

Why Does Increased Exercise Decrease Migraine?

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Abstract Several lines of evidence affirm a positive role for exercise in the management of migraine. This review highlights the latest research supporting this view, covering not only its epidemiologic aspects but also the pain modulatory systems that are likely to be engaged by exercise. Recent research provides broad and consistent evidence indicating that cardiovascular exercise can activate multiple pain modulatory mechanisms, if not the underlying mechanisms that initiate the attack. Specifically, a synthesis of independent lines of recent research would indicate that exercise activates endogenous neurotransmitter signals that could be effective in reducing the intensity of migraine pain, though it may not have a direct effect on its overall frequency or duration.

Keywords Migraine · Exercise · Pain · Cannabinoid · Trigeminal

Introduction

Just about everybody would be better off with at least a little more exercise. For most patients whose lives are affected by migraine, exercise would promote good health in innumerable ways, so any counseling that could be provided on the likely association between exercise and migraine health would be of value. Although the present data are imperfect, it does provide compelling evidence that the patient with problem migraine could benefit from exercise in the treatment of problem migraine.

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Epidemiology of Migraine and Exercise

Several epidemiologic studies of migraine could be of relevance to a consideration of migraine and exercise. The American Migraine Prevalence and Prevention (AMPP) study provided longitudinal population-based data, initially surveying a population of 120,000 US households and followed >10,000 migraine sufferers annually [1]. The frequency of common comorbidities for adults with chronic migraine (CM) and episodic migraine (EM) in this large population-based sample indicated a range of comorbid conditions that were significantly more likely to be reported in those with CM compared with EM, including depression, anxiety, chronic pain, respiratory disorders, cardiovascular risk factors including hypertension, diabetes, high cholesterol, and obesity. Though indirect, the presence of a high body mass index can be seen as a condition that implicates a relative absence of exercise.

In the face of the alarming data observing the increasing prevalence of obesity in the population, the potential benefit of encouraging exercise is well in line with the need to avert the present catastrophic trend in our society towards rising obesity and its associated conditions, the increasing cost of caring for those conditions, and the attendant decline in the overall health and economic security of our society.

Although there is clearly a sensible role for exercise in combating this present trend and risk factor for chronic migraine, what are the data supporting a relationship between exercise and migraine? One impressive line of evidence derives from a large epidemiological study of health and lifestyle of all the adult inhabitants of Nord-Trøndelag county in Norway – HUNT2 [2].

This was a remarkable population study. There were 92,566 participants who responded to an extensive questionnaire containing more than 200 questions about their health and lifestyle. Of these 51,383 (56%) responded to questions about

headache, with 46,648 of these (91% of those answering questions about headache) who also answered at least 1 question about the frequency, duration, and intensity of their physical activity. Although this was essentially a cross-sectional study, there was limited data obtained from a subset of these respondents in an earlier iteration of this study (HUNT1). This earlier study obtained data about exercise but contained no specific questions about headache, so only limited inferences could be made from the responses from many of these same respondents on a prospective, longitudinal basis.

In HUNT2 there were 12 questions that followed up on a “yes” response to whether a respondent had a headache in the last 12 months, that served to determine whether they were migraine, and their overall frequency. In addition, there were several questions about physical activity that assessed the frequency, duration, and intensity of the exercise. The study showed that low physical activity was clearly and linearly associated with increasing risk and greater frequency of both migrainous and non-migrainous headache.

The large number of subjects who participated in the study, as well as the high level of detail obtained about lifestyle and exercise, are notable assets of this study. However, due to the cross-sectional nature of the data there remain questions about whether people with frequent headache are just less likely to exercise vigorously, or whether there is a causal or protective role for exercise. There is clearly a compelling need for a follow-up study, in which we have much to learn about the relationship between headache and exercise from the adult inhabitants of Nord-Trøndelag county, Norway.

Design of an Exercise “Intervention”

To fully explore whether exercise could cause a reduction in headache, however, would ideally utilize an intervention and a randomized trial. Varkey and colleagues recently pursued this question directly by designing and validating a 3 times per week, 12-week indoor cycling intervention in migraine patients, using an increase in maximal oxygen uptake as a measure of cardiovascular conditioning [3]. This was a supervised intervention, in which the subjects met with the investigator weekly, who was an exercise physiologist and physical therapist. Here they also characterized how they would assess the migraine history, including the diary, the recording of headache medications, side effects, and overall quality of life (MSQoL).

Varkey and colleagues then went on to undertake a prospective, randomized, controlled trial of adults meeting the ICHD-II criteria for migraine with a frequency of 2–8 attacks per month, among those who were not already exercising regularly [4•]. The study of 91 subjects randomized with the intention to treat 30

subjects with home relaxation, 30 subjects with exercise, and 31 subjects with topiramate at up to 100 mg twice a day. The evaluation period included a 4- to 12-week baseline headache calendar, a 12-week intervention period, in which the frequency of migraine attacks during the last 4 weeks of the intervention was the primary outcome, and an extended follow-up period.

At the end of the intervention, a mean reduction of 0.93 attacks in the exercise group, 0.83 attacks in the relaxation group, and 0.97 attacks in the topiramate group showed that all 3 interventions were equivalent with respect to the primary measured outcome. Other variables included adverse side effects, in which there were none for the exercise and relaxation groups, whereas 8 participants in the topiramate group (33%) reported adverse events while on topiramate, and 3 reported AEs as the reason for their withdrawal from the study.

In some ways, the study was a victim of its own success, in that all 3 arms of the study produced a modest but statistically significant reduction in headache frequency. Taking into account the methodological challenges that are an inherent part of studies on migraine [5], limitations of the study include the fact that it was in essence an “open-label” study and thus not controlled for subject expectation and observer bias, and that it was unable to show a significant improvement over a control arm that could have been predicted to have no clear benefit.

Another factor may have been that the attack frequency was an important risk factor for treatment response [6]. That is, the criteria for enrollment of subjects with a modest attack frequency, though well in line with IHS recommended guidelines, may not have been the optimal target population for the study. Specifically, if exercise has an indirect effect on migraine, through the reversal or neutralization of an associated risk factor for migraine, then a population of subjects with a relatively low attack rate might not have represented a subset of the migraine population with a substantial burden of risk factors for the exercise intervention to have a measureable benefit.

Another small study [7] was in line with a review of the prior literature on exercise and migraine [8•], which concluded that while there is little evidence for a significant reduction in attack frequency or duration due to exercise, the studies do indicate that there may be an overall reduction in pain intensity due to exercise. If this broad insight were true, that exercise may preferentially reduce migraine pain intensity more effectively than migraine frequency or duration, this could focus our attention more precisely on the pain regulatory systems could be engaged by exercise, and it may be most instructive to consider migraine from the perspective of the modulation of pain in general.

Neural Systems That Modulate Pain

The neural systems engaged by pain are complex, and include both the somatosensory detection of tissue injury—nociception—as well as the affective, cognitive, and motivational systems that are engaged by the injury or potential injury—the experience. From this perspective, exercise would be extremely well poised to be an effective modulator of both of these aspects of pain processing.

On the one hand, the data on the effects of exercise on nociceptive processing are complex and conflicting. Staud, as well as several other studies, have shown that strenuous exercise has an anti-nociceptive effect in otherwise healthy subjects, but that in those with fibromyalgia, such activity may enhance both peripheral and central sensitization [9]. However, for those with fibromyalgia, which is often comorbid with migraine, graded exercise therapy, involving increasing periods of regular cardiovascular exercise, is broadly accepted as the most effective treatment for this condition. One large hurdle to its implementation is that the fear of pain and fear of movement in some patients is a major barrier in participating [10•].

Does a Runner's High Modulate Pain?

On the other hand, recent studies suggest that exercise can indeed have an important role in the modulation of pain processing from an affective-motivational perspective though the activation of endogenous cannabinoid signaling [11••] in an intensity-dependent manner [12]. The initial studies on this subject focused on the “runner's high,” referring to the sense of well-being and perhaps even euphoria associated with prolonged cardiovascular activity. Traditionally thought to be due to the activation of endogenous opioids [13], the activation of opioid receptor binding activity within the brain has been recently demonstrated, showing that there are likely complex changes in opioid signaling in the brain that take place with both pain and exercise [14•].

However, another recent line of investigation explored an alternate hypothesis, that human endurance exercise has intrinsically rewarding properties, possibly even hedonic properties, through the production of natural ligands of the endogenous cannabinoid (CB1 and CB2) receptors. The 2 best-recognized so-called endocannabinoids (eCB) are anandamide (AEA) and 2-arachidonylglycerol (2-AG).

It turns out that both central and peripheral eCBs are produced with exercise, and are well suited to the modulation of reward and pain. Moderate intensity exercise increases plasma levels of highly lipophilic eCBs [15] that readily cross the blood brain barrier [16] and are sufficient to activate brain reward centers through the inhibition of GABA-ergic terminals in the mesolimbic dopamine system via CB1

receptors [17]. The resulting increase in dopamine signaling to reward centers such as the nucleus accumbens [18] are sufficient to stimulate reward-seeking behaviors in animal models [19]. These eCBs can also have an analgesic effect not only through the descending modulation of pain [20•], but also through the activity of CB1 receptors on sensory afferents [21]. These analgesic effects may help to suppress exercise-related discomfort and sustain greater endurance and higher performance during the exercise.

In addition, these effects may also support the analgesic effects that are observed in the above trials of exercise in migraine. More specifically, in animal models of headache and trigeminal pain transmission, Akerman and colleagues have shown that activation of cannabinoid receptors have a clear role in modulating trigeminal responses to dural stimulation both by activating a descending modulation of C-fiber activation [22] but also through the direct activation of CB1 receptors in dural trigeminovascular nociceptive neurons [23•]. These results are significant for not only driving home the link between eCBs and headache, but also the therapeutic implications of eCB receptors in the management of migraine, not the least of which would be to encourage cardiovascular exercise.

Conclusions

There are several lines of evidence supporting the role of exercise in migraine management. Though individually these studies have some limitations, they are still altogether compelling because this view still emerges clearly from several independent lines of investigation. However, there still remain significant challenges in getting patients to utilize this modality. In this regard research on fibromyalgia and chronic fatigue syndrome have taken a huge lead in identifying those patients who are “at risk” of not being able to undergo graded cardiovascular exercise, and have set a research agenda towards finding ways to identify these patients and engage in studies to enhance interventions for them [10•]. In addition to there being a role for exercise in migraine, the knowledge about whether a patient is increasing exercise for migraine control is a useful behavioral sample, being an interesting indicator of patient self-efficacy that the patient is engaged in their own treatment and is motivated to take control of their own health.

Compliance with Ethics Guidelines

Conflict of Interest Andrew H. Ahn reported no potential conflicts of interest relevant to this article.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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