Review

The effects of exercise on the hormonal and immune systems in rheumatoid arthritis

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Regular exercise has a favourable influence over many systems throughout the body [1] and improves one’s sense of well-being and general fitness. Much research has been carried out on the effects of exercise on immune and hormonal parameters in healthy individuals, and a number of papers have been published on how the immune system is affected by exercise in patients with rheumatoid arthritis (RA). Very little research has been published on the endocrine response to exercise in RA. However, a number of papers have cited abnormalities of cortisol and prolactin in these patients and their effects on disease activity. The aim of this paper is to review the literature on how the immune system is affected by exercise in RA, deduce the likely effect of exercise on the hormonal system and predict its possible clinical effects.

The immune response to exercise in health

Leucocytosis, which appears to be mediated initially by catecholamines and at later stages by cortisol, occurs during exercise [2, 3]. This leucocytosis is due to neutrophilia and the recruitment of B and T cells to the peripheral blood. After acute moderate exercise, there is a fall in the ratio of CD4+ (helper) to CD8+ (cytotoxic-suppressor) T cells [4] and a rise in natural killer (NK) cell activity [5]. The fall in CD4/CD8 ratio is mainly due to an increase in the number of CD8+ T cells. The change in the lymphocyte subsets is transient, basal levels usually being reached again within 1.5 h, while the neutrophil count remains elevated for a longer period. The rise in NK cell activity is short-lived, levels falling to below normal within 2 h. The post-exercise suppression of NK cell activity is mediated by prostaglandins, as this effect can be reversed by the administration of indomethacin [6].

During and following exercise, there is a rise in the proinflammatory cytokines interleukin (IL) IL-1β, IL-6 and tumour necrosis factor [7]. The level of IL-2 (T-cell growth factor) falls immediately after exercise, but has been found to be elevated 24 h afterwards [8]. Cytokine release is thought to be due in part to micromuscular damage caused by exercise [9].

Healthy individuals who take regular amounts of moderate exercise show no change in basal immune parameters. In contrast, athletes who undergo long-term repetitive intensive training (e.g. marathon training) have lower resting levels of immunoglobulins and circulating lymphocytes [10] and reduced lymphocyte responsiveness [11, 12].

The immune response to exercise in RA

Regular exercise appears to have little effect on the resting immune state in RA patients. An 8-week bicycle exercise programme carried out by patients with RA demonstrated an increase in the lymphoproliferative response during the acute phase of exercise. However, all immune changes were temporary and no significant difference could be found in the resting levels of blood mononuclear cell populations, NK cell activity, IL-1 and IL-6 [13]. The control group in this study was another group of RA patients in which training was prohibited, so no conclusions can be drawn on how the immune response of RA patients compares with that of a group of healthy individuals undergoing the same training regimen.

The hormonal response to exercise in health

The immune and hormonal systems have close inter-regulatory links [14]. IL-1β, in particular, has a powerful effect on the endocrine system and glucose homeostasis. This cytokine acts at the hypothalamic level, causing the secretion of corticotrophin-releasing hormone (CRH) [15]. CRH induces the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland, which in turn stimulates adrenal cortisol secretion. IL-6 has been shown to stimulate the release of prolactin (PRL) [16].

Exercise increases the production and catabolism of cortisol. The level rises transiently during exercise of both moderate and severe intensity, and falls rapidly to the basal level or below within a few hours of completion of the exercise. There is a rise of similar proportions in both fit and unfit individuals when exercising to exhaustion [17]. For a given amount of
exercise, there is a greater rise in the unfit. The magnitude of the rise in cortisol declines as training continues and subjects improve their fitness [18].

Regular moderate training has no significant effect on the basal levels of glucocorticoids. However, it is reported that highly trained endurance athletes have a raised basal level of cortisol and a reduced level of testosterone. The catabolic potential of this hormonal state has not been shown to have an adverse effect on the athletes’ performance [19, 20].

The anterior pituitary hormones and growth hormone show marked increases in plasma levels in response to physical exercise, often by as much as 230 and 2000% respectively [21]. The magnitude of the PRL release appears to depend on exercise intensity.

Cortisol and prolactin secretion in RA

Glucocorticoids have an immunosuppressive effect and play an important role in the treatment of RA. Endogenous secretion of glucocorticoids appears to have an anti-inflammatory effect [22] and disease activity throughout a 24-h cycle appears to correlate closely with the serum level of cortisol [23].

In RA there appears to be a loss of the normal diurnal variation in the cortisol level, the more abnormal circadian rhythms being associated with patients with highly active disease [24, 25].

PRL is a proinflammatory peptide and its presence is essential for the development of a number of experimental autoimmune diseases. For example, rats that are depleted of PRL by hypophysectomy or bromocriptine treatment only develop adjuvant arthritis when the PRL is replaced by injection [26]. PRL induces IL-2 receptor expression on splenocytes [27, 28] and is essential for the proliferation of T lymphocytes in response to IL-2 [29].

The PRL level bears some relation to disease activity and the timing of disease onset in RA. The development of RA for the first time and a flare of disease are associated with the post-partum period, when the PRL level is at its greatest [30–32], suggesting that the proinflammatory properties of PRL may play a role in disease pathogenesis.

In response to major surgery, RA patients show a minimal and insignificant rise in cortisol level, despite a larger than normal rise in IL-1β. In contrast, patients with osteoarthritis (OA) and chronic osteomyelitis showed large cortisol rises in the immediate postoperative period [33], suggesting that chronic inflammation was not the cause of suppression of the hypothalamic–pituitary–adrenal (HPA) axis in RA. Patients with RA and healthy individuals showed similar cortisol responses to infusion of CRH, suggesting that the defect lies at the hypothalamic level, with a failure to secrete CRH [33, 34]. RA patients showed a significantly greater increase in PRL after surgery compared with the other two groups [35]. A more recent report [36] failed to show significant increases in cortisol and PRL in OA and RA patients after surgery. It has been suggested that cytokines may activate the HPA axis via the prostaglandin pathway [37–39], with the consequence that non-steroidal anti-inflammatory drug (NSAID) therapy may have an inhibitory effect on CRH release.

The clinical effects of exercise in healthy individuals

Regular and moderate amounts of exercise appear to enhance immunity and reduce the number of infectious episodes that an individual suffers. The incidence of upper respiratory tract infection was studied in two groups of sedentary obese women, and was found to be significantly lower in the group who took up regular exercise than in the group that remained inactive [3].

The degree of immune enhancement appears to rise as an individual increases the regularity and intensity of training. However, there does appear to be a point at which training becomes so intense that exercise starts to have a negative effect on the immune system [11, 40]. Excessive training in marathon runners (defined as running > 97 km per week) was associated with an increased risk of an infectious episode [41].

The clinical effects of exercise in RA

Anecdotal opinion was that dynamic exercise was harmful to patients with RA as it was thought to cause further damage to affected joints. These thoughts have been disproved, and one study even found that the number of swollen joints decreased by 35% when training was carried out in the muscles over the affected joints [42], whilst another group found that there was an improvement in the progression of X-ray destruction [43]. However, a more recent, randomized study comparing the effect of regular exercise in a group of RA patients who trained regularly with its effect in a sedentary group failed to detect any significant difference in the rate of radiological joint progression. There were also no significant changes in erythrocyte sedimentation rate, haemoglobin, joint count, pain score, early morning stiffness (EMS), health assessment questionnaire (HAQ) score and medicine cost [44].

Exercise was reported to have a favourable effect on general health, improving the well-being of patients and their ability to perform normal activities of daily living [45]. Considerable improvement in aerobic capacity, the time taken to walk 50 feet (15.2 m), depression and anxiety were observed in patients who were participating in regular aerobic exercise, but no significant difference in the disease activity was seen, as measured by the number of active joints, duration of EMS and grip strength [46].

There have been a number of reviews on the therapeutic effects of exercise in RA patients [47–49], all of which conclude that there is no adverse effect on disease activity or radiological joint destruction. It has been suggested that aerobic is superior to non-aerobic exercise and that dynamic exercise, requiring muscle
work, appears to be better than static or isometric exercise [50]. For example, a recent systematic review of six randomized controlled trials analysing the effects of dynamic exercise on patients with RA concluded that exercise improves physical capacity but has no adverse effects on pain or disease activity [47]. Four of the six studies reviewed showed that there was an improvement in functional ability, but the changes were small and one study even reported a decrease in the HAQ score in patients who had exercised. None of the six trials reported any significant change in acute-phase reactants or joint inflammation.

There is evidence that exercising an inflamed joint results in a hypoxic–reperfusion injury leading to the generation of reactive oxygen species (ROS) [51]. ROS are potent oxidizing agents which may react with IgG, leading to the oxidation of rheumatoid factor and hyaluron and resulting in fragmentation products that may subsequently alter immune function and consequently cause further joint damage.

Discussion

Dynamic exercise in RA patients has no adverse effect on the long-term outlook with regard to disease activity and radiological joint destruction. Healthy individuals who undertake regular exercise, particularly if it is intense, show a degree of immune enhancement that in theory could have an adverse effect on RA disease activity, but this has not been borne out by all the recent literature. The possible reasons for this are threefold. First, regular exercise of the type described above [49] has no significant effect on the resting immune state of RA patients. Secondly, RA patients may have a degree of immune paralysis compared with healthy individuals. Finally, the level of exercise undertaken by an average patient may be insufficient to have any significant clinical effect on the immune system. During exercise a lymphoproliferative response does occur and it could have clinical consequences; however, there is a rapid return to the basal state, so any joint pain and stiffness is likely to be short-lived.

Although a small number of studies have suggested that regular exercise has a beneficial effect on disease activity, the great majority of reports do not support these findings. If regular training was to have a favourable effect on disease activity, exercise would be expected to have an immunosuppressive effect. Severe endurance training like that described above may well induce immunosuppression and potentially has a therapeutic effect on disease activity; however, this degree of exercise is clearly not going to be possible in RA patients.

There appears to be no literature on the PRL and cortisol responses of RA patients to exercise and how they compare with those of healthy individuals. Any study of this nature would be difficult to control satisfactorily, as there will be marked differences between the two groups in aerobic capacity and the ability to carry out exercise. The mechanisms by which cortisol and PRL vary during exercise are likely to be mediated in part by the cytokines IL-1β and IL-6, both of which increase during exercise. At the hypothalamic level, a possible insensitivity to IL-1β has been described in RA. Whether this is due to the disease itself or the use of NSAIDs remains to be tested, but both anti-inflammatory medication and corticosteroids are likely to have a further effect on the feedback mechanisms and impair the normal HPA axis response to exercise. Exercising RA patients, particularly those on NSAIDs or corticosteroids, may well lead to a subnormal cortisol response. Given the greater metabolic rate that occurs during exercise—and hence the catabolism of cortisol—a possible fall in cortisol level is likely. However, a comparative study with healthy individuals [51] in which the effects of high-intensity training for 6 weeks on circulating levels of CRH were evaluated found that, although the starting levels of CRH were significantly lower in RA, a small but significant increase in CRH was observed in the patient group. This increase was not seen in healthy individuals, but the resting levels of CRH in RA after training remained lower than those observed in healthy individuals. The reason for the difference between the two groups is likely to be the greater increase in IL-1β in RA. Further studies are needed to determine whether this small increase in CRH is sufficient to avoid a fall in cortisol in response to high-intensity exercise.

Conclusion

The probable influence of exercise on the immune and hormonal systems is such that regular training is unlikely to have any therapeutic benefit or adverse effect on the RA disease process. Patients with well-controlled disease should therefore be encouraged to undertake regular aerobic exercise for all its positive effects on their general psyche, on their ability to perform normal activities of daily living and on other systems, including the cardiovascular and respiratory systems.

References


