Review Article

Inflammation, physical activity, and chronic disease: An evolutionary perspective

Roberto Carlos Burini [a], Elizabeth Anderson [b], J. Larry Durstine [b], James A. Carson [c,*]

[a] Botucatu Medical School, Sao Paulo State University - UNESP, Botucatu, SP, Brazil
[b] Arnold School of Public Health, Department of Exercise Science, University of South Carolina, Columbia, SC, USA
[c] College of Health Professions, Division of Rehabilitation Science, University of Tennessee Health Science Center, Memphis, TN, USA

ABSTRACT

Low-grade inflammation is emerging as a common feature of contemporary metabolic, psychiatric, and neuro-degenerative diseases. Both physical inactivity and abdominal adiposity are associated with persistent systemic low-grade inflammation. Thus, the behavioral, biological, and physiological changes that cause a predisposition to obesity and other co-morbidities could have epigenetic underpinnings in addition to various evolutionary scenarios. A key assumption involves the potential for a mismatch between the human genome molded over generations, and the issue of adapting to the modern high calorie diet and common built environments promoting inactivity. This biological mismatch appears to have dire health consequences. Therefore, the goal of this article is to provide a brief overview on the importance of inflammation as part of human survival and how physical activity (PA) and physical inactivity are critical regulators of systemic inflammation. The review will highlight anti-inflammatory effects of PA and exercise training from a metabolic and systemic signaling perspective, which includes skeletal muscle to utilization of fatty acids, TLR4 signaling, and myokine/adipokine effects. The available evidence suggests that PA, regular exercise, and weight loss offer both protection against and treatment for a wide variety of chronic diseases associated with low-grade inflammation through an improved inflammatory profile.

Introduction

Chronic diseases are the foremost cause of death globally and this prevalence continues to rise for both men and women, every ethnicity, and all age groups.[1] Low-grade inflammation is emerging as a common feature of contemporary metabolic, psychiatric, and neurodegenerative diseases.[2] Decreased physical activity (PA) and increased abdominal adiposity are associated with persistent systemic low-grade inflammation. Thus, the environmental changes that cause a predisposition to obesity and physical inactivity have the potential to alter or accelerate evolutionary scenarios through epigenetic regulation of gene expression.

The goal of this article is to provide a brief overview of the importance of inflammation as part of human survival and the current understanding of PA and physical inactivity as critical regulators of systemic inflammation which can negatively impact health. Physical inactivity is associated with persistent systemic low-grade inflammation associated with an increased likelihood for disease while increased PA and regular exercise are associated with an anti-inflammatory effect reducing disease

risk.[3] For these reasons, physical inactivity and increased PA and exercise are discussed separately.

Inflammation - A thrifty means for survival

Infection, mechanical force, chemicals, and extreme heat or cold can damage tissue, causing the nonspecific process of inflammation. As progressive destruction of the tissue would compromise the survival of the organism, inflammation is a protective attempt by the organism to initiate the healing process. Without inflammation, wounds and infections would not heal. Therefore, systemic inflammation is a tightly regulated process required for our existence. Inflammation is categorized as a stereotypical response as part of the tissues' biological responses to harmful stimuli, such as pathogens, damaged cells, or irritants.

Inflammation role in damaged-repaired tissues

Inflammation is initiated when damaged tissues release primary

* Corresponding author. 930 Madison Avenue, Suite 633, Memphis, TN, 38163, USA.
E-mail address: jcarso16@uthsc.edu (J.A. Carson).
URL: https://www.uthsc.edu/health-professions/about/carson.php (J.A. Carson).

mediators that are vasoactive amines and eicosanoids. These chemical messengers include histamine, bradykinins, prostaglandins, and leukotrienes.[4–6] In some cases, small molecules are involved in tissue autonomous inflammation. These chemicals signal nearby blood vessels to expand and become more permeable allowing for increased blood flow to the damaged area. Overall, the dying cells and tissue debris through chemotactic factors attract circulating phagocytic cells, and neutrophil recruitment to the damaged tissue. Soon following acute injury, TNF-alpha release by mast cell degranulation occurs, followed by neutrophil accumulation in the muscle bed, which promotes additional TNF-alpha release. These actions are followed by monocyte infiltration, and subsequent differentiation into macrophages. The major cells involved in acute inflammation are primary neutrophils followed by eosinophils and mononuclear cells (monocytes and macrophages). These white blood cells are attracted to the site for removal of debris. Thus, the goal of inflammation is to clean up the damage and start the repair process.

Overall, the tissue injury repair process from initiation to resolution starts with a pro-inflammatory phase at the site of damage resulting in immune cell infiltration and phagocytosis of necrotic and/or apoptotic cells. The infiltrating macrophages can also acquire anti-inflammatory phenotypes. Infiltrating monocytes differentiate into macrophages and polarize to acquire pro- or anti-inflammatory phenotypes. The pro-inflammatory M1 macrophages of the initial infiltration phase subsequently attain an M2-polarization profile that promotes wound healing and tissue remodeling.[7] The inflammatory response further activates the surrounding cells (T lymphocytes, mesenchymal stem cells and endothelial cells and their progenitors) to support tissue regeneration.[8]

Inflammation role in pathogen clearance

Both infection and sterile tissue injury that generate inflammation are followed by strong immune responses. Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) signal the threat of either infection (microbial sensors) or injury to the organism independent of their non-self- or self-identity.[9,10] PAMPs and DAMPs lead to the acute inflammatory response necessary for pathogen clearance and tissue repair. Cells release DAMPs as endogenous signals that alert the innate immune system to unscheduled cell death, microbial invasion, and stress.

PAMPs and DAMPs serve as 'Signal zeros' and bind to specific receptors such as toll-like receptors (TLRs), nucleotide oligomerization domain (NOD)-like receptors (NLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLRs), absent in melanoma 2 (AIM2)-like receptors (ARLs), C-type lectin receptors (CLRs), and the receptor for advanced glycation end-products (RAGE).[11] Once bound, these receptors are found either on the membrane surface (TLRs and CLRs) or inside the cytoplasm (NLRs, RLRs, ALRs), and on the RAGE. NLRs sensors are found intracellularly, located either in cytoplasm (NALP3) or in the nucleus (NALP1).[12] Following PAMP/DAMP recognition, activated TLRs and other pattern recognition receptors (PRRs) provide signals to the host indicating the presence of a microbial infection/out place molecule and trigger pro-inflammatory and antimicrobial responses by activating a multitude of intracellular signaling pathways, including adapter molecules, kinases, and transcription factors such as nuclear factor-κB (NF-κB), activator protein-1 (AP-1), and IFN regulatory factors (IRFs). Thus, exogenous PAMPs are recognized by cells of the innate and acquired immune system, primarily through TLRs. As a result, some cells are activated to destroy the pathogen and/or pathogen-infected cells. An immunological response is then triggered in order to produce specific T-cell receptors and antibodies best suited to recognize the pathogen on a future occasion.[10]

Activation of the NLRP3 inflammasome results in IL-1β/IL-18 processing, and numerous conditions can induce variations of programmed inflammatory cell death. The association of NALP3 with pro–caspase-1 via the adaptor molecule ASC results in auto- activation of caspase-1. Active caspase-1 promotes the cleavage and, therefore, maturation of pro-inflammatory cytokines [pro–interleukin-1β (pro–IL-1β), pro–IL-18, and IL-33] to promote/sustain inflammation. Three models exist to explain inflammasome activation: (*a*) induction by reactive oxygen species, (*b*) lysosomal destabilization, or (*c*) pore formation, K^+ efflux, and possibly PAMP influx.[13] The activation of specific TLRs has been suggested to play a role in the development of obesity- induced insulin resistance, type 2 diabetes, and atherosclerosis.[14]

Inflammation-related thriftiness of insulin resistance

Survival of multicellular organisms depends on the organism's ability to fight infections, but these defense processes require high amounts of energy. Fever boosts energy consumption while an undernourished state is immunosuppressive. An activated immune system usually requires substantial energy in a quiescent state.[15] To meet the challenges of infection and other environmental stress, an activated immune system has an urgent need for energy-rich substrates allocated from internal energy stores (glycogen, proteins, triglycerides, or FFAs). Therefore, to meet these energy needs, fuel from energy storage found primarily in fat tissue and skeletal muscle must be utilized. Hence, body's ability to fight infections depends on their ability to store energy for times of low nutrient availability or high energy needs.[15] Inflammation's energy requirement rises into an active phase which strongly inhibits food intake and anabolic processes such as those controlled by insulin signaling. The fasting physiological response includes increased lipolysis, lipid oxidation, ketone body synthesis, endogenous glucose production and uptake, and decreased glucose oxidation. These processes are crucial for survival and protect from excessive protein loss. Conceptually, this theory is based on the knowledge that the greater the insulin resistance, the greater the ability to reduce proteolysis (preserve lean body mass) when faced with caloric deprivation. The more efficient an individual is in conserving muscle protein, the better the chances to withstand prolonged periods of deprivation.[16] Thus, infection-induced impairment to health and the related anorexia not only exacerbates a reduction in intake of energy-rich substrates, but an acute infectious disease increases the demand for energy. However, the response to an acute inflammatory episode may reflect the strong coordination between these processes needed for the immune and energy system to successfully fight infection.

Cells of the immune system and nervous system are heavily dependent on glucose, similar to many cell types involved in tissue regeneration. Blood glucose is provided to these cells in an insulin-independent manner. Hence, neurons, leukocytes and fibroblasts are considered as insulin insensitive tissues. Insulin is an anabolic hormone playing an important role in the regulation of glucose, lipid homeostasis, and energy storage through insulin's metabolic effects on classic insulin-responsive tissues.[17] Specifically, insulin promotes the storage of glucose as glycogen in the liver and skeletal muscle while facilitating deposition of fatty acids in the form of triglycerides in adipose tissue. Humans are extremely sensitive to blood glucose deficits, and insulin resistance in insulin-dependent tissues is the primary means to maintain blood glucose levels during starvation, pregnancy, and infection/inflammation.[16]

The mechanisms impairing the biological effects of insulin include serine/threonine kinase activation,[18] and cytokine signaling (SOCS) proteins interaction with the insulin receptor.[19–21] The serine/threonine inhibitory phosphorylation of insulin receptor substrate is completed by fatty acid accumulation, pro-inflammatory cytokines, and reactive oxygen species, and are mediated through specific intracellular signaling pathways involving C-Jun NH2 Terminal Kinase (JNK), Activating Protein-1 (AP-1), nuclear factor kappa beta (NF–kB) and IkB kinase (IKK) signaling molecules.[22–24]

Starvation, infection, trauma, and physical stress are processes associated with insulin resistance.[16] Insulin resistance promotes reallocation of glucose from major tissues (skeletal muscle, adipose tissue and liver) to the brain, tissue repair, and immune system. As a result of insulin resistance, blood levels of glucose are elevated to provide energy

sources, maintain the function of vital organs, and combat infection. Hence, insulin resistance is an essential part of normal homeostasis to facilitate redirection of nutrients to pivotal organs as a physiological adaptive mechanism to promote survival. Therefore, negative regulation of insulin signaling could be viewed as a physiologic adaptive mechanism that is activated in certain conditions such as fasting, inflammation, stress, and pregnancy.[16] Thus, the formation of a systemic and/or local tissue-specific insulin resistance due to inflammatory cell activation may be a protective mechanism that co-evolved with the repartition of energy sources within the body during times of stress and infection.

Insulin resistance-related thriftiness of sodium retention

Regulation of energy storage and the preservation of body fluids are critical for an organism's fight against famine, infection, and physical stress. To cope with the injury responses, a coordination of neuroendocrine, energy storage, water economy, and immune systems have evolved. One hypothesis is that a positive selection of genes responsible for energy regulation and sodium preservation exist. Over time, development of energy storage and water retention provided survival mechanisms in response to acute inflammatory episodes. Thus, to overcome a systemic water loss during acute inflammatory episodes, a water retention was activated. Much like energy storage, insulin-mediated sodium preservation is likely an adaptive mechanism for human survival evolving from ancient times. In fact, in addition to the metabolic effects, insulin can induce vaso-relaxation by stimulating the production of nitric oxide (NO) in the endothelium as well as regulating sodium homeostasis by enhancing sodium reabsorption in the kidney; thereby, contributing to the regulation of blood pressure. The increased blood pressure brought about by insulin resistance does contribute to increased blood perfusion to the brain during starvation, infection, and to the fetus during pregnancy.[25]

Water loss and sodium deprivation due to insufficient sodium intake or excess sodium loss is tightly regulated and involves the renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, or the neuroendocrine system to preserve sodium and body fluid consequently increasing blood pressure.[26] A determinant for body fluid distribution is sodium and accumulation of sodium causes water retention. Sodium transport through various nephron segments is important in regulating sodium reabsorption and blood pressure regulation. Overall, in a normal physiological state, insulin stimulates endothelial NO production to exert a vasorelaxation and anti-inflammatory effect. Whereas, in a state of insulin resistance, the insulin-stimulated NO pathway is selectively impaired and the compensatory hyperinsulinemia activates the mitogen-activated protein kinase (MAPK) pathway, resulting in enhancement of vasoconstriction, increased pro-inflammation, increased sodium and water retention, and blood pressure elevation.[26]

To cope with the injury, an elegant coordination of neuroendocrine, energy storage, and immune systems adaptations have evolved. Inflammatory cytokines released from activated immune cells inhibits the insulin signaling pathway. As a result, blood glucose levels are elevated to provide energy sources to maintain the function of vital organs (heart, brain, and immune cells) and to combat infection. In addition, water loss and sodium deprivation due to insufficient sodium intake or excess sodium loss activates RAAS, the sympathetic nervous system, and the neuroendocrine systems to preserve sodium and body fluid, and properly regulate blood pressure.[26] Natural selection has likely allowed the sodium-conserving genotype to persist, which may be maladaptive to the modern environment of sodium abundance, resulting in hypertension.[25]

The roles of physical inactivity and physical activity

Inflammation related to physical inactivity

In general, physical inactivity leads to visceral fat accumulation-induced chronic inflammation and is commonly accompanied by fatigue and muscle wasting. Together with other comorbidities and disease-specific symptoms, deconditioned muscles and exacerbated inflammation negatively affects cardiovascular performance and the ability to perform PA, closing the sedentarism-vicious (unhealthy lifestyle) cycle.[27] Therefore, the consequences of increased abdominal adiposity and physical inactivity are similar. However, the association between chronic systemic inflammation and physical inactivity is independent of obesity status.[28]

Both physical inactivity and abdominal adiposity are associated with persistent systemic low-grade inflammation. When considering this information, one would suspect that muscle disuse may lead to IL-6 resistance, and the elevated circulating levels of IL-6 that accompany obesity and physical inactivity may represent a common compensatory mechanism.[2] A link between physical inactivity, central obesity, and inflammation likely exists. Overall, a sedentary lifestyle is a strong and independent risk factor for many chronic diseases, including diseases associated with persistent systemic inflammation. These associations are related to increased morbidity and mortality, and reduced quality of life and overall life expectancy.[29] Physical inactivity might be considered the biggest public health problem of the 21st century.[30] A decrease in or removal of this unhealthy behavior would substantially improve health worldwide.[31]

IL-6 resistance

IL-6 is described as a pleiotropic cytokine involved in regulating processes that traverse from cancer-induced muscle wasting to beneficial metabolic exercise responses.[32] The mechanistic underpinnings of these differential effects of IL-6 on target tissues remain elusive but are thought to be related to the temporal expression of the cytokine and the cellular origin of the IL-6 release[33] on the target tissue. To this end, white adipose tissue is reported to be responsible for 30% or more of the circulating IL-6 at rest.[4–6] IL-6 concentration in the interstitial fluid of adipose tissues is markedly higher than circulating IL-6[6]. Interestingly, approximately 10% of IL-6 is attributed to adipocytes with the remainder coming from adipose tissue-resident macrophages.[4]

In humans during exercise, hepatosplanchnic viscera remove IL-6 from the circulation.[34] An interesting speculation is that the liver's removal of IL-6 could constitute a mechanism that serves to limit the potential negative effects of chronically elevated circulation IL-6 levels.[32] Moreover, plasma IL-6 levels are not changed after one year of exercise training.[35] However, regular exercise training has been reported to attenuate the systemic IL-6 response to exercise.[36] Several epidemiological studies report a negative association between the amount of regular PA and basal plasma IL-6 levels: the more physically active, the lower the basal plasma IL-6. While plasma IL-6 appear to be down regulated by exercise training, the muscular expression of the IL-6 receptor (IL-6Rα) is reported up regulated. In fact, in response to endurance training, the basal IL-6Rα mRNA content in muscle is increased by approximately 100%.[37] Accordingly, a possibility is that the down regulation of IL-6 is partially counteracted by an enhanced expression of IL-6R. Thus, with exercise training, the downregulation of IL-6 is partially counteracted by an enhanced expression of IL-6Rα such that IL-6 sensitivity is either maintained or increased.[32] These alterations in IL-6 and IL-6 receptor expression provide the basis for the theory that IL-6 resistance exists as a biological phenomenon.

The anti-inflammatory effects of PA and exercise

Skeletal muscle adaptations from exercise will increase pre-exercise skeletal muscle glycogen content, enhance the activity of key enzymes

involved in β-oxidation, increase sensitivity of adipose tissue to epinephrine-stimulated lipolysis, and increase oxidation of intramuscular triglycerides. Exercise training increases mitochondrial content and the capacity of skeletal muscle to oxidize fatty acids in obese patients.[51] As a consequence, the trained skeletal muscle is better able to utilize fat as a substrate and is less dependent on blood glucose and muscle glycogen as substrates during exercise.

An increase in adipose tissue is a hallmark of human obesity. A hallmark of acute exercise or a single exercise session is an increase in lipolysis and consequently a rise in circulating levels of free fatty acids (FFAs) to be delivered to the contracting muscle.[52] The primary function of the exercise-induced lipolysis is to provide the contracting skeletal muscle with fuel to maintain continued contraction.[52] When activated, such as by PA and exercise, the adenosine monophosphate-activated protein kinase (AMPK), an essential mediator of fatty acid metabolism,[53] results in an increased β-oxidation of FFAs in mitochondria and decreased overall lipid storage inside cells.[54] Increased muscle β-oxidation is an important tool against fat accumulation within cells and consequent cell lipotoxicity. A current hypothesis is that exercise training can induce an anti-inflammatory effect via an increased skeletal muscle capacity to utilize fatty acids, which results in decreased lipid content. Accordingly, regular PA and exercise can ameliorate obesity-induced changes in the adipose tissue immune cell profile by limiting the adipose tissue expansion. These changes lead to decreased recruitment of macrophages and potentially other immune cells into skeletal muscle and thus limit pro-inflammatory signaling activation (e.g., JNK). At the same time however, unaccustomed PA or exercise can also invoke muscle inflammation.

Present findings support an anti-inflammatory effect from regular PAand exercise via a reduction in visceral fat mass and/or by induction of an anti-inflammatory environment with each PAand exercise session. However, several features of a single exercise session and chronic exercise training suggest that the effects on TLR pathway activation may have an anti-inflammatory effect. Hence, an important anti-inflammatory effect of exercise training may constitute not only as a decrease in the capacity of FFAs presented to TLR4, but also as a reduction in the levels of specific TLR ligands. Therefore, the downregulation of TLR4 expression is an important anti-inflammatory effect of PA and exercise.[4,55] PA and exercise could reduce the availability of endogenous TLR4 ligands and decrease the expression of TLR4 the activation of TLR4 signaling. Overall, PA and exercise reduce activation of both TLR4 and the NLRP3 inflammasome, and therefore, reduces the levels of IL-1beta. A number of pro-inflammatory cytokines are elevated in individuals having inadequate PA levels,[56] and exercise-induced benefits are well known to prevent harmful effects of pro-inflammatory adipokines (Tumor necrosis factor, chemokine C–C motif ligand 2, and plasminogen activator inhibitor-1) through skeletal muscle-secreted proteins[32]. Hence, myokines secreted by an active muscle might counter-balance the adipokine-pro-inflammatory effects and therefore contribute to the systemic beneficial effects of exercise.[57]

The cytokine profile induced by PA and exercise is classically anti-inflammatory,[50,58] comprised of several potent anti-inflammatory cytokine increases such as IL-10, IL-1 receptor antagonist (IL-1ra), and IL-6.[59] During exercise, IL-6 is the first detectable cytokine released into the blood from the contracting skeletal muscle and is associated with subsequent increases in the production of IL-1 receptor antagonist (IL-1ra) and IL-10 by blood mononuclear cells, thus promoting an anti-inflammatory effect.[27] Moreover, IL-6 and other myokines, such as IL-15 and FSTL-1, mediate long-term exercise-induced improvements in cardiovascular risk factors (for example, fat distribution and endothelial function), and thus potentially having indirect anti-inflammatory effects.[32,60] Consequently, regular PA and weight loss offers prevention and treatment for a wide variety of chronic diseases associated with low-grade inflammation. Critical to this response is an improved inflammatory profile involving a decrease in the pro-inflammatory molecules and an increase in the anti-inflammatory molecules.[61]

Ancient physicians believed in the value of "exercise factor" of PA for health. Today, these PA and exercise-induced humoral factors mediating crosstalk between contracting muscles and other organs are well known as myokines.[32] Myokines modulate the function of many physiological systems through epigenetic chromatin remodeling. Most of the "exercise factor" effect of these "humoral factors" is ascribed to anti-inflammatory effects. PA and exercise could therefore be viewed as a natural therapy for recovering part of the imbalance caused by modern lifestyles. This remedy is inexpensive and without the side effects of many pharmacological treatments.[3]

Exercise-derived sources of IL-6

Since IL-6 is historically considered a classical pro-inflammatory cytokine, exercise-induced IL-6 levels were first thought to be a consequence of an immune response involving local damage in working muscle[38] with macrophages hypothesized as responsible for this increase.[39] However, the IL-6 mRNA level in monocytes does not increase as a result of exercise[40] as confirmed at the protein level.[41] Moreover, IL-6 produced by macrophages likely leads to an inflammatory response, whereas muscle cells produce and release IL-6 that may not activate classical pro-inflammatory pathways.[2,42–44] Human skeletal muscle is unique by producing IL-6 during contraction in a strictly TNF-independent fashion.[45] Hence, exercise increases circulating IL-6 levels independent of muscle damage.[42] Although studies do demonstrate that connective tissue, the brain, and adipose tissue are sources of IL-6[43], the most accepted primary source is contracting skeletal muscle in response to exercise.[2]

Although resting human skeletal muscle IL-6 mRNA content is very low, IL-6 protein, predominantly in type I fibers, is detected using sensitive immunohistochemical methods.[46] Microdialysis studies suggest IL-6 concentration within the contracting skeletal muscle are fivefold to 100-fold higher than the IL-6 levels found in the circulation, providing evidence for IL-6 accumulation within muscle fibers and the interstitial fluid during and following exercise.[47] Additionally, the simultaneous measurement of arteriovenous IL-6 concentrations and blood flow across an exercising leg has demonstrated that large amounts of IL-6 are also released into the circulation from the exercising muscle.[48]

The IL-6 exercise response is sensitive to work intensity which indirectly represents the muscle mass involved and the endurance capacity of the muscle.[49] Alterations in the expression of the IL-6 receptor on the sarcolemma of muscle fibers could impact muscle sensitivity to IL-6. Current evidence suggests that healthy, well-trained humans are more sensitive to IL-6, whereas untrained people have impaired IL-6 signaling and compensatory high circulating IL-6 levels.[50]

Conclusion

Infection, mechanical forces, chemicals, and extreme heat or cold are factors that cause tissue damage which initiates the inflammation processes. Healing damaged tissue requires energy needs, which would ultimately compromise survival. However, the pro-inflammatory response is followed by strong immune responses which are normal and tightly regulated. The inflammation healing process begins with the release of primary chemical messengers such as histamine, bradykinins, prostaglandins, and leukotrienes. Thus, inflammation is a stereotypical response considered as a mechanism of innate immunity and is part of the complex series of normal biological tissue responses to harmful stimuli, such as pathogens, damaged cells, or irritants. Physical inactivity is associated with many chronic health conditions and diseases, and visceral fat accumulation is a consequence of inactivity and associated with chronic inflammation, which leads to an increased risk of anemia, fatigue, and loss of muscle mass. Inflammation is exacerbated by other comorbidities, disease specific symptoms, and deconditioning of muscles. Ultimately, physical inactivity negatively impacts cardiovascular performance and the ability to perform PA and exercise. These series of

unhealthy events close the sedentarism-vicious (unhealthy lifestyle) cycle.[27,28] PA and exercise have a tremendous impact on the body's ability to optimally perform. PA and regular exercise adaptations include increased skeletal muscle glycogen stores, enhanced enzyme activity involved in glucose metabolism and β-oxidation, increased adipose tissue sensitivity to epinephrine-stimulated lipolysis, increased oxidation of intra-muscular triglycerides, and reduced visceral body fat stores. The overriding consequences of PA and exercise include reduced body fat stores in trained individuals. Trained skeletal muscle has an enhanced ability to utilize fat as a substrate and is less dependent on blood glucose and muscle glycogen as substrates during exercise. Regular PA, exercise, and weight loss are therapeutic treatments that offer protection against a wide variety of chronic diseases associated with low-grade inflammation. As a result of an improved inflammatory profile, the risk for chronic diseases are reduced.

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The manuscript has not been published and is not under consideration for publication elsewhere.

Authors' contributions

RCB provided the conceptual bases for this manuscript and the first draft. JLD, EA, and JC added content, editing, and formatting in the drafting of this manuscript.

Conflict of interest

The authors have no conflict of interest to report.

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