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Does aerobic exercise induced-analgesia occur through hormone and inflammatory cytokine-mediated mechanisms in primary dysmenorrhea?

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A B S T R A C T

The popular accepted explanation for the pathogenesis of primary dysmenorrhea is elevated levels of uterine prostaglandins. Aetiological studies report that production of prostaglandins is controlled by the sex hormone progesterone, with prostaglandins and progesterone displaying an inverse relationship (i.e. increased progesterone levels reduce prostaglandin levels). Pro-inflammatory cytokines (interleukin-6 [IL-6] and tumor necrosis factor-alpha [TNF-α]) are also implicated in the pathogenesis of primary dysmenorrhea. High-intensity aerobic exercise is effective for decreasing pain quality and intensity in women with primary dysmenorrhea. However, why and how aerobic exercise is effective for treatment of primary dysmenorrhea remain unclear. Our preliminary non-randomized controlled pilot study to examine the effects of high-intensity aerobic exercise on progesterone, prostaglandin metabolite (13,14-dihydro-15-keto-prostaglandin F2 alpha ($KDPGF_{2\alpha}$), TNF-α, and pain intensity found increases in progesterone and decreases in $KDPGF_{2\alpha}$, TNF-α, and pain intensity following high-intensity aerobic exercise relative to no exercise. Given these promising preliminary findings, as well as what is known about the pathogenesis of primary dysmenorrhea, we propose the following scientific hypothesis: high-intensity aerobic exercise utilizes hormone (progesterone) and inflammatory cytokine-mediated mechanisms to reduce the pain associated with primary dysmenorrhea.

Introduction

The role of prostaglandins in the pathogenesis of primary dysmenorrhea

The pathogenesis of primary dysmenorrhea is predominantly linked to the overproduction of uterine prostaglandins [1]. Release of excessive prostaglandins, during endometrial sloughing, induces greater uterine contractions resulting in ischemic pain [1,2]. Prostaglandins are intracellular substances synthesized from polyunsaturated fatty acids, such as arachidonic acid [1,3], which is derived from phospholipids by the lysosomal enzyme phospholipase A_2 [1,3] (Fig. 1). The stability of lysosomal activity is controlled by several factors, one of which is the progesterone levels in the late luteal phase of the menstrual cycle [1,4–6]. The decrease in progesterone levels in the late luteal phase of the menstrual cycle labializes the lysosomal activity, the release of phospholipase A2 to generate additional arachidonic acid [1]. Consequently, greater amount of prostaglandins are produced [1] (Fig. 1). Thus, progesterone controls the production of prostaglandins: drop in progesterone levels during the late luteal phase (just prior to menstruation) causes prostaglandins levels to increase [1,6]. The abnormal prostaglandin levels causes frequent/dysrhythmic uterine contractions leading to ischemia and hypoxia which are regarded as the major contributor for primary dysmenorrhea pain [7,8]. In addition, elevated prostaglandin levels during the menstrual cycle stimulate nociceptors (A-delta and C-fibres) distributed throughout the body. These nociceptors transform the stimuli into electrical signals, which are then carried to the central nervous system via the spinothalamic or spinoreticular tracts [9–11]. Signals are transmitted from the thalamus to the somatosensory cortex and pain is perceived [9–11].

Pro-inflammatory cytokines and primary dysmenorrhea-associated pain

Pro-inflammatory cytokines, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are also known to play a role in the pathogenesis of primary dysmenorrhea [12–14]. Activated macrophages produce pro-inflammatory cytokines that are responsible for the up-regulation of inflammatory reactions [15]. These mediators are also reported to stimulate the synthesis or release of prostaglandins [12,14,16,17] causing hyper-contractility of the uterine muscle leading to the ischemic pain of primary dysmenorrhea. The plasma concentration of IL-6 and TNF-α was found to be higher in women with dysmenorrhea compared to non-dysmenorrheic women [12,13].

Efficacy of aerobic exercise on primary dysmenorrhea-associated pain

Previous studies found that primary dysmenorrhea-associated pain intensity was reduced with aerobic exercise [18–25]. Several observational studies have been supportive of a significant positive association

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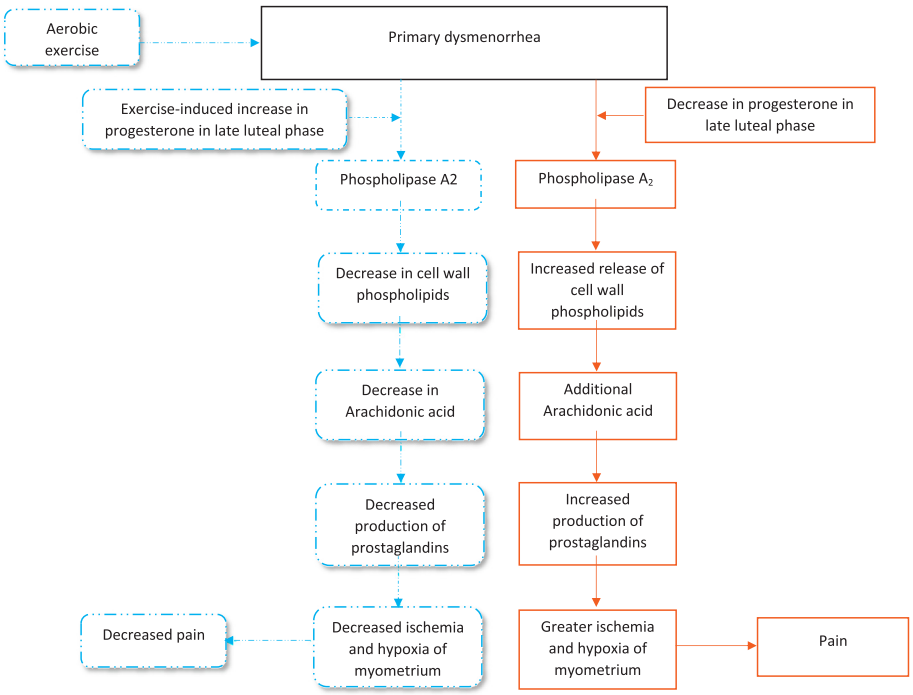

Fig. 1. Synthesis of prostaglandins and proposed hypothesis. Red lines: formation of prostaglandins in women with primary dysmenorrhea. Blue dotted lines with shadow: Proposed hypothesis-Aerobic exercise-induced increases in progesterone resulting in decreased formation of prostaglandins and consequently reduced pain. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

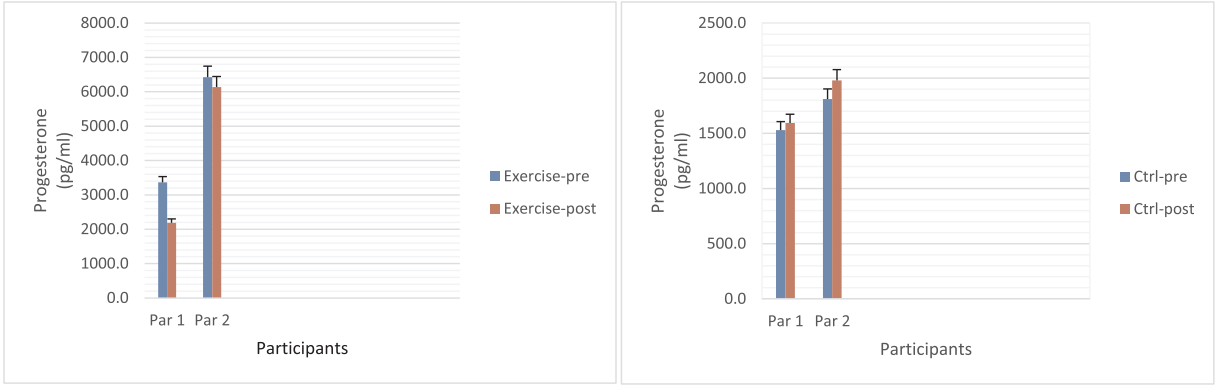

Fig. 2. Pre-and post-progesterone levels of participants from exercise and control groups. Note: Par = Participant.

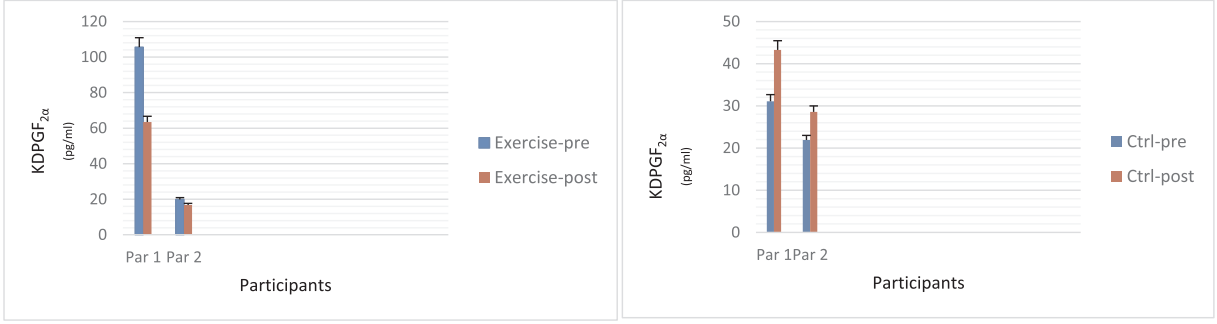

Fig. 3. Pre-and post-KDPGF$_{2\alpha}$ (Prostaglandin F2 alpha metabolite) levels of participants from exercise and control groups. Note: KDPGF$_{2\alpha}$ = 13,14-dihydro-15-keto-prostaglandin F2 alpha.

between high-intensity aerobic exercise and reduced severity of symptoms of primary dysmenorrhea compared to low/moderate-intensity exercise [18,19,21]. Several non-randomized [24,26] and randomized controlled trials (RCTs) [22,25] also support the efficacy of aerobic exercise for managing primary dysmenorrhea. Our preliminary studies [23,27] identified high-intensity aerobic exercise for 30 min, three days a week, at 70–85% age-adjusted maximum heart rate (MHR) as effective for decreasing pain quality, intensity, and interference in women with primary dysmenorrhea. However, why and how aerobic exercise is effective for treatment of primary dysmenorrhea remain unclear.

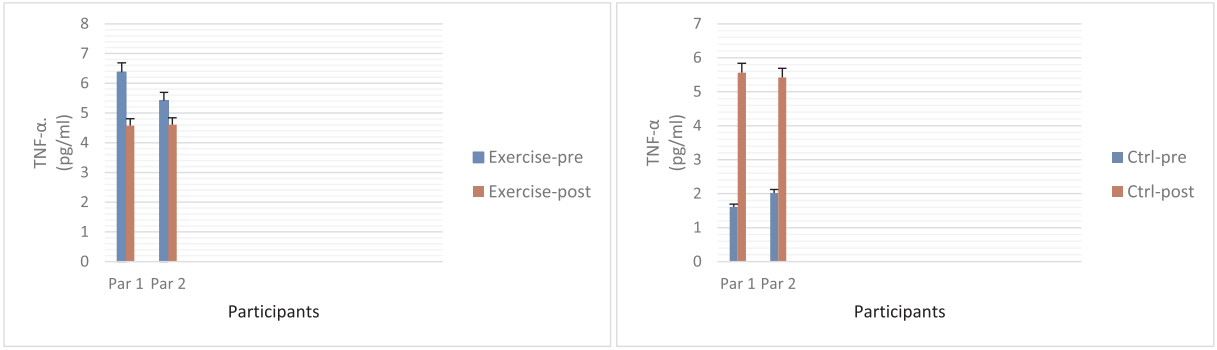

Fig. 4. Pre-and post-tumor necrosis factor-alpha (TNF-α) levels of participants from exercise and control groups. Note: TNF-α = Tumor Necrosis Factor-alpha.

Evidence in literature: exercise-induced analgesia

The most commonly tested hypothesis for exercise-induced analgesia is the release of endogenous opioids that contribute to pain modulation [28]. A recent systematic review of the endogenous systems involved in exercise-induced analgesia reported that during and following exercise, various endogenous systems are activated, which releases substances (e.g. neurotransmitter, opioids, serotonin etc.) that modulate pain perception [29]. The endocannabinoid-mediated mechanism is also thought to contribute to exercise-induced analgesia [28,30]. Endocannabinoids are receptors that contribute to the control of pain transmission within the brain and spinal cord [28]. Elevations in peripheral blood endocannabinoids concentrations have been reported following aerobic exercise, and it is has been suggested that the activation of cannabinoid receptors produces analgesia [28]. These mechanisms have been investigated in healthy humans and individuals with chronic pain conditions (for instance, rheumatoid arthritis, osteoarthritis, fibromyalgia, diabetic neuropathy) [28,30–32]. Nevertheless, there are multiple other mechanisms that might contribute to changes in pain intensity resulting from aerobic exercise.

Current understanding of the mechanisms underlying aerobic exercise-induced analgesia in primary dysmenorrhea and knowledge gaps

There are a number of hypotheses proposed for the effectiveness of aerobic exercise in relieving the pain associated with primary dysmenorrhea. Mosler [33] was the first to speculate that exercise relieves congestion in the pelvis by “shunting uterine blood flow” [34]. Other proposed mechanisms include the exercise-induced release of endogenous opiates, specifically β-endorphins [22]; and increased vasodilatation and subsequently decreased ischemia [35,36]. However, these mechanisms have not yet been evaluated empirically. Studies of primary dysmenorrhea have also postulated that aerobic exercise might also decrease the pain of primary dysmenorrhea by suppression of release of prostaglandins [22,35–38]. However, the specific mechanism of how aerobic exercise might suppress the pain or production of prostaglandins has not been completely clarified.

Aerobic exercise, progesterone, prostaglandins, and inflammatory markers

The hormones dominating menstrual cycles are affected by exercise. Several studies have found that exercise can increase progesterone levels during the luteal phase [39–42]. Specifically, high-intensity aerobic exercise or vigorous physical activity is found to induce alterations in levels of circulating progesterone in young [43,44] and premenopausal women [45,46]. Research has found an inverse relationship between progesterone and prostaglandins [1,6]. Thus, aerobic exercise suppresses the production of prostaglandins through its effect on progesterone.

Regular exercise changes cytokine profiles with decreases in release of pro-inflammatory cytokines (IL-6, TNF-α) known for nociceptor activation and increases in anti-inflammatory cytokine such as Interleukin-10 (IL-10) [47–49]. A systematic review [49] cites numerous studies that consistently identified lower inflammatory cytokines in individuals who engaged in frequent and more intense physical activity. A recent study comparing pre-post plasma levels of cytokines in marathon runners identified decreased IL-6 and TNF-α levels and increased levels of IL-10 after the marathon race [50]. Thus aerobic exercise inhibits the production of prostaglandins by decreasing the levels of IL-6 and TNF-α in women with primary dysmenorrhea.

Animal and human studies have found that exercise induces the release of regulatory macrophages in the physically active muscles [47,51–54]. These regulatory macrophages are known for their ability to secrete anti-inflammatory cytokines and counteract the effect of other activated macrophages which secrete pro-inflammatory cytokines [47]. Therefore, following physical activity, the overall effect is an increase in anti-inflammatory cytokines (IL-10) and a decrease in pro-inflammatory cytokines (IL-6, TNF-α) which are responsible for pain reduction. Thus, aerobic exercise relieves primary dysmenorrhea-associated pain through inflammatory cytokine-mediated mechanisms.

There has been considerable research of the association between physical activity and C-reactive protein (CRP). Cross-sectional studies of healthy adults, runners and older-adults have demonstrated an inverse relationship between regular physical activity and serum CRP levels [55–58]. A systematic review of the association between physical activity and CRP in healthy and older adults reported lower CRP levels in individuals who participated in high-intensity physical activity compared with individuals who engaged in low/moderate intensity physical activity [55]. Furthermore, pro-inflammatory cytokines (IL-6, TNF-α) and CRP are directly related. Hepatic production of CRP is induced by IL-6 and to a lower extent by TNFα [55]. Therefore, decrease in IL-6 and TNFα decreases the levels of CRP [49,59,60]. Thus, following high-intensity aerobic exercise, pro-inflammatory cytokines and CRP levels will be lower in blood plasma of women with primary dysmenorrhea.

Hypotheses

Considering the influence of aerobic exercise on progesterone and the analgesic effect of aerobic exercise on primary dysmenorrhea, we hypothesize that high-intensity aerobic exercise will utilizes hormone (progesterone) mediated mechanisms to reduce the pain associated with primary dysmenorrhea: high-intensity aerobic exercise will increase the levels of progesterone resulting in reduced levels of prostaglandin and thereby reduce pain.

Considering the influence of physical activity on inflammatory cytokines, we hypothesize that high-intensity aerobic exercise will produce analgesia in primary dysmenorrhea by acting on the inflammatory mediators including pro-and anti-inflammatory cytokines.

Evaluation of the hypotheses

Our recent controlled non-randomised pilot study (Ethics approval ref: HSEARS20180426001; trial registration ref: ACTRN12618000784213) performed with 20 women to evaluate the effects of high-intensity aerobic exercise on progesterone, prostaglandin metabolite (13,14-dihydro-15-keto-prostaglandin F2 alpha (KDPGF2α), and TNF-α indicated a trend towards increase (medium effect size) in progesterone levels (Fig. 2) and decreases in $KDPGF_{2\alpha}$ (Fig. 3), and TNF-α (Fig. 4) in the exercise group compared with the control group. Our pilot study also identified a medium effect size difference in pain levels between the high-intensity aerobic exercise and no-exercise groups. These findings suggest the possibility that aerobic exercise may be effective for primary dysmenorrhea-associated pain through its effects on these mediators.

Summary, conclusion, and consequences of the hypothesis

The pathophysiology of primary dysmenorrhea is primarily linked to elevated levels of prostaglandins. Low progesterone levels in the late luteal phase of the menstrual cycle is reported to increase the synthesis of prostaglandins. Pro-inflammatory cytokines (IL-6 and TNF-α) are also implicated in the pathogenesis of primary dysmenorrhea. Our previous studies and studies by other researchers have demonstrated that high-intensity aerobic exercise for 30 min, three times a week at 70–85% of MHR range is effective for decreasing pain quality and intensity in women with primary dysmenorrhea. However, why and how aerobic exercise is effective for treatment of primary dysmenorrhea remain unclear.

Results from our preliminary pilot study to examine the effects of high-intensity aerobic exercise on progesterone, $KDPGF_{2\alpha}$ (prostaglandins metabolite), and TNF-α found increases in progesterone and decreases in $KDPGF_{2\alpha}$ and TNF-α following high-intensity aerobic exercise relative to no exercise. Given these promising preliminary findings, as well as what is known about the pathogenesis of primary dysmenorrhea, we hypothesize that, in primary dysmenorrhea, aerobic-exercise-induced analgesia will occur through hormone (progesterone) and inflammatory (IL-6, TNF-α, IL-10) cytokine-mediated mechanisms. Understanding the mechanisms underlying aerobic exercise-induced analgesia in primary dysmenorrhea-associated pain would help design future studies that could identify mediators of pain interventions for clinical improvements, which could themselves be the target of interventions. A better understanding of the mediators of these interventions may lead to streamlined treatments that distil the most critical change factors into those that are maximally effective.

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Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2018.12.011.

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