 mg/L should be considered acute inflammatory events and another specimen taken (Pearson; 2003). Moreover, practitioners need also be aware that individual variation might result from factors such

as genetics, gender, smoking, elevated HbA1C, and some medications (Macgregor et al., 2004, Ruckerl et al., 2009, Shen and Ordovas, 2009.)

Cytokine involvement is multifaceted in both cause and effect. The increase in the cytokines IL-6 and TNF- $\alpha$  both promote and maintain obesity (Aoi et al., 2011; Martin-Cordero et al., 2011). Normally, inflammatory cytokines from damaged tissue stimulate the hypothalamic-pituitary-adrenal axis to increase glucocorticoids and support inflammation and the immune response (Martin-Cordero et al., 2011). However, adipose tissue also releases IL-6 and TNF- $\alpha$  (adipocytokines or adipokines) and it is the additive effect of these adipocytokines that initiates a cascade of events that stimulates inflammation and disrupts glucose transport with a potential result of insulin resistance (Aoi et al., 2011; Mathur and Pedersen, 2008). The exact role of IL-6 remains in debate, whereas a highly active role for TNF- $\alpha$  has been demonstrated in lipolysis, LGCI, and other metabolic irregularities (Mathur and Pedersen, 2008). Individuals who are both overweight and sedentary further escalate pro-inflammatory signaling and perpetuate LGCI.

Knowing disease origins and sleuthing out catalysts can prove perplexing, and remains a challenge for researchers. However, mounting evidence suggests that physical inactivity and obesity appear to contribute the most to LGCI (Aoi et al., 2011). Martin-Cordero, Garcia, Hinchado, and Ortega, demonstrated that LGCI is reduced as a result of lower body fat and this fat loss can then serve as a means to control inflammation (Martin-Cordero et al., 2011). Ameliorating chronic inflammation via exercise has also shown potential in combating age-

associated ailments like sarcopenia, neural degeneration, and Alzheimer's (Hurley et al., 2011; Walsh et al., 2011). Although gaps in reported studies persist, it is within reason to be optimistic that physical activity impacts cytokines derived from adipose tissue and can create an anti-inflammatory environment post activity.

Acute bouts of exercise also activate the immune system and inflammatory responses similar to irritants; however, the two events are not the same. Dissimilarities in an inflammatory response between exercise and an infection, in general, include a lack of response to physical activity from cytokines TNF- $\alpha$  and IL-1 $\beta$ . Inversely, elevated concentrations of IL-1ra, IL-6, IL-10 and the hormones epinephrine, cortisol, growth hormone, and prolactin are observed during and post exercise. The summation of these cytokines and hormones yield an environment that is anti-inflammatory and promotes healing/adaptation (Walsh et al., 2011). Furthermore, longitudinal studies suggest that decreased C-reactive protein levels are correlated with LGCI suppression as a result of regular physical activity (Mathur and Pedersen, 2008). Exercise invokes an initial and limited pro-inflammatory period followed by a longer period of anti-inflammatory activity (Golbidi et al., 2012). From a perspective of homeostatic balance, sufficient quantities of physical activity can be prophylactic in regulation of inflammation.

Various interventional studies have shown that individuals of all ages demonstrate a reduction in serum C-reactive protein following a minimum of physical activity on 3 days per week for 3 months. Both resistance training ( $\leq 70\%$  one repetition maximum) and 20 minutes

of aerobic training (70 – 80% of maximum heart rate) promote the decline of C-reactive protein (Milani et al., 2004; Nakajima et al., 2010; Stewart et al., 2010; Thompson et al., 2010; Touvra et al., 2011). Furthermore, signifying that the combined effect of both aerobic and resistance training provides greater benefits with lower circulating pro-inflammatory agents and higher anti-inflammation markers. However, not all researchers agree with this conclusion; rather, suggesting that reductions in C-reactive protein concentration appears to be more closely associated with decreases in body fat as opposed to a direct influence of exercise (Pischon et al., 2012, Campbell et al., 2008, Hammett et al., 2004). Furthermore, Campbell et al (2008), offers results that show insignificant changes in C-reactive protein levels associated with increased maximal oxygen consumption over a 12-month aerobic based intervention with no substantial changes in body composition. From these conflicting results, it is evident that more information is needed in order to understand the exact mechanisms that positively affect inflammation in the body.

Contrary to the engagement in concomitant moderate strength and aerobic training, recent publications from studies in Norway suggest that aerobic interval training yields a less significant inflammatory reaction as opposed to strength training in individuals with metabolic syndrome. Metabolic syndrome is classified as a low grade chronic inflammatory state expressed by a combination of obesity, dyslipidemia, hypertension and elevated fasting glucose levels (American Heart Association, 2002). Although beneficial changes did not include IL-6, TNF- $\alpha$  or C-reactive

protein, Stensvold et al assert that the effect of aerobic interval training on IL-18 invokes a more favorable inflammatory environment; based on research from J.Hung et al, implicating IL-18 in the pathogenesis of metabolic syndrome. Stensvold et al's findings show a lower volume of circulating IL-18 following a 12 week program comparing aerobic interval training and strength training. Interval training consisted of four 4 minute bouts at 90% of maximal heart rate interspersed with three minutes of active recovery. The strength training sub-group participated in 12 weeks of resistive exercises at 40-50% of their 1-repetition maximum. If aerobic interval training proves a viable prescription for inflammatory diseases, this would be most advantageous considering the positive effects on individual's quality of life, enhanced left ventricular function and endothelial function (Wisloff, et al). However, until data emerges that demonstrates aerobic interval training as a superior modality; one must question the safety for sedentary persons with inflammatory ailments (Cooper et al., 2007). Will an individual be better-off with quick implementation of aerobic interval training or better served with a progressive protocol to guard against flare-ups, unnecessary tissue damage, and/or increased injury potential?

Exercise prescriptions for individuals with elevated pro-inflammatory markers, or previously diagnosed with a disease, should tend toward less intense activities. Furthermore, health professionals should employ caution in prescribing exercises that promote tissue damage and invoke an inflammatory response. Specifically heavy resistive movements that yield localized injury aggressively recruit neutrophil proliferation and subsequent

secretion of TNF- $\alpha$  – often recognized as delayed onset muscle soreness; this cascade of events stimulates a pro-inflammatory environment (Pizza et al., 2002). Moreover, resistive exercises greater than 70% 1-RM has shown the same inflammatory effect when preformed to fatigue (Nakajima et al., 2010). Cardiovascular exercises stimulate no deleterious inflammatory activity at intensities lower than 80% of heart rate reserve (Stewart et al., 2010). When aerobic training and strength training are performed together below the TNF- $\alpha$  expression threshold, individuals who participate 3-4 times per week obtain a reduction in inflammation (Touvra et al., 2011).

Thus, optimal exercise prescription may best be served with resistive exercises for the major muscle groups, 1-3 sets and 12-15 repetitions, below 70% 1 repetition maximum and cease before fatigue (Stewart et al., 2010). Initial cardiovascular intensity should be less than 80% of heart rate reserve and modes should be less weight bearing, such as biking or swimming, so as to decrease the likelihood of circulating TNF- $\alpha$ . The initial session durations for cardiovascular endurance and resistive exercise should be as tolerated, with conservative progressions. The mindfulness of the healthcare professional is essential in prescribing appropriate intensities as well as progressions. Inappropriate recommendations can aggravate symptoms as well as discourage individuals from further exercise involvement. Lastly, as individuals who show positive adaptations and improved exercise tolerance, the implementation of aerobic interval training should be encouraged.

### Conclusions

Unhealthy lifestyles have become more prevalent as well as the resultant ailments and diseases. Not only is it the increase in adipose tissue and sedentary occupations, but the concomitant lack of recreational activity that promotes chronic inflammation. It has been proven that surplus fat mass and sedentary behaviors support the circulation of pro-inflammatory cytokines IL-6 and TNF- $\alpha$ , with systemic increases in C-reactive protein. Moreover, it is the lack of activity that does not generate an anti-inflammatory environment that finishes the one-two punch. Persistent signaling encourages inflammation and, theoretically, ailments and diseases. Physical activity has demonstrated a promising role in alleviating inflammatory signaling and potentially staving off sickness and disease. Both strength training and aerobic exercise have shown positive results when reasonably utilized. To the contrary, exercises performed in excess to the detriment of tissue integrity can prove deleterious. Individuals with pre-existing inflammation or disease may unintentionally exacerbate conditions they seek to ease. Healthcare providers need to appreciate the benefits of physical activity in addition to its injurious capabilities by not only encouraging participation, but also advocating moderation in initiation and progression.

### Authors' Qualifications

The authors' qualifications are as follows: Chris Schotzko, M.A., ACSM HFS, C.S.C.S., and Shawn Simonson, Ed.D., C.S.C.S., ACSM HFS.

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