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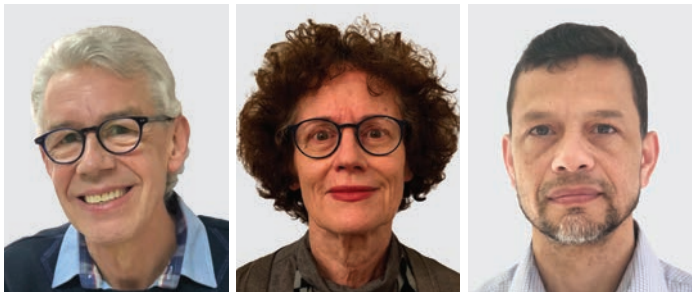
Editorial

How Could Physical Activity Reduce Inflammation and Inflammatory Gene Expression in Rheumatoid Arthritis?



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Exposure to adverse life events and acute physical injury such as that caused by trauma or infection trigger activation of the sympathetic nervous system (SNS) in response to direct signaling from the brain.[1-3] This instantly results in enhanced production of adrenaline and noradrenaline by the adrenal glands. Within minutes, the hypothalamic-pituitary-adrenal (HPA) axis is stimulated, leading to increased adrenal gland cortisol secretion. The SNS and HPA axis comprise the main components of the stress system. Stress system activation also involves reduced growth hormone, insulin-like growth factor-1 (IGF-1), androgen and thyroid hormone production, decreased vagal nerve activity, and increased renin-angiotensin-aldosterone system (RAAS) activation. The purpose of these neuroendocrine changes is to orchestrate the release of energy from its stores including the liver, adipose tissue, and muscle in the form of glucose, free fatty acids, and amino acids, and provide it to the activated immune system. This engenders an adequate inflammatory response and its subsequent resolution to reestablish homeostasis.

Rheumatoid arthritis (RA) is a prototypic chronic inflammatory disease. Whereas the stress system is also activated in response to RA activity, it does not succeed in resolving the inflammatory process and is therefore unable to restore homeostasis.[4] Even though cortisol levels are normal or slightly elevated in patients with RA who have not been treated with exogenous glucocorticoids (GCs), these levels appear to be too low to fully suppress the inflammatory process. This low GC level is thought to be due to cytokine-mediated desensitization of the HPA axis in RA. Additionally, some patients with RA experience GC resistance that may, at least in part, be genetically mediated. This seemingly inadequate cortisol response to RA-induced chronic inflammation may, however, serve to protect patients against persistent hypercortisolemia-induced sepsis. Still, HPA axis sensitivity to stressors other than inflammation, such as hypoglycemia stress, appears to be preserved in RA.

Besides the failure of the stress system to resolve chronic inflammation, its ongoing activation actually perpetuates inflammation and causes a catabolic state as well as metabolic abnormalities that contribute to enhanced cardiovascular risk in RA. This issue was elegantly reviewed in a report by Straub.[5]

In addition to alterations in cortisol production and sensitivity, other morphological and hormonal changes that contribute to ongoing inflammation in RA comprise loss of sympathetic nerve fibers in inflamed tissue, impaired activity of the vagus nerve, reduced androgen[6] and IGF-1 production, insulin[7] and IGF-1 resistance, increased RAAS activation, and low triiodothyronine levels (summarized in Table 1). In addition to excessive cytokine production, an increased insulin resistance in RA can be also caused by hypoandrogenism, excessive RAAS activation, and low thyroid hormone concentrations.[8] Importantly, whereas the liver, adipose tissue, and muscle become insulin-resistant, this does not apply to leukocytes.[5] Apart from insulin resistance and its related effects on lipid and glucose metabolism, another frequent metabolic abnormality in RA is hypertension, which can be mediated by SNS overactivity and increased RAAS activation. Increased cytokine production and GC therapy are known to mediate rheumatoid cachexia.[9] With regard to neuroendocrine abnormalities, insulin and IGF-1 resistance, hypoandrogenism,

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Table 1. Neuroendocrine alterations in RA and potential corrective effects of physical activity.

Neuroendocrine Alterations in RA	Potential Corrective Effects of Physical Activity
Relatively low cortisol production in relation to inflammation	Improved cortisol production
Cortisol resistance	Improved monocyte sensitivity to glucocorticoids
Increased SNS activity and inflamed tissue sympathetic nerve fiber loss	Reduced SNS activity
Reduced vagal nerve activity	Increased vagal nerve activity
Reduced androgen production	Increased androgen production
Reduced IGF-1 production	Increased IGF-1 production
Insulin resistance	Increased insulin sensitivity
Increased RAAS activity	Reduced RAAS activity

IGF-1: insulin-like growth factor 1; RA: rheumatoid arthritis; RAAS: renin-angiotensin-aldosterone system; SNS: sympathetic nervous system.

endogenous hypercortisolemia, increased SNS activity, and RAAS activation are also each implicated in rheumatoid cachexia.[5]

Along with comorbidities, including catabolism with muscle wasting and cardiometabolic abnormalities, patients with RA also experience chronic pain, decreased functional capacity, and fatigue.[10] It is therefore not surprising that most patients with RA do not perform regular physical activity. Yet, regular physical activity not only protects against many chronic diseases but also improves their outcomes.[11]

In this issue of *The Journal of Rheumatology*, Patterson and colleagues[12] report that physical activity is associated with reduced systemic inflammatory gene expression in RA. The authors assessed physical activity by actigraphy and performed RNA sequencing in 35 patients with RA. Physical activity and gene expression were compared between patients in the greatest vs lowest physical activity tertiles, in age-, sex-, race-, and ethnicity-adjusted analyses. Notably, none of the participants performed vigorous physical activity and the most vs least active groups spent an average of only 4.3 hours per day vs 1.1 hours per day, in moderate activity. The median gene count across all samples was 5.8×10^5. At an adjusted P value of < 0.1, 767 genes were differentially expressed in high compared to low physical activity patients. Compared to patients with RA in the low physical activity tertile, the participants in the high physical activity tertile experienced a dose-dependent downregulation of a range of signaling pathways that are implicated in the pathogenesis of RA. These included CD40, signal transducer and activator of transcription 3 (STAT3), triggering receptor expressed on myeloid cells 1 (TREM-1), interleukin (IL)-17A, IL-8, Toll-like receptor (TLR), and interferon (IFN) signaling. Upstream cytokine activation state analysis predicted reduced activation of tumor necrosis factor (TNF)-α and IFN, and increased erythropoietin activation in the most active group. These findings were mostly consistent upon additional adjustment for disease activity as evaluated by the RA Disease Activity Index and physical function as assessed by the Patient-Reported Outcomes Measurement Information System (PROMIS) physical function scale. Limitations of this investigation include its small size and the lack of physician evaluation and joint counts upon assessing disease activity, as well as lack of data on joint damage. Despite these shortcomings, this study, as the authors conclude, does provide mechanistic evidence in support of a disease-modifying effect induced by physical activity.

Do the reported findings by Patterson and colleagues relate to recently reported evidence that deals with the effects of physical activity on chronic inflammation–related outcomes in RA?[12] In a large 2-year randomized controlled trial, de Jong and colleagues[13] compared the effects of high-intensity weight-bearing exercise (2 sessions of 1.25 hours per week) to those of physical therapy (usual care) on disease outcomes in RA. High-intensity weight-bearing exercise improved physical fitness, physical capacity, and emotional status. Disease activity improved slightly but to the same extent in both participating groups, whereas the erythrocyte sedimentation rate did not change. Despite the lack of an apparent effect on disease activity, high-intensity weight-bearing exercise reduced the progression of radiographic damage, particularly in the feet and, to a lesser extent, in the hands. These findings suggest that physical activity can have a disease-modifying effect in RA. Other studies have shown that aerobic and/or resistance exercise programs do not change or improve disease activity and levels of acute-phase reactants and cytokines including IL-1α, IL-1β, IL-2, IL-6 and TNF-α.[10] High-intensity interval walk training reduced proinflammatory monocyte numbers and their cell surface TLR expression in RA.[14] Equally important in the context of chronic inflammation–induced comorbidities, aerobic and/or resistance exercises were reported to improve blood pressure, lipid profiles, insulin resistance, endothelial function, autonomic function, muscle mass and strength, excess adiposity, and self-reported fatigue and quality of life in RA.[10]

Given that patients in the Patterson study performed only moderate physical activity, a striking finding was the extent to which inflammatory signaling pathways were downregulated.[12] In the general population, regular bouts of moderate and vigorous physical activity cause transient increases in neutrophils, selective lymphocyte subsets, and antiinflammatory cytokines that, over time, enhance immunosurveillance and lower systemic inflammation.[11] Physically active and fit persons experience lower white blood cell counts and cytokines including IL-6 and IL-18. This is only partly explained by lower levels of abdominal obesity. Proposed mechanisms underlying the beneficial effects of physical activity on inflammation include reduction in visceral fat mass with decreased macrophage infiltration, release of IL-6 from contracting muscles, stress system activation, downregulation of TLRs, reduced numbers of proinflammatory monocytes, and increased circulating numbers of regulatory T cells.[3,15]

How could physical activity reduce inflammation and inflammatory gene expression in RA? As alluded to above, the HPA axis desensitization in RA is stimulus-specific.[4] Hence, it would be expected that regular physical activity can improve chronic cytokine-mediated inadequate cortisol production in relation to inflammation among patients with RA. Notably, in contrast to trained individuals, physically unfit persons experience a

significant increase in cortisol production at the end of even a low-intensity exercise session of 15 minutes.[16] Physical training can also increase the sensitivity of monocytes to GCs during bouts of exercise.[17] Regular physical activity improves plasticity in the neural networks that regulate SNS activity.[18] This results not only in reduced SNS activity but also in increased vagal nerve activity.[19] A recent systematic review revealed that regular physical activity augments testosterone, dehydroepiandrosterone, growth hormone, and IGF-1 levels.[20] Exercise training can reduce RAAS activation.[21] The beneficial effects of exercise training on insulin resistance are well recognized and, as mentioned previously, have also been documented previously in patients with RA.[10] Taken together, it appears likely that regular physical activity can reduce chronic inflammation by favorably affecting the different components of the dysfunctional stress system in patients with RA. These effects are also summarized in Table 1.

Data on the effects of physical activity on inflammatory gene expression as reported in the Patterson study[12] are in line with findings in different non-RA investigations. As given in Table 2, physical activity has been reported to reduce circulating soluble CD40 ligand concentrations in athletes, skeletal muscle STAT3 signaling in tumor-bearing mice, IFN-γ and IL-17 in serum and the supernatant of peripheral blood lymphocytes of women with multiple sclerosis, serum IL-8 concentrations in lean and overweight/obese individuals, and TLR levels. Improved functioning of the stress system upon physical activity could at least partly account for decreased inflammatory gene expression in RA. For example, as shown in Table 3, GCs can have favorable effects on CD40 ligand-induced nuclear factor kappa B (NF-κB) activation, TREM-1, IFN and TLR signaling, and IL-8 production. Also, GCs can induce apoptosis of proinflammatory monocytes by inhibiting ERK activity, and expand T regulatory cells in patients with autoimmune diseases.

In the Patterson study,[12] the mean (SD) body mass index was similar at 29.0 (6.8) kg/m^2 vs 28.6 (4.1) kg/m^2 in the most vs least physically active patients with RA. However, measures of abdominal obesity were not made. In this regard, excess and dysfunctional visceral adiposity is consistently associated with systemic inflammation.[15] This is mediated by production of proinflammatory cytokines and aberrant adipokine metabolism. A reduction in visceral fat mass is strongly implicated in exercise-mediated reduction of systemic inflammation. Whether the same applies in patients with RA needs further study.

Table 2. Selected reported effects of physical activity on inflammation in non-RA studies.

First Author (Year)	Effect
Geertsema (2008)[26]	Reduced circulating CD40 ligand levels by ultraendurance exercise in athletes
Testa (2022)[27]	Skeletal muscle STAT3 inhibition in tumor-bearing mice by resistance exercise training
Golzari (2010)[28]	Reduced IL-17 and IFN-γ production by combined exercise in women with multiple sclerosis
Dorneles (2016)[29]	Reduced IL-8 and increased IL-10 production in lean and overweight/obese persons by high-intensity interval exercise
Favere (2021)[30]	Reduced TLR levels by chronic resistance and combined exercise (systematic literature review)

IFN: interferon; IL: interleukin; RA: rheumatoid arthritis; STAT3: signal transducer and activator of transcription 3; TLR: Toll-like receptor.

Table 3. Selected reported effects of GCs on inflammation in non-RA studies.

First Author (Year)	Effect
Cechin (2014)[31]	Favorable effect of glucocorticoids on CD40 ligand and TNF-α induced NF-κB–induced activation in sensor cells
Dos Santos Dantas (2020)[32]	Inhibition of TREM-1 signaling (critical review)
Flammer (2010)[33]	Inhibition of IFN-stimulated gene expression in macrophages
Moynagh (2003)[34]	TLRs are key targets for the antinflammatory and immunosuppressive effects of GCs (commentary)
Barnes (2006)[35]	GCs reduce IL-8 gene transcription
Achuthan (2018)[36]	GCs promote apoptosis of proinflammatory monocytes by inhibiting ERK activity
Cari (2019)[37]	GCs expand T regulatory cells in autoimmune diseases (review)

GC: glucocorticoid; IFN: interferon; NF- κB; nuclear factor kappa B; RA: rheumatoid arthritis; TLR: Toll-like receptor; TNF: tumor necrosis factor.

In RA, immunocyte-derived IL-6 is known for its pronounced proinflammatory and catabolic effects.[22] Treatment with the IL-6 receptor antagonist tocilizumab (TCZ) in RA is highly effective to control disease activity, increase lean mass, improve fat distribution, and reduce insulin resistance.[22,23] In this regard, an intriguing and important recent development in exercise physiology is the discovery that skeletal muscle represents an endocrine organ.[10,22] In response to exercise, skeletal muscle produces several hundreds of myokines, which are peptides that exert autocrine, paracrine, and endocrine effects. An intensively investigated myokine is, in fact, IL-6. The effects of IL-6 on inflammation and metabolism are strongly context-dependent.[10,22] Both the upward and downstream signaling pathways for IL-6 differ markedly between myocytes and immunocytes. In contrast to exercise in myocytes, TNF-α and IL-1 precede IL-6 production in immunocytes. Myocyte-derived IL-6 upon exercise induces the production of IL-1 receptor antagonist and IL-10, which are main antiinflammatory cytokines. Myocyte-derived IL-6 can also account for exercise-mediated increased cortisol production in response to exercise. TCZ abolishes the exercise-induced loss of visceral and cardiac fat as well as the increase in left ventricular mass among abdominally obese adults. It follows that skeletal muscle–derived IL-6 in response to exercise has antiinflammatory and anabolic effects.[10,22]

Overall, intense and particularly prolonged exercise involving a substantial muscle mass is required to trigger markedly increased myocyte-induced IL-6 production.[24] Hence, it appears unlikely that this mechanism played an important role in the observations made in the Patterson study[12] as the

respective participants led a mostly sedentary life. Nevertheless, whether treatment with TCZ can affect potential vigorous and high-intensity exercise-induced antiinflammatory and beneficial metabolic effects in RA requires further investigation.

In conclusion, physical activity is distinctly associated with reduced inflammatory gene expression in RA. We hypothesize that this effect can be mediated by favorable influences of physical activity on the dysfunctional stress system components in RA. Encouraging adequate physical activity should be consistently included in RA management strategies.[25]

REFERENCES

1. Tsigos C, Chrousos GP. Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res 2002;53:865-71.
2. Ising M, Holsboer F. Genetics of stress response and stress-related disorders. Dialogues Clin Neurosci 2006;8:433-44.
3. Scheffer DdL, Latini A. Exercise-induced immune system response: anti-inflammatory status on peripheral and central organs. Biochim Biophys Acta Mol Basis Dis 2020;1866:165823.
4. Straub RH, Cutolo M. Glucocorticoids and chronic inflammation. Rheumatology 2016;55:ii6-14.
5. Straub RH. Interaction of the endocrine system with inflammation: a function of energy and volume regulation. Arthritis Res Ther 2014;16:203.
6. Dessein PH, Joffe BI, Stanwix AE, Moomal Z. Hyposecretion of the adrenal androgen dehydroepiandrosterone sulfate and its relation to clinical variables in inflammatory arthritis. Arthritis Res 2001;3:183-8.
7. Dessein PH, Joffe BI. Insulin resistance and impaired beta cell function in rheumatoid arthritis. Arthritis Rheum 2006;54:2765-75.
8. Dessein PH, Joffe BI, Stanwix AE. Subclinical hypothyroidism is associated with insulin resistance in rheumatoid arthritis. Thyroid 2004;14:443-6.
9. Dessein PH, Solomon A, Hollan I. Metabolic abnormalities in patients with inflammatory rheumatic diseases. Best Pract Res Clin Rheumatol 2016;30:901-15.
10. Benatti FB, Pedersen BK. Exercise as an anti-inflammatory therapy for rheumatic diseases-myokine regulation. Nat Rev Rheumatol 2015;11:86-97.
11. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. J Sport Health Sci 2019;8:201-17.
12. Patterson SL, Sun S, Rychkov D, et al. Physical activity associates with lower systemic inflammatory gene expression in rheumatoid arthritis. J Rheumatol 2022;49:1320-7.
13. de Jong Z, Munneke M, Zwinderman AH, et al. Long term high intensity exercise and damage of small joints in rheumatoid arthritis. Ann Rheum Dis 2004;63:1399-405.
14. Bartlett DB, Willis LH, Slentz CA, et al. Ten weeks of high-intensity interval walk training is associated with reduced disease activity and improved innate immune function in older adults with rheumatoid arthritis: a pilot study. Arthritis Res Ther 2018;20:127.
15. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Immunol 2011;11:607-15.
16. Anderson T, Berry NT, Wideman L. Exercise and hypothalamic-pituitary-adrenal axis: a special focus on acute cortisol and growth hormone responses. Curr Opin Endocr Metab Res 2019;9:74-7.
17. Duclos M, Gouarne C, Bonnemaison D. Acute and chronic effects of exercise on tissue sensitivity to glucocorticoids. J Appl Physiol 2003;94:869-75.
18. Mueller PJ. Exercise training and sympathetic nervous system activity: evidence for physical activity dependent neural plasticity. Clin Exp Pharmacol Physiol 2007;34:377-84.
19. Gourine AV, Ackland GL. Cardiac vagus and exercise. Physiology 2019;34:71-80.
20. Zouhall H, Jayaval A, Parasuraman K, et al. Effects of exercise training on anabolic and catabolic hormones with advanced age: a systematic review. Sports Med 2022;52:1353-68.
21. Wan W, Powers AS, Li J, Ji L, Erikson JM, Zhang JQ. Effect of post-myocardial infarction exercise training on the renin-angiotensin-aldosterone system and cardiac function. Am J Med Sci 2007;334:265-73.
22. Kistner TM, Pedersen BK, Lieberman DE. Interleukin 6 as an energy allocator in muscle tissue. Nat Metab 2022;4:170-9.
23. Castaneda S, Remuzgo-Martinez S, Lopez-Mejias R, et al. Rapid beneficial effect of IL-6 receptor blockade on insulin resistance and insulin sensitivity in non-diabetic patients with rheumatoid arthritis. Clin Exp Rheumatol 2019;37:465-73.
24. Fischer CP. Interleukin-6 in acute exercise and training: what is the biological relevance? Exerc Immunol Rev 2006;12:6-33.
25. Solomon A, Stanwix AE, Castaneda S, et al. Points to consider in cardiovascular disease risk management among patients with rheumatoid arthritis living in South Africa, an unequal middle income country. BMC Rheumatol 2020;4:42.
26. Geertsema L, Lucas SJE, Cotter JD, Hock B, McKenzie J, Fernyhough LJ. The cardiovascular risk factor, soluble CD40 ligand (CD154), but not soluble CD40 is lowered by ultra-endurance exercise in athletes. Br J Sports Med 2011;45:42-5.
27. Testa MTdJ, Cella PS, Marinello PC, et al. Resistance training attenuates activation of STAT3 and muscle atrophy in tumor-bearing mice. Front Oncol 2022;12:880787.
28. Golzari Z, Shabkhiz F, Soudi S, Kordi MR, Hashemi SM. Combined exercise training reduces IFN-γ and IL-17 levels in the plasma and supernatant of peripheral blood mononuclear cells in women with multiple sclerosis. Int Immunopharmacol 2010;10:1415-9.
29. Dorneles GP, Haddad DO, Fagundes VO, et al. High intensity interval training decreases IL-8 and enhances the immunomodulatory cytokine interleukin-10 in lean and overweight-obese individuals. Cytokine 2016;77:1-9.
30. Favere K, Bosman M, Delputte PL, et al. A systematic literature review on the effects of exercise on human Toll-like receptor expression. Exerc Immunol Rev 2021;27:84-124.
31. Cechin SR, Buchwald P. Effects of representative glucocorticoids on TNF-α- and CD40L-induced NF-κB activation in sensor cells. Steroids 2014;85:36-43.
32. Dos Santos Dantas PH, de Oliveira Matos A, da Silva Filho E, Silva-Sales M, Sales-Campos H. Triggering receptor expressed on myeloid cells-1 (TREM-1) as therapeutic target in infectious and non-infectious disease: a critical review. Int Rev Immunol 2020;39:188-202.
33. Flammer JR, Dobrovolna J, Kennedy MA, et al. The type I interferon signaling pathway is a target for glucocorticoid inhibition. Mol Cell Biol 2010;30:4564-74.
34. Moynagh PN. Toll-like receptor signalling pathways as key targets for mediating the anti-inflammatory and immunosuppressive effects of glucocorticoids. J Endocrinol 2003;179:139-44.
35. Barnes PJ. Corticosteroid effects on cell signalling. Eur Resp J 2006;27:415-26.
36. Achuthan A, Aslam ASM, Nguyen Q, et al. Glucocorticoids promote apoptosis of proinflammatory monocytes by inhibiting ERK activity. Cell Death Dis 2018;9:267.
37. Cari L, De Rosa F, Nocentini G, Riccardi C. Context-dependent effects of glucocorticoids on proliferation, differentiation, and apoptosis of regulatory T cells: a review of the empirical evidence and clinical applications. In J Mol Sci 2019;20:1142.