REVIEW

Physical Activity and Inflammation Phenotype Conversion

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ABSTRACT

Inflammation is a protective response to infection or injury; however, persistent microtraumas at the tissue level may result in chronic low-grade inflammation that plays both direct and indirect roles in the development of many diseases and aging. The purpose of this review is to describe the underlying physiology of low-grade inflammation and highlight potential inflammation lowering effects of physical activity (PA). Unique contributions of this review are to introduce the concept of *inflammation phenotype flexibility* in contrast to the low-grade inflammation state and describe how PA influences inflammation phenotype by altering muscle, gut, adipose, and postprandial metabolism. Pro-inflammatory M1 macrophages and cytokines—such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6—contribute to low-grade inflammation. Among the mechanisms that commonly contribute to low-grade inflammation are dysfunctional adipose tissue, a leaky gut, gut microbiota that promotes inflammation, and large postprandial glycemic and lipidemic responses. Physical activity may lower inflammation by decreasing M1 macrophages in visceral adipose tissue, decreasing adipose tissue volume, production of anti-inflammatory myokines, promotion of butyrate-producing members of the gut microbiota, improved gut barrier function, and lowering of postprandial glycemic and lipidemic responses. While exercise has many anti-inflammatory mechanisms, phenotype conversion is complex, multifaceted, and difficult to achieve. Our understanding of how PA influences inflammation must include acute exercise-induced anti-inflammatory effects, contribution to the inflammation state from multiple sources in the body, and phenotypic shifts underpinning low-grade inflammation. *Journal of Clinical Exercise Physiology*. 2019;8(2):64–73.

Keywords: macrophage, myokine, interleukin-6, gut microbiome, visceral adipose

INTRODUCTION

Lowering of inflammation is an important but often confusing health benefit attributed to physical activity (PA). Understanding how PA influences inflammation is important because inflammatory processes play direct and indirect roles in the aging process as well as the development of many diseases, including type 2 diabetes, atherosclerotic cardiovascular diseases, neurodegenerative diseases, cancer, and others (1–5). Decreasing inflammation has the potential to slow or reverse the disease development processes and represents one of the many therapeutic benefits of PA for disease prevention. Changes in adipose and production of anti-inflammatory compounds are generally accepted mechanisms for lowering inflammation; however, evidence is presented in this review that changes in the gut, gut microbiota, and postprandial metabolism are additional mechanisms to consider.

How these PA-related mechanisms affect inflammation may be confusing to understand for several reasons. For example, distinctions between acute inflammation and chronic, low-grade inflammation are often difficult to discern when the same cells and mediators are involved in both processes (5,6). Another point of confusion is that PA can cause acute inflammation in some situations and lower inflammation in others (7–9). Further, there are inflammatory mediators that have pro-inflammatory effects in some contexts and anti-inflammatory effects in others, for example, IL-6 (10). The aim of this review is to clarify 1) the

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Conflict of Interest: No conflict of interest

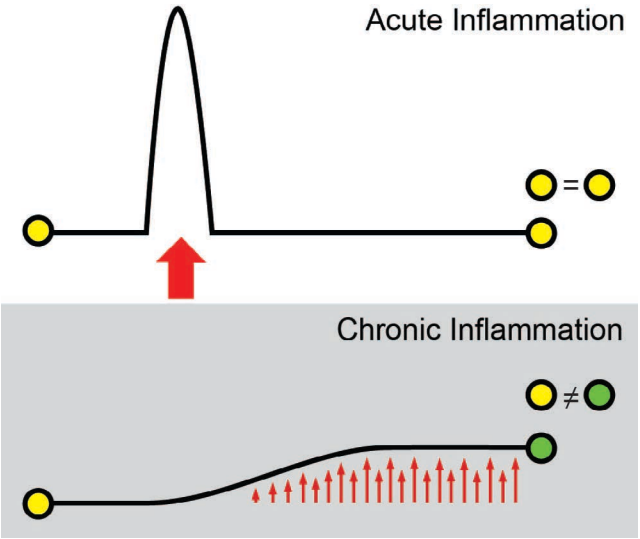

FIGURE 1. Acute versus chronic, low-grade inflammation. Acute inflammation is characterized by an abrupt initiation of a clear and large inflammation response that is terminated when the underlying injury or infection is eliminated. Chronic low-grade inflammation is characterized by asynchronous, micro-inflammatory activity at the low, simmering level that persists over an indefinite period. The homeostatic set point for inflammation is approximately three-fold higher in individuals with chronic, low-grade inflammation.

distinction between acute and chronic, low-grade inflammation; 2) potential causes of chronic, low-grade inflammation; and 3) the many mechanisms in which PA may lower inflammation.

ACUTE VERSUS CHRONIC, LOW-GRADE INFLAMMATION

Inflammation is a generalized response to tissue damage, infection by pathogens, or the presence of irritants. The primary function of the process is to protect the host by eliminating initiating stimuli, clear out the damage, and initiate repair and remodeling as needed (5,11,12). The immune system is primarily responsible for inflammation in coordination with the endocrine, hepatic, nervous, lymphatic, and vascular systems. Inflammatory responses may be small and localized (e.g., a paper cut or minor bruise) or they may be large enough to evoke a systemic protective response (e.g., an infection or significant injury). A systemic response involves vascular changes, production of acute phase proteins by the liver, and increases in circulating immune mediators, immune cells, and acute phase proteins (6).

Acute and chronic inflammation are fundamentally different in many ways. While acute inflammation is a desirable, highly regulated, protective response to distinct tissue injury or infectious stimuli, chronic low-grade inflammation is an undesirable, dysregulated state caused by progressive micro-changes in one or more tissues over a long period of time (Figure 1) (1,5,6,8). In a healthy system, the homeostatic level of inflammation is low owing to the ubiquitous presence of inactive immune cells poised to respond to stimuli. When an injury or infection occurs, these cells are activated, a clear and proportional response is initiated, local infection or damage is eliminated, the response is terminated, and homeostasis is restored (11,12). In the dysregulated system, small levels of dysfunction or trauma in one or more tissues continuously increase the inflammatory activity without eliminating the underlying stimuli and terminating the response (5,6,9).

LOW VERSUS HIGH INFLAMMATION PHENOTYPES

Differences in inflammatory cells residing in tissues and soluble mediators and biomarkers of inflammation in the systemic circulation allow for the differentiation of low and high inflammation phenotypes (9,13). Strategies incorporating PA to lower inflammation and associated disease outcomes may be designed to convert from high to low inflammation phenotypes (14).

M1 versus M2 Macrophages

Macrophages are mononuclear phagocytes residing in tissues and play a pivotal role in shifting the local environment between low and high inflammation states (Figure 2). There are two distinct macrophage phenotypes, the pro-inflammatory M1 phenotype with M1a and M1b forms and the anti-inflammatory/regulatory M2 phenotype with M2a, M2b, and M2c forms (11,14). In the healthy, low inflammation state, M2 macrophages predominate and act as an inflammation buffer by producing and releasing inflammatory mediators that downregulate inflammatory activity. These mediators are typically small signal molecules (known as cytokines) that elicit responses in other immune and non-immune cells to influence function. The characteristic cytokines of M2 macrophages are IL-4, IL-10, IL-13, and transforming growth factor-β (11,14). Key actions of these cytokines include activation of subclasses of T cells that act to maintain a regulated and healthy tissue environment, T helper (Th) type 2 (Th2) and T regulatory (Treg) lymphocytes. The characteristic cytokines of M1 macrophages, particularly the M1b subclass, are IL-1, IL-12, IL-23, tumor necrosis factor (TNF)-α, and interferon (IFN)-γ (11). Additionally, M1 macrophages release free radical molecules to create a hostile local environment to damage proteins, lipids, and nucleotides, and kill local pathogens, such as intracellular bacteria. The cytokines produced by M1 macrophages and signal molecules from damaged tissue or infectious agents, known as damage-associated (DAMP) and pathogen-associated molecular patterns (PAMP), promote activation of additional immune cells. These cells include incoming monocytes that may differentiate to become M1 macrophages, neutrophils, Th1, Th17, and natural killer (NK) lymphocytes (11,14).

Serum Cytokine Profiles

The hallmark of chronic, low-grade inflammation is a persistent elevation in inflammatory cytokines and other soluble mediators. Concentrations of these biomarkers may

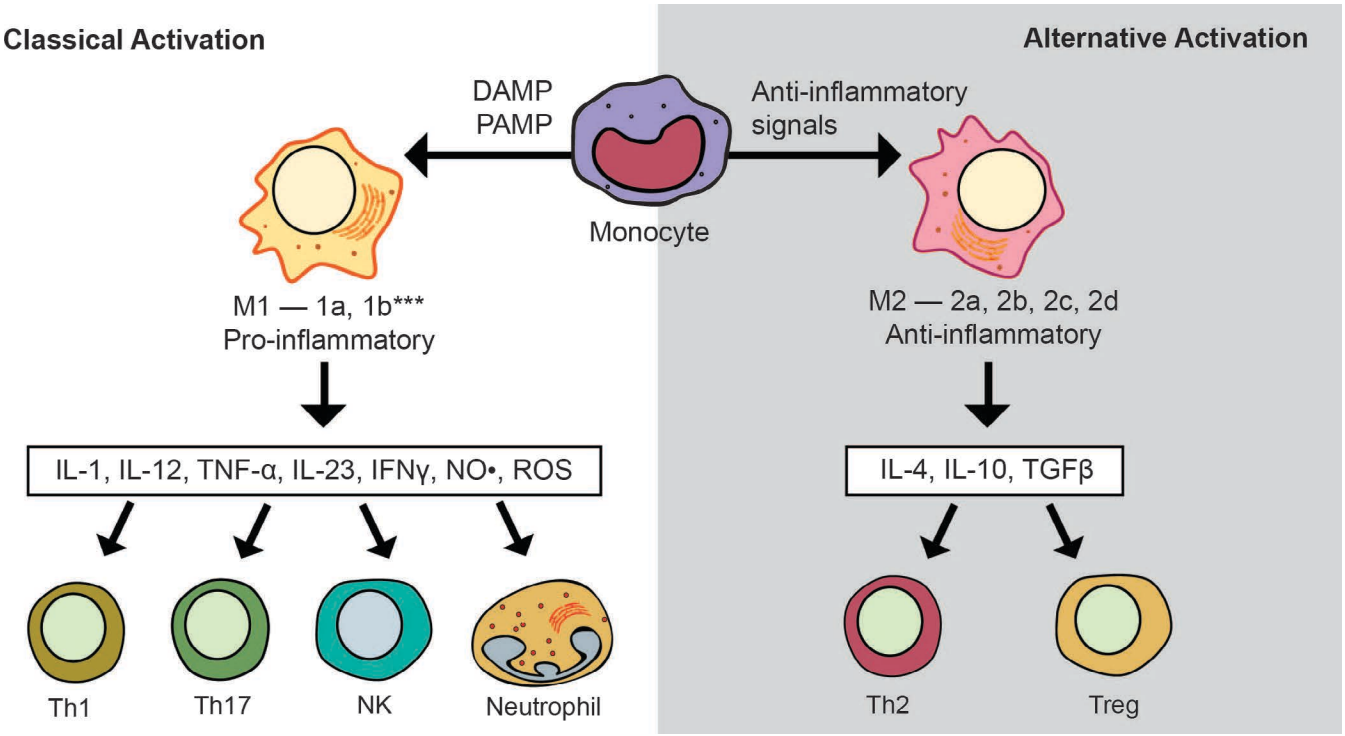

FIGURE 2. Macrophages of M1 and M2 phenotypes have different impacts on the inflammatory environment. As they infiltrate tissues, monocytes are signaled by the local environment to differentiate into M1 macrophages in the presence of DAMPs, PAMPs, and proinflammatory cytokines and mediators and into M2 macrophages in the presence of anti-inflammatory signals. The cytokines produced and cells activated by M1 increase inflammatory activity and inhibit M2 activity, and those activated by M2 macrophages promote immunotolerance and inhibit M1 activity (11). DAMP = damage-associated molecular patterns; IL = interleukin; IFN-γ = interferon – γ; PAMP = pathogen-associated molecular patterns; NK = natural killer; NO• = nitric oxide; ROS = reactive oxygen species; Th = T helper; TNF-α = tumor necrosis factor- α; TGF-β = transforming growth factor – β; Treg = T regulatory.

fluctuate and ranges for low versus high phenotypes have not been established, except for the acute phase protein, C-reactive protein (CRP). Increases in the M1 cytokines IL-1β, TNF-α, and IL-6 induce production of CRP by the liver, and CRP is considered a marker of systemic inflammation. Optimal levels of CRP are <1 $mg \cdot L^{-1}$, and levels >3 $mg \cdot L^{-1}$ indicate high risk for cardiovascular disease (15). Similarly, it is generally accepted that individuals with low-grade inflammation have levels of an array of cytokines that are roughly two- to three-fold higher than their non-inflamed counterparts (7,8).

Inflammation Phenotype Flexibility

There are sequential macrophage phenotype shifts from predominance of M2 macrophages in healthy tissues to M1 when damage or infection occur, and back to M2 when the insult is resolved (Figure 3) (11,16). We propose that this paradigm of shifting back and forth between M2 and M1 macrophage states to meet changing demands may be referred to as *inflammation phenotype flexibility*. This paradigm is analogous to shifting back and forth between oxidation of fat and glucose between fasting and insulin-stimulated conditions known as metabolic flexibility (17). In both cases, a high degree of flexibility is characteristic of a well-regulated and healthy system, while loss of flexibility is indicative of dysregulation.

TISSUE CROSS-TALK

Pro- and anti-inflammatory immune and metabolic activities in one tissue may affect all tissues in the body because of tissue cross-talk. For example, adipose tissue can become dysfunctional as cell volumes increase and cellular functions are stressed and impaired (e.g., endoplasmic reticulum stress). This causes cell injury that elicits production of DAMP to activate M1 macrophages (8). Over time, the inflammatory environment of the adipose tissue converts from M2 to M1 predominance (18). Inflammatory cytokines such as TNF-α, IL-1β, IL-6, and others effuse from the adipose to the blood and circulate to stimulate inflammation in distant tissues (e.g., stimulation of the inflammatory cells residing in atherosclerotic plaques or interference with skeletal muscle insulin signaling) (5). With respect to inflammation, adipose to other tissue cross-talk is important because this is a key mechanism linking increased adiposity to chronic, low-grade inflammation and obesity-associated diseases (14).

CHRONIC, LOW-GRADE INFLAMMATION AND DEVELOPMENT OF DISEASE

The evolving picture painted in this review is of the connection between elevated inflammation levels and the development of disease. Inflammation plays direct and indirect roles in the development and progression of many (if not most) diseases. Table 1 shows some of the many diseases linked to

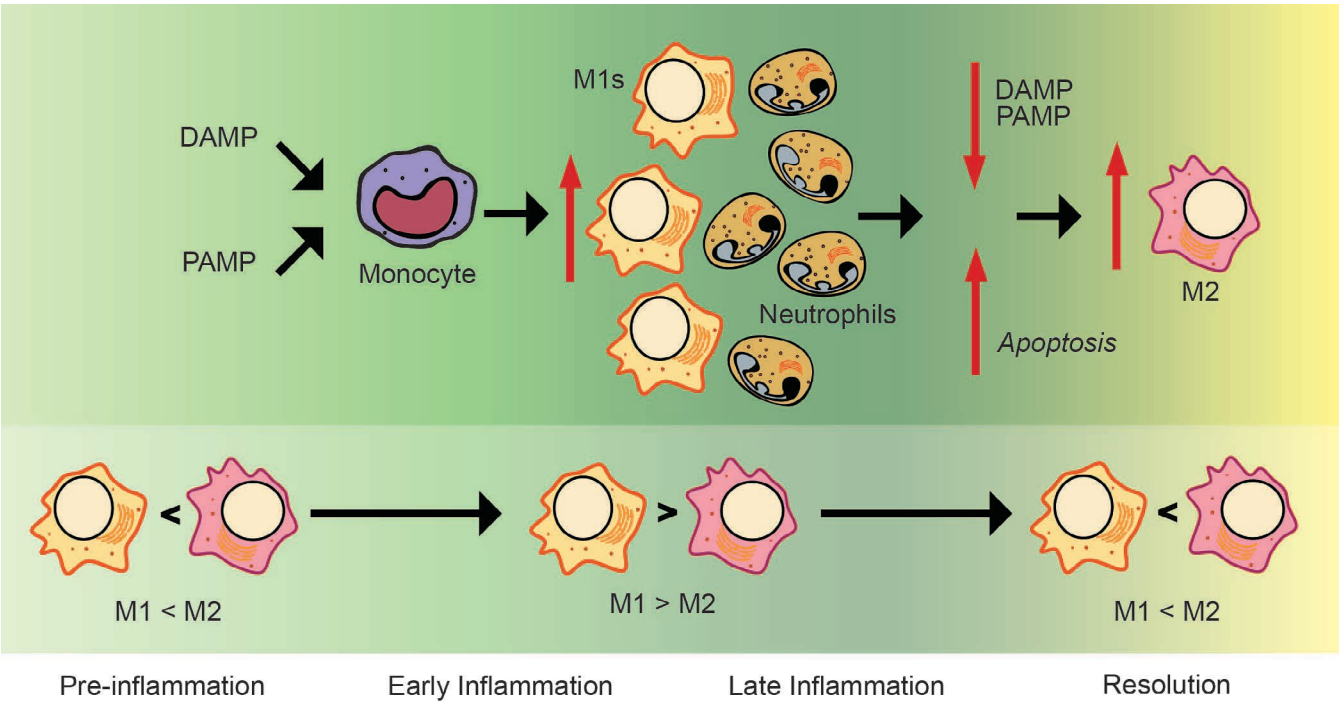

FIGURE 3. In healthy, uninflamed tissues M2 macrophages predominate. DAMP and or PAMP produced by injury or infection activate incoming monocytes to differentiate into M1 macrophages. Inflammatory activity of M1 macrophages and accompanying leukocytes, particularly infiltrating neutrophils, eliminate the underlying source of inflammation using the actions of free radicals to target damaged cellular components and cells for phagocytic removal. Elimination of DAMP and PAMP from the area will induce apoptosis of neutrophil apoptosis, which induces incoming monocytes to differentiate to become M2 rather than M1 macrophages (11). DAMP = damage-associated molecular patterns; PAMP = pathogen-associated molecular patterns.

TABLE 1. Diseases and physiological processes promoted by inflammation.

Disease or Process	Underlying Mechanism(s) Linked to Inflammation	Ref.
Type 2 diabetes	Insulin resistance caused by: ↑ activation of the NLRP3 inflammasome ↑ IL-1β, and TNF-α Dysfunction of pancreatic β-cells stimulated by: ↑ IL-1β	(1,2,19)
Atherosclerotic plaque formation	Plaque progression driven by: ↑ ROS ↑ NLRP3 inflammasome activation ↑ cytokines including IL-1β, and TNF-α ↑ macrophage infiltration and activation	(1,2)
Neurodegenerative diseases and aging associated cognitive decline	Deterioration of cognitive function and development of lesions stimulated by: ↑ chemokines, IL-1β, TNF-α, IL-6 and other cytokines from microglia ↑ recruitment and activation of inflammatory cells (+) feedback loop accelerates dysfunction in neural tissue	(3)
Cancer	Cell damage and cell proliferation to promote tumorigenesis stimulated by: ↑ ROS and activation of the NF-κB signaling pathways	(4)
Aging and age-related diseases	Age-related redox imbalance, slowing of autophagy, and accumulation of senescent immune cells stimulates: ↑ ROS and activation of the NF-κB signaling ↑ NLRP3 activation ↑ IL-1β, TNF-α, IL-6 and other cytokines (+) feedback pro-inflammatory loop to promote all diseases in table above and promote overall decline in function	(5)

IL = interleukin; NF-κB = nuclear factor-κB; NLRP3 = NOD-like receptor family pyrin domain containing 3; ROS = reactive oxygen species; TNF-α = tumor necrosis factor-α

inflammation and one or more key mechanisms underlying the connection between inflammation and the disease pathology.

ANTI-INFLAMMATORY MECHANISMS OF PHYSICAL ACTIVITY

There are many potential mechanisms for PA to lower inflammation that parallel the many mechanisms by which low-grade inflammation can occur. It is difficult to isolate the relative contribution of any one mechanism to the lowering of inflammation because there is no way to know the sources of blood borne biomarkers. Further, it may be that small contributions of multiple mechanisms accumulate over time, in the same manner that adaptations to increase in PA or exercise occur. As described in the following sections, decreases in visceral adiposity, increases in anti-inflammatory myokines and adipokines, improvements in gut barrier function and makeup of the gut microbiome, as well as attenuation of postprandial glycemic and lipidemic are potential mechanisms that may act individually or in tandem to induce conversion from high to low inflammation phenotypes.

Changes in Adipose Tissue

Higher levels of visceral (VAT) and subcutaneous (SAT) adipose tissue increase risk for low-grade inflammation (13). The VAT typically has greater inflammatory activity than SAT, and increased adipocyte size may induce tissue dysfunction, potentially triggered by stress to the endoplasmic reticulum caused by large cell volume (13,20). Saturated fatty acids released from adipocytes may act as PAMPs to bind toll-like receptor-4 (TLR4) of local macrophages and stimulate inflammatory activity through the nuclear factor (NF)-κB pathway (13,21). Additionally, stress to the endoplasmic reticulum from large adipocyte volume causes dysfunction and production of unfolded proteins that act as DAMPs to stimulate accumulation of M1 macrophages as well as Th1 and Th17 lymphocytes to create local inflammation than contributes to systemic inflammation levels (20,22). Individuals with elevated VAT or waist circumference (highly correlated with VAT) have higher levels of circulating inflammation biomarkers (cytokines, soluble cytokine receptors, acute phase proteins) (7). In addition, elevated waist circumference also may differentiate metabolically healthy from non-metabolically healthy obese individuals (23).

Higher levels of PA may lower inflammation through mechanisms that can be either dependent or independent of decreases in VAT and SAT. Decreasing VAT and SAT volume may decrease fatty acid stimulation of TLR4 and endoplasmic reticular stress and allow for M2 macrophage dominance to re-establish. This phenotype switch has been demonstrated in mice (24) but is less clear in humans. Macrophage numbers and inflammation in adipose have been demonstrated to decrease with exercise in humans (25), but the extent to which M1 and M2 macrophage ratios change is not clear (14,26–28).

There is an inverse relationship between PA levels and both levels of VAT and VAT-associated inflammation. This has been demonstrated with increased VAT in lean males during bed rest to decrease PA and in a large cross-sectional cohort in which PA energy expenditure was negatively associated with quantity of visceral adipose tissue (29,30). Alternatively, in a large prospective cohort, higher levels of moderate to vigorous PA were associated with lower levels of IL-6, leptin, and resistin, and higher levels of adiponectin that were independent of central adiposity (31). Collectively, these studies demonstrate that individuals with similar adipose volumes may vary in inflammation level and that PA may lower inflammation without reducing central adiposity.

Anti-inflammatory Myokines

Skeletal muscle produces and releases a number of bioactive compounds, referred to as myokines, that act in an endocrine manner. Examples of myokines include leukemia inhibitory factor, myostatin, brain-derived neurotrophic factor, irisin, insulin-like growth factor (IGF)-1 and IGF-2, and IL-4, IL-6, IL-7, and IL-15 (32,33). Many of these are beneficial in ways that may alleviate the contribution of tissue dysfunction to low-grade inflammation, e.g., increased lipolysis to reduce volume of VAT by IL-15, the browning of adipose tissue stimulated by irisin, or stimulation of muscle hypertrophy by myostatin, LIF, IL-4, IL-6, IL-7, and IL-15 (32,34). The myokine with the most pronounced anti-inflammatory activity and greatest increase during PA is IL-6 (32,33).

The main anti-inflammatory effects of IL-6 are to serve as a negative feedback mechanism to downregulate production of the "alarm cytokines" IL-1β and TNF-α and to induce production of anti-inflammatory regulators IL-10, IL-1 receptor antagonist (IL-1ra), and soluble TNF receptor-1 (sTNFR1) (33). When IL-6 is produced by muscle during exercise these effects predominate and provide anti-inflammatory tissue cross-talk to lower inflammation in other tissues (8). A pro-inflammatory effect of IL-6 is to act synergistically with IL-1β and TNF-α to induce production of CRP in the liver (35,36). When produced as a myokine without coproduction of IL-1β and TNF-α, the negative feedback and induction of anti-inflammatory mediators is the prevailing influence both locally and systemically; for instance, IL-6 from muscle and subsequent IL-10, IL-1ra, and sTNFR1 may downregulate M1 macrophage activity in adipose tissue. The anti-inflammatory effect of IL-6 produced during exercise has been demonstrated in a study in which participants were treated with a low-dose of endotoxin to induce inflammation in separate trials at rest, during exercise, and during IL-6 infusion. Both exercise and IL-6 markedly blunted the TNF-α response to the endotoxin (37). Similarly, blood with elevations in IL-6 and IL-1ra collected during exercise inhibits ex vivo production of IL-1β and TNF-α (38).

Interleukin-6 as a marker of and enhancer of low-grade inflammation versus an anti-inflammatory myokine can be further differentiated by temporal relationship to exercise.

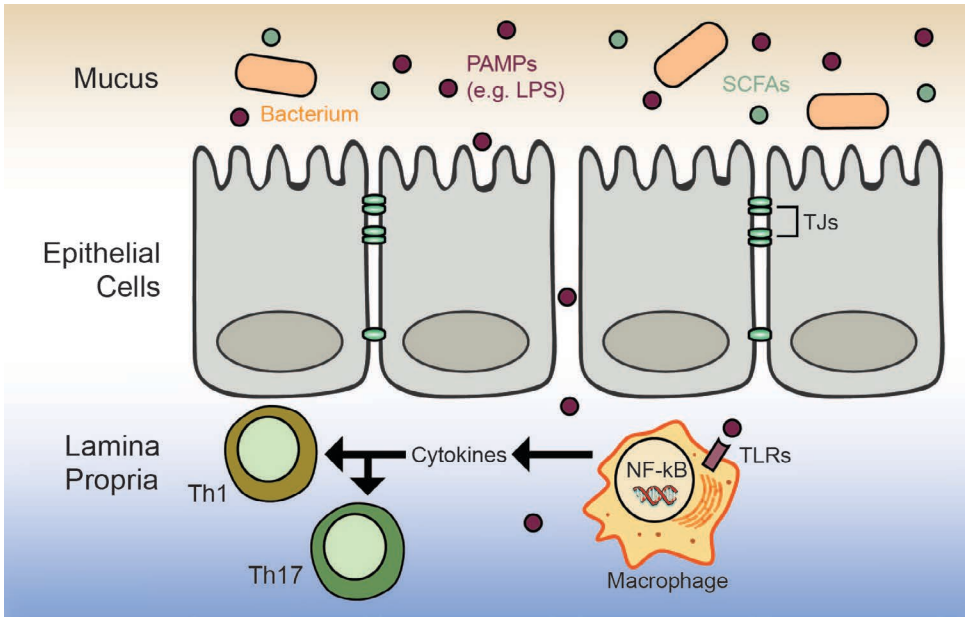

FIGURE 4. Tight junction proteins link intestinal epithelial cells to form a barrier. Loss of barrier function allows for entry of PAMPs like LPS into the lamina propria. The recognition of LPS by TLR4 of M1 macrophages stimulates a pro-inflammatory cascade which includes production of cytokines and accumulation of Th1 and Th17 lymphocytes. NF-κβ = nuclear factor – κβ; PAMP = pathogen-associated molecular patterns; SCFA = short chain fatty acid; Th = T helper; TJ = tight junction; TLR = toll-like receptor.

Resting levels of IL-6 reflect low-grade inflammation. A delayed increase in IL-6 four to eight hours post-exercise is generally the result of exercise-induced muscle damage (39–41). In contrast, IL-6 as a myokine peaks during exercise and returns to baseline levels within a two to three hours post-exercise (42). Two- to 100-fold increases in IL-6 during exercise associate positively with intensity and duration of exercise and inversely with carbohydrate availability (10,42–45).

Improved Gut Barrier Function and Makeup of the Gut Microbiome

Inflammation may also be modulated by the diverse community of microorganisms (microbiota) residing in the gastrointestinal tract (GIT) in both a PA-dependent and PA-independent manner. Several studies have now shown PA can alter GIT microbiota and lower inflammation (46,47). One potential mechanism connecting PA, the GIT microbiota, and inflammation is a commonly-reported increase in the relative abundances of major butyrate-producing bacterial species (46,48,49). Butyrate, a short chain fatty acid produced by bacterial fermentation of dietary fiber, plays a significant role in anti-inflammatory mechanisms. Acting in a dose-dependent manner, butyrate can inhibit pro-inflammatory cytokine production, including IL-12, IFN-γ and TNF-α, and decrease NF-kB activation (50,51). Butyrate also plays an important role in sustaining barrier function; an important epithelial feature preventing passive paracellular diffusion of toxins, pathogens, and PAMPs between the apical and basolateral membranes of the GIT. Barrier function is mediated by tight junctions (TJ) that join intestinal epithelial cells together with a single TJ unit comprised of various proteins including claudins, occludins, and zonulins. A reduction in barrier integrity is associated with increases in circulatory PAMPs, such as lipopolysaccharide (LPS), which is a potent pro-inflammatory stimulator derived from the outer membrane of Gram-negative bacteria (Figure 4). Members of the *Enterobacteriaceae* family, within the Proteobacteria phylum, produce LPS with greater pro-inflammatory stimulation capacity (52,53). Butyrate promotes barrier integrity both through its anti-inflammatory activities and, more directly, through its modulation of TJ gene expression including claudins-1 and -2 (54–56).

Increased relative abundances of major butyrate-producing bacteria from *Clostridium* cluster XIVa, including *Butyrivibrio* spp., *Dorea* spp., and *Roseburia*, and *Clostridium* cluster IV including *Faecalibacterium,* have been measured in active adults compared to their sedentary counterparts (46,57), and studies in murine models have shown PA increases butyrate concentrations in the distal GIT relative to sedentary controls (58). However, studies of exercise have also commonly shown increases of Proteobacteria, including members of the *Enterobacteriaceae* family (46,48). Murine studies indicate forced exercise protocols, in particular, can dramatically increase the relative abundances of these potent LPS-possessing bacterial taxa relative to both sedentary mice and voluntary exercise mice controls (48). This is notable because GIT permeability can actually increase during prolonged strenuous exercise events, resulting in temporary elevation of circulatory LPS 21% to 68% above resting concentrations (59,60). Thus, the duration of and degree of

stress associated with PA may be important considerations in the benefit of PA to inflammatory phenotype.

Attenuation of Postprandial Glycemic and Lipidemic Responses

Large postprandial increases in glucose and or triglycerides stimulate inflammation and associate with risk for atherosclerotic CVD and T2D (61–64). A greater proportion of time is spent in the postprandial relative to the fasted state, thus lowering of non-fasting glucose and lipids is highly relevant to health.

Lowering glycemic responses may attenuate glucose stimulated inflammation. Glucose-induced increases in ROS and advanced glycation end products (AGE) stimulate M1 macrophage pro-inflammatory cytokine production and release (1,65,66), which may have a greater inflammatory impact when more M1 macrophages are available to respond. For example, increased IL-6 after a high glycemic index meal was measured in healthy women with, but not without, low-grade inflammation and high (>80 cm) waist circumference, despite no difference in the magnitude of glycemic responses (7). Additionally, the magnitude of the IL-1β response to exercise-induced muscle damage was associated ($r = 0.84$, $P < 0.05$) with waist circumference with a high carbohydrate but not a high protein/fat recovery diet (67). In a review of randomized crossover research trials, Haxhi et al. (68) concluded that exercise following a meal was more effective at lowering glycemic responses to the meal. The glucose lowering benefit of pre-meal exercise is typically limited to exercise within about one hour of the meal (7,68).

Postprandial inflammation following meals containing 30–100 g of dietary fat has been documented in over 50 research studies (69). Potential causes include interactions between free fatty acids in the gut and gut associated immune cells, co-absorption of LPS with ingested fat, and interactions between lipoprotein remnants and leukocytes in the circulation (21,62,70). Research findings favor exercising before a meal to lower postprandial triglyceridemia; however, many studies have found beneficial effects for studies of exercise after a meal (68,71,72). Moderate aerobic exercise, for instance, 60 minutes at 60% VO2max, performed 12 to 0.5 hours prior to a high-fat meal attenuates the magnitude of the postprandial triglyceride response (68,71,73). More research is needed to verify whether PA lowers the inflammation response to a high-fat meal.

INFLAMMATION LOWERING WITH PHYSICAL ACTIVITY

Without elucidating underlying mechanisms, numerous studies have demonstrated lowering of inflammation with increasing levels of PA. C-reactive protein and IL-6 are two of the most studied biomarkers of systemic inflammation in these studies, but there are a wide variety of biomarkers of low-grade inflammation (see [74,75] for reviews). These benefits have been both dependent and independent of changes in adiposity and measured for diverse populations from children to frail elderly, normal weight, overweight and obese, and with a wide variety of diseases such as type 2 diabetes, cancer, coronary artery disease, and arthritis. It should also be noted that cross-sectional and prospective cohort studies are more consistent in reporting inverse associations between physical activity levels and inflammation than are physical activity clinical trials (75). The reasons for this are unclear, but possible explanations may be that physical activity is more effective for prevention than for treatment, slower to change phenotype than the duration of most clinical trial studies, or not of sufficient dose or duration in many intervention trials.

SUMMARY

Low-grade inflammation is a common phenomenon resulting from tissue dysfunction in one or more locations throughout the body. Adipose tissue is one of the most common contributors, but there are many other possible sources. Inflammation in one location can promote inflammation in other locations via cells and mediators in the circulation. Physical activity has many potential mechanisms for lowering inflammation including changes to adipose, release of anti-inflammatory myokines, improving gut barrier function and microbial makeup, attenuating postprandial lipemic and glycemic responses, and potentially others. While many studies support the inverse association between physical activity and inflammation, more clinical trial research is needed to determine effective strategies to eliminate low-grade inflammation.

Acknowledgments: This work was supported by Montana University Research Initiative 51040-MSUR12015-03 and USDA-NIFA 2017-67018-26367.

REFERENCES

1. Sharma A, Tate M, Mathew G, Vince JE, Ritchie RH, de Haan JB. Oxidative stress and NLRP3-Inflammasome activity as significant drivers of diabetic cardiovascular complications: therapeutic implications. Front Physiol. 2018;9:114.
2. Katakami N. Mechanism of development of atherosclerosis and cardiovascular disease in diabetes mellitus. J Atheroscler Thromb. 2018;25(1):27–39.
3. Denver P, McClean PL. Distinguishing normal brain aging from the development of Alzheimer's disease: inflammation, insulin signaling and cognition. Neural Regen Res. 2018; 13(10):1719–30.
4. Park CH, Eun CS, Han DS. Intestinal microbiota, chronic inflammation, and colorectal cancer. Intest Res. 2018;16(3): 338–45.
5. Rea IM, Gibson DS, McGilligan V, McNerlan SE, Alexander HD, Ross OA. Age and age-related diseases: role of inflammation triggers and cytokines. Front Immunol. 2018; 9:586.

6. Medzhitov R. Origin and physiological roles of inflammation. Nature. 2008;454(7203):428–35.
7. Miles MP, Horrigan LC, Jay SE, Brown KM, Porter JW, Steward AN. Concentric and eccentric exercise, glycemic responses to a postexercise meal, and inflammation in women with high versus low waist circumference. Appl Physiol Nutr Metab. [Physiologie appliquee, nutrition et metabolism]. 2016;41(12):1262–70.
8. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. J Appl Physiol. 2005;98(4):1154–62.
9. Leal LG, Lopes MA, Batista ML Jr. Physical exercise-induced myokines and muscle-adipose tissue crosstalk: a review of current knowledge and the implications for health and metabolic diseases. Front Physiol. 2018;9:1307.
10. Fischer CP. Interleukin-6 in acute exercise and training: what is the biological relevance? Exerc Immunol Rev. 2006;12: 6–33.
11. Lech M, Anders HJ. Macrophages and fibrosis: how resident and infiltrating mononuclear phagocytes orchestrate all phases of tissue injury and repair. Biochim Biophys Acta. 2013; 1832(7):989–97.
12. Novak ML, Koh TJ. Phenotypic transitions of macrophages orchestrate tissue repair. Am J Pathol. 2013;183(5):1352–63.
13. Engin A. The pathogenesis of obesity-associated adipose tissue inflammation. Adv Exp Med Biol. 2017;960:221–45.
14. Silveira LS, Antunes Bde M, Minari AL, Dos Santos RV, Neto JC, Lira FS. Macrophage polarization: implications on metabolic diseases and the role of exercise. Crit Rev Eukaryot Gene Expr. 2016;26(2):115–32.
15. Ridker PM. High-sensitivity C-reactive protein: potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. Circulation. 2001;103(13):1813–8.
16. Serhan CN, Savill J. Resolution of inflammation: the beginning programs the end. Nat Immunol. 2005;6:1191.
17. Kelley DE, Goodpaster B, Wing RR, Simoneau JA. Skeletal muscle fatty acid metabolism in association with insulin resistance, obesity, and weight loss. Am J Physiol. 1999; 277(6):E1130–41.
18. Aron-Wisnewsky J, Tordjman J, Poitou C, Darakhshan F, Hugol D, Basdevant A, Aissat A, Guerre-Millo M, Clément K. Human adipose tissue macrophages: m1 and m2 cell surface markers in subcutaneous and omental depots and after weight loss. J Clin Endocrinol Metab. 2009;94(11):4619–23.
19. Zand H, Morshedzadeh N, Naghashian F. Signaling pathways linking inflammation to insulin resistance. Diabetes Metab Syndr. 2017;11 (Suppl 1):S307–9.
20. Ringseis R, Eder K, Mooren FC, Kruger K. Metabolic signals and innate immune activation in obesity and exercise. Exerc Immunol Rev. 2015;21:58–68.
21. Suganami T, Tanimoto-Koyama K, Nishida J, Itoh M, Yuan X, Mizuarai S, Kotani H, Yamaoka S, Miyake K, Aoe S, Kamei Y, Ogawa Y. Role of the Toll-like receptor 4/NF-kappaβ pathway in saturated fatty acid-induced inflammatory changes in the interaction between adipocytes and macrophages. Arterioscler Thromb Vasc Biol. 2007;27(1):84–91.
22. Engin AB. Adipocyte-macrophage cross-talk in obesity. Adv Exp Med Biol. 2017;960:327–43.
23. Shah RV, Murthy VL, Abbasi SA, Blankstein R, Kwong RY, Goldfine AB, Jerosch-Herold M, Lima JA, Ding J, Allison MA. Visceral adiposity and the risk of metabolic syndrome across body mass index: the MESA Study. JACC Cardiovasc Imaging. 2014;7(12):1221–35.
24. Kawanishi N, Mizokami T, Yano H, Suzuki K. Exercise attenuates M1 macrophages and CD8+ T cells in the adipose tissue of obese mice. Med Sci Sports Exerc. 2013;45(9): 1684–93.
25. Gordon PM, Liu D, Sartor MA, IglayReger HB, Pistilli EE, Gutmann L, Nader GA, Hoffman EP. Resistance exercise training influences skeletal muscle immune activation: a microarray analysis. J Appl Physiol. (Bethesda, MD: 1985). 2012;112(3):443–53.
26. Spencer M, Yao-Borengasser A, Unal R, Rasouli N, Gurley CM, Zhu B, Peterson CA, Kern PA. Adipose tissue macrophages in insulin-resistant subjects are associated with collagen VI and fibrosis and demonstrate alternative activation. Am J Physiol Endocrinol Metab. 2010;299(6): E1016–27.
27. Lee S, Norheim F, Langleite TM, Noreng HJ, Storas TH, Afman LA, Frost G, Bell JD, Thomas EL, Kolnes KJ, Tangen DS, Stadheim HK, Gilfillan GD, Gulseth HL, Birkeland KI, Jensen J, Drevon CA, Holen T; NutriTech Consortium. Effect of energy restriction and physical exercise intervention on phenotypic flexibility as examined by transcriptomics analyses of mRNA from adipose tissue and whole body magnetic resonance imaging. Physiol Rep. 2016;4(21).
28. Liu D, Morales FE, IglayReger HB, Treutelaar MK, Rothberg AE, Hubal MJ, Nadler EP, Robidoux J, Barakat H, Horowitz JF, Hoffman EP, Burant CF, Gordon PM. Expression of macrophage genes within skeletal muscle correlates inversely with adiposity and insulin resistance in humans. Appl Physiol Nutr Metab. [Physiologie appliquee, nutrition et metabolisme]. 2018;43(2):187–93.
29. Philipsen A, Hansen AL, Jorgensen ME, Brage S, Carstensen B, Sandbaek A, Almdal TP, Gram J, Pedersen EB, Lauritzen T, Witte DR. Associations of objectively measured physical activity and abdominal fat distribution. Med Sci Sports Exerc. 2015;47(5):983–9.
30. Harder-Lauridsen NM, Nielsen ST, Mann SP, Lyngbaek MP, Benatti FB, Langkilde AR, Law I, Wedell-Neergaard AS, Thomsen C, Møller K, Karstoft K, Pedersen BK, Krogh-Madsen R. The effect of alternate-day caloric restriction on the metabolic consequences of 8 days of bed rest in healthy lean men: a randomized trial. J Appl Physio. (Bethesda, MD: 1985). 2017;122(2):230–41.
31. Vella CA, Allison MA, Cushman M, Jenny NS, Miles MP, Larsen B, Lakoski SG, Michos ED, Blaha MJ. Physical activity and adiposity-related inflammation: the MESA. Med Sci Sports Exerc. 2017;49(5):915–21.
32. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol. 2012;8(8):457–65.
33. Ost M, Coleman V, Kasch J, Klaus S. Regulation of myokine expression: Role of exercise and cellular stress. Free Radic Biol Med. 2016;98:78–89.
34. Pedersen BK. Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease. Eur J Clin Invest. 2017;47(8):600–11.
35. Fantuzzi G, Zheng H, Faggioni R, Benigni F, Ghezzi P, Sipe JD, Shaw AR, Dinarello CA. Effect of endotoxin in IL-1 beta-deficient mice. J Immunol. (Baltimore, MD: 1950). 1996; 157(1):291–6.
36. Marino MW, Dunn A, Grail D, Inglese M, Noguchi Y, Richards E, Jungbluth A, Wada H, Moore M, Williamson B, Basu S, Old LJ. Characterization of tumor necrosis factor-

deficient mice. Proc Natl Acad Sci U S A. 1997;94(15): 8093–8.
37. Starkie R, Ostrowski SR, Jauffred S, Febbraio M, Pedersen BK. Exercise and IL-6 infusion inhibit endotoxin-induced TNF-alpha production in humans. FASEB J. 2003;17(8):884–6.
38. Drenth JP, Van Uum SH, Van Deuren M, Pesman GJ, Van der Ven-Jongekrijg J, Van der Meer JW. Endurance run increases circulating IL-6 and IL-1ra but downregulates ex vivo TNF-alpha and IL-1 beta production. J Appl Physiol. 1995;79(5): 1497–503.
39. Depner CM, Kirwan RD, Frederickson SJ, Miles MP. Enhanced inflammation with high carbohydrate intake during recovery from eccentric exercise. Eur J Appl Physiol. 2010;109(6):1067–76.
40. Miles MP, Andring JM, Pearson SD, Gordon LK, Kasper C, Depner CM, Kidd JR. Diurnal variation, response to eccentric exercise, and association of inflammatory mediators with muscle damage variables. J Appl Physiol. (Bethesda, MD: 1985). 2008;104(2):451–8.
41. Miles MP, Keller JM, Kordick LK, Kidd JR. Basal, circadian, and acute inflammation in normal versus overweight men. Med Sci Sports Exerc. 2012;44(12):2290–8.
42. Ostrowski K, Hermann C, Bangash A, Schjerling P, Nielsen JN, Pedersen BK. A trauma-like elevation of plasma cytokines in humans in response to treadmill running. J Physiol. 1998;513 (Pt 3):889–94.
43. Ostrowski K, Schjerling P, Pedersen BK. Physical activity and plasma interleukin-6 in humans – effect of intensity of exercise. Eur J Appl Physiol. 2000;83(6):512–5.
44. Ostrowski K, Rohde T, Zacho M, Asp S, Pedersen BK. Evidence that interleukin-6 is produced in human skeletal muscle during prolonged running. J Physiol. 1998;508 (Pt 3):949–53.
45. Suzuki K, Nakaji S, Yamada M, Liu Q, Kurakake S, Okamura N, Kumae T, Umeda T, Sugawara K. Impact of a competitive marathon race on systemic cytokine and neutrophil responses. Med Sci Sports Exerc. 2003;35(2):348–55.
46. Clarke SF, Murphy EF, O'Sullivan O, Lucey AJ, Humphreys M, Hogan A, Hayes P, O'Reilly M, Jeffery IB, Wood-Martin R, Kerins DM, Quigley E, Ross RP, O'Toole PW, Molloy MG, Falvey E, Shanahan F, Cotter PD. Exercise and associated dietary extremes impact on gut microbial diversity. Gut. 2014;63(12):1913–20.
47. Campbell SC, Wisniewski PJ, Noji M, McGuinness LR, Haggblom MM, Lightfoot SA, Joseph LB, Kerkhof LJ. The effect of diet and exercise on intestinal integrity and microbial diversity in mice. PLoS One. 2016;11(3):17.
48. Allen JM, Miller MEB, Pence BD, Whitlock K, Nehra V, Gaskins HR, White BA, Fryer JD, Woods JA. Voluntary and forced exercise differentially alters the gut microbiome in C57BL/6J mice. J Appl Physiol. 2015;118(8):1059–66.
49. Evans CC, LePard KJ, Kwak JW, Stancukas MC, Laskowski S, Dougherty J, Moulton L, Glawe A, Wang Y, Leone V, Antonopoulos DA, Smith D, Chang EB, Ciancio MJ. Exercise prevents weight gain and alters the gut microbiota in a mouse model of high fat diet-induced obesity. PLoS One. 2014; 9(3):14.
50. Nancy S, Bienvenu J, Coffin B, Andre F, Descos L, Flourie B. Butyrate strongly inhibits in vitro stimulated release of cytokines in blood. Dig Dis Sci. 2002;47(4):921–8.
51. Saemann MD, Bohmig GA, Osterreicher CH, Burtscher H, Parolini O, Diakos C, Stöckl J, Hörl WH, Zlabinger GJ. Anti-inflammatory effects of sodium butyrate on human monocytes: potent inhibition of IL-12 and up-regulation of IL-10 production. FASEB J. 2000;14(15):2380–2.
52. Copeland S, Warren HS, Lowry SF, Calvano SE, Remick D; Inflammation and the Host Response to Injury Investigators. Acute inflammatory response to endotoxin in mice and humans. Clin Diagn Lab Immunol. 2005;12(1):60–7.
53. Gronbach K, Flade I, Holst O, Lindner B, Ruscheweyh HJ, Wittmann A, Menz S, Schwiertz A, Adam P, Stecher B, Josenhans C, Suerbaum S, Gruber AD, Kulik A, Huson D, Autenrieth IB, Frick JS. Endotoxicity of lipopolysaccharide as a determinant of T-cell-mediated colitis induction in mice. Gastroenterology. 2014;146(3):765–75.
54. Daly K, Shirazi-Beechey SP. Microarray analysis of butyrate regulated genes in colonic epithelial cells. DNA Cell Biol. 2006;25(1):49–62.
55. Wang H-B, Wang P-Y, Wang X, Wan Y-L, Liu Y-C. Butyrate enhances intestinal epithelial barrier function via up-regulation of tight junction protein Claudin-1 transcription. Dig Dis Sci. 2012;57(12):3126–35.
56. Plöger S, Stumpff F, Penner GB, Schulzke JD, Gäbel G, Martens H, Shen Z, Günzel D, Aschenbach JR. Microbial butyrate and its role for barrier function in the gastrointestinal tract. Ann N Y Acad Sci. 2012;1258(1):52–9.
57. Bressa C, Bailen-Andrino M, Perez-Santiago J, Gonzalez-Soltero R, Perez M, Montalvo-Lominchar MG, Maté-Muñoz JL, Domínguez R, Moreno D, Larrosa M. Differences in gut microbiota profile between women with active lifestyle and sedentary women. PLoS One. 2017;12(2):e0171352.
58. Matsumoto M, Inoue R, Tsukahara T, Ushida K, Chiji H, Matsubara N, Hara H. Voluntary running exercise alters microbiota composition and increases n-butyrate concentration in the rat cecum. Biosci Biotechnol Biochem. 2008;72(2): 572–6.
59. Gill SK, Teixeira A, Rama L, Rosado F, Hankey J, Scheer V, Hemmings K, Ansley-Robson P, Costa RJ. Circulatory endotoxin concentration and cytokine profile in response to exertional-heat stress during a multi-stage ultra-marathon competition. Exerc Immunol Rev. 2015;21:114–28.
60. Jeukendrup AE, Vet-Joop K, Sturk A, Stegen J, Senden J, Saris WH, Wagenmakers AJ. Relationship between gastro-intestinal complaints and endotoxaemia, cytokine release and the acute-phase reaction during and after a long-distance triathlon in highly trained men. Clin Sci (Lond). 2000; 98(1):47–55.
61. Cavalot F, Petrelli A, Traversa M, Bonomo K, Fiora E, Conti M, Anfossi G, Costa G, Trovati M. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. J Clin Endocrinol Metab. 2006;91(3):813–9.
62. de Vries MA, Klop B, Janssen HW, Njo TL, Westerman EM, Castro Cabezas M. Postprandial inflammation: targeting glucose and lipids. Adv Exp Med Biol. 2014;824:161–70.
63. Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA. 2007;298(3):299–308.
64. Varbo A, Nordestgaard BG, Tybjaerg-Hansen A, Schnohr P, Jensen GB, Benn M. Nonfasting triglycerides, cholesterol, and ischemic stroke in the general population. Ann Neurol. 2011;69(4):628–34.
65. Xiong DD, Zhang M, Li N, Gai JF, Mao L, Li M. Mediation of inflammation, obesity and fatty liver disease by advanced

glycation endoproducts. Eur Rev Med Pharmacol Sci. 2017;21(22):5172–8.
66. Dandona P, Chaudhuri A, Ghanim H, Mohanty P. Proinflammatory effects of glucose and anti-inflammatory effect of insulin: relevance to cardiovascular disease. Am J Cardiol. 2007;99(4A):15B–26B.
67. Miles MP, Depner CM, Kirwan RD, Frederickson SJ. Influence of macronutrient intake and anthropometric characteristics on plasma insulin after eccentric exercise. Metabolism. 2010;59(10):1456–64.
68. Haxhi J, Scotto di Palumbo A, Sacchetti M. Exercising for metabolic control: is timing important? Ann Nutr Metab. 2013;62(1):14–25.
69. Herieka M, Erridge C. High-fat meal induced postprandial inflammation. Mol Nutr Food Res. 2014;58(1):136–46.
70. Vors C, Pineau G, Drai J, Meugnier E, Pesenti S, Laville M, Laugerette F, Malpuech-Brugère C, Vidal H, Michalski MC. Postprandial endotoxemia linked with chylomicrons and lipopolysaccharides handling in obese versus lean men: a lipid dose-effect trial. J Clin Endocrinol Metab. 2015;100(9): 3427–35.
71. Hashimoto S, Ootani K, Hayashi S, Naito M. Acute effects of shortly pre- versus postprandial aerobic exercise on postprandial lipoprotein metabolism in healthy but sedentary young women. J Atheroscler Thromb. 2011;18(10):891–900.
72. Farah NM, Malkova D, Gill JM. Effects of exercise on postprandial responses to ad libitum feeding in overweight men. Med Sci Sports Exerc. 2010;42(11):2015–22.
73. Zhang JQ, Thomas TR, Ball SD. Effect of exercise timing on postprandial lipemia and HDL cholesterol subfractions. J Appl Physiol. (Bethesda, MD: 1985). 1998;85(4): 1516–22.
74. Palmefors H, DuttaRoy S, Rundqvist B, Borjesson M. The effect of physical activity or exercise on key biomarkers in atherosclerosis – a systematic review. Atherosclerosis. 2014; 235(1):150–61.
75. Beavers KM, Brinkley TE, Nicklas BJ. Effect of exercise training on chronic inflammation. Clin Chim Acta. 2010;411 (11–12):785–93.