

# Exercise, Not to Exercise, or How to Exercise in Patients With Chronic Pain? Applying Science to Practice

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**Background:** Exercise is an effective treatment strategy in various chronic musculoskeletal pain disorders, including chronic neck pain, osteoarthritis, headache, fibromyalgia and chronic low back pain. Although exercise can benefit those with chronic pain (CP), some patients (eg, those with fibromyalgia, myalgic encephalomyelitis/chronic fatigue syndrome and chronic whiplash associated disorders) encounter exercise as a pain inducing stimulus and report symptom flares due to exercise.

**Objectives:** This paper focuses on the clinical benefits and detrimental effects of exercise in patients with CP. It summarizes the positive and negative effects of exercise therapy in migraine and tension-type headache and provides an overview of the scientific evidence of dysfunctional endogenous analgesia during exercise in patients with certain types of CP. Further, the paper explains the relationship between exercise and recovery highlighting the need to address recovery strategies as well as exercise regimes in the rehabilitation of these patients. The characteristics, demands and strategies of adequate recovery to compensate stress from exercise and return to homeostatic balance will be described.

**Methods:** narrative review.

**Results:** Exercise is shown to be effective in the treatment of chronic tension-type headache and migraine. Aerobic exercise is the best option in migraine prophylaxis, whereas specific neck and shoulder exercises is a better choice in treating chronic tension-type headache. Besides the consensus that exercise therapy is beneficial in the treatment of CP, the lack of endogenous analgesia in some CP disorders should not be ignored. Clinicians should account for this when treating CP patients. Furthermore, optimizing the balance between exercise and recovery is of crucial merit in order to avoid stress-related detrimental effects and achieve optimal functioning in patients with CP.

**Conclusion:** Exercise therapy has found to be beneficial in CP, but it should be appropriately and individually tailored with emphasis on prevention of symptom flares and applying adequate recovery strategies.

**Key Words:** exercise, chronic pain, dysfunctional exercise-induced analgesia, stress recovery

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Despite extensive research efforts, chronic pain (CP) remains a pervasive medical and socioeconomic problem affecting 11% to 55% of the general, adult population and consuming a large amount of health care resources around the globe.<sup>1–4</sup> CP is a feature of many disorders including osteoarthritis (OA), fibromyalgia (FM), chronic whiplash-associated disorders (CWAD), chronic low back pain (CLBP), headache, and myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) and affects physical<sup>1,5</sup> as well as psychological health-related quality of life. Treating patients with CP is a challenging issue for clinicians.

There are a multitude of guidelines describing how to manage patients with CP, all stating exercise as a central component of the treatment. Exercise is defined as “planned, structured, and repetitive bodily movements that are performed to improve or maintain one or more components of physical fitness.”<sup>6</sup> It is found to be an effective treatment strategy to relieve pain and improve patient’s level of functioning in daily activities in various chronic musculoskeletal pain disorders, including chronic neck pain,<sup>7–10</sup> OA,<sup>9,11</sup> headache,<sup>12</sup> FM,<sup>13</sup> and CLBP.<sup>9,14</sup> Aerobic exercise programs reduce pain, fatigue, and depression, and improve peak oxygen uptake, health-related quality of life, and physical fitness in patients with FM.<sup>15,16</sup> In CLBP, aerobic endurance exercises are also commonly used and have been shown to reduce pain perception.<sup>17</sup>

Aerobic exercise at an intensity of at least 70% of the maximum aerobic capacity triggers the production of endorphins and activates other pain inhibitory mechanisms orchestrated by the brain.<sup>18–20</sup> Regular exercise is related to weight loss and helps to strengthen the muscles, providing a natural brace that takes the load off bones and cartilage.<sup>21,22</sup> Although regular exercise programs can have beneficial effects for those with CP, some patients encounter exercise as a pain-inducing stimulus and report a worsening of their symptoms due to physical activity and exercise. Patients with FM, ME/CFS, and CWAD demonstrate decreased pain thresholds and show symptom flares in response to aerobic exercise.<sup>23–25</sup> Muscle contractions result in an increased generalized pain sensitivity in patients with FM.<sup>26</sup> The typical release of endorphins and activation of other brain-orchestrated pain inhibitory mechanisms (ie, serotonergic, opioidergic, and adenosinergic systems) seem to be dysfunctional in some chronic pain disorders. This makes the therapeutic window for exercise in chronic musculoskeletal pain very narrow, with too little exercise averting beneficial effects and too much exercise aggravating symptoms.

Notwithstanding, exercising is of great importance to improve functional ability and health-related quality of life in patients with CP. To get fitter, the body needs to be exposed to stressors (ie, exercise or training). Equally important is the role of recovery in the stress-recovery-

performance relationship. A long-term imbalance between stress (including exercise) and recovery may initiate a process that results in elevated stress and, hence, symptom increase in patients with CP. This detrimental process can be avoided when recovery is adequate. Clinicians need to be informed about the features and requirements of adequate recovery.

The present paper focuses on appropriate exercise therapy and recovery in patients with CP. The first part describes the clinical benefits and detrimental effects of exercise in patients with headache and, more specifically, migraine and tension-type headache. Headaches are a common CP condition, both of which can be treated with and aggravated by exercise. It will be discussed how the application of exercise therapy should be performed in patients with headache. In line with this, the current knowledge of the biology of exercise-induced endogenous analgesia (EA) in humans will be summarized in the next part. It provides an overview of the scientific evidence of dysfunctional EA during exercise in patients with CP. Dysfunctional EA is present in some chronic pain disorders (eg, FM, ME/CFS), whereas other CP populations (eg, CLBP) show a normal activation of EA in response to exercise. The dysfunctional EA in response to exercise as seen in some types of CP might be reflective of the dysfunctional stress response system, as so often seen in CP patients. Hence, in the next part, the paper explains the relationship between stress (eg, exercise) and recovery, applied to exercise for CP patients. The characteristics, demands, and strategies of adequate recovery to compensate stress and return to homeostatic balance will be described. Finally, the findings will be summarized in terms of clinical relevance to rehabilitation practice in CP.

## EXERCISE IN HEADACHE

Headache is a public health problem with enormous consequences from both a societal and an individual perspective.<sup>27,28</sup> The most common types of headache are migraine and tension-type headache and about 4% of the population have chronic daily headache.<sup>29</sup> For patients with severe headache, finding suitable prevention and therapy strategies which intend to relieve pain as well as restore function is extremely important.

A large cross-sectional study from Norway showed that both migraine and nonmigrainous headaches are associated with a low level of physical activity.<sup>30</sup> In migraine prevention, submaximal aerobic exercise has benefits, both in reducing the frequency of attacks and in increasing the quality of life.<sup>31</sup> A variety of physiological and psychological pathways have been hypothesized to mediate these effects and, most likely, there is a combination of many factors. An increase of endogenous opioids and levels of serotonin (5-HT) as well as effects on psychological health and improvements of symptoms like depression and anxiety are important from a migraine perspective.<sup>12</sup>

As in migraine treatment, regular exercise is a common recommendation in the treatment of tension-type headache. However, the effects of aerobic exercise in this group of patients have never been studied. Strength training for neck and shoulder muscles has shown to improve chronic tension-type headache with positive effects on intensity, frequency, and quality of life.<sup>32</sup> More studies are recommended to strengthen these results and the level of evidence.

## Are There Reasons not to Exercise in Headache?

Despite all positive effects, exercising can be frustrating for patients as both migraine and tension-type headache can be triggered by strenuous physical activity.<sup>33,34</sup> In up to 44% of the migraine patients, exercise is reported as a triggering factor. Although the reason is still unknown, it is speculated that the reduction of cerebral oxygenation during exercise triggers a wave of cortical spreading depression, supposed as the underlying phenomenon of migraine aura.<sup>35</sup> Besides the fact that exercise may trigger the onset of a migraine attack, exercise may also increase pain during an attack.<sup>36</sup> Therefore, exercise is preferably performed between migraine attacks. In contrast, others found that exercise may abort a migraine attack when applied at the early onset of the headache period.<sup>37</sup>

In CP, dysfunctional EA in response to exercise has found,<sup>24,25,38</sup> which makes it difficult and sometimes painful to exercise. Pain thresholds are generally (at cephalic as well as extracephalic regions) decreased in chronic tension-type headache, not only during headache but also during headache-free periods, suggesting changes in central perception of pain.<sup>39,40</sup> In the clinic, patients with chronic tension-type headache sometimes report worsening of symptoms after strength training. However, according to the criteria, this type of headache normally does not worsen during physical activity.<sup>36</sup> In a study wherein 30 patients with chronic tension-type headache performed strength training 2 to 3 times/week, the pain intensity did not increase but, rather, decreased after 3 months of treatment.<sup>32</sup>

## How Should Exercise be Performed in Headache Treatment?

Scientific evidence regarding *how* exercise should be performed during headache treatment is still lacking. An exercise program based on submaximal aerobic exercise for 40 minutes, 3 times a week, including a warm-up and cool down phase, decreased the attack frequency in migraine.<sup>41</sup> In this study, also patients reporting exercise as a triggering factor for the attacks were included. Exercise may trigger attacks in the beginning of an exercise period, but the risk of migraine decreases when the patient gets used to exercise. In line with the notion that habituation of the brain to ordinary sensory signals is disturbed in migraine, it might be better training the brain to habituate rather than avoiding the specific trigger.<sup>42</sup> Therefore, a slow increase of intensity and duration is important when starting an exercise period. Clinicians need to guide patients in finding a suitable way of performing exercise. It is also important to reduce as many other possible triggering factors in combination with exercise therapy.<sup>33</sup>

In tension-type headache, strength training for neck and shoulder muscles is often used in clinical practice and found to be effective.<sup>32</sup> Including craniocervical flexion exercises seemed to be valuable as well.<sup>43</sup> Specific strength training is recommended with low to moderate quality of evidence in chronic neck pain, which is a very common symptom in tension-type headache.<sup>44,45</sup> Andersen et al<sup>46</sup> compared specific locally strength training with aerobic exercise in patients with neck pain. After 10 weeks, pain intensity was significantly decreased in the strength group compared with the other groups. The aerobic group showed a reduction in pain immediately after training, whereas the strength group demonstrated a pain increase immediately after exercise during the first weeks and a pain decrease during the last weeks. This suggests that strength exercise is

the best option in patients with tension-type headache. Symptom exacerbation may occur during the initial exercise stage but should cease after a few weeks, when exercise routine is established.<sup>46</sup>

Although the clinical benefits of exercise therapy are well established, caution is assumed when applying exercise therapy to patients with CP. Abnormal responses to exercise have been observed in some CP disorders such as FM, ME/CFS, and CWAD, each of which are often associated with headache. Those patients are unable to activate central descending nociceptive inhibition (EA) when exposed to exercise, but studies examining EA in response to exercise in headache patients are essentially lacking. Although exercise normally elicits pain relief, it may result in symptom exacerbation in CP patients.<sup>47</sup>

### EA DURING EXERCISE

In healthy individuals aerobic exercise of sufficient intensity ( $\pm 200$  W or 70%  $\text{VO}_{2\text{max}}$ ) activates pain inhibition for up to 30 minutes postexercise.<sup>48</sup> Resistance exercise triggers EA as well, but it lasts for no more than a couple of minutes postexercise.<sup>48</sup> Several partly overlapping mechanisms are suggested to play a role in exercise-induced EA, including release of endogenous opioids and growth factors<sup>49,50</sup> and activation of (supra)spinal nociceptive inhibitory mechanisms orchestrated by the brain.<sup>20,51</sup> Exercise-induced blood pressure increase activates arterial baroreceptors, resulting in increased supraspinal inhibition<sup>52,53</sup> and stimulation of brain centers involved in pain modulation.<sup>54</sup> Exercise triggers the release of  $\beta$ -endorphins from the pituitary (peripherally) and the hypothalamus (centrally), which in turn enables analgesic effects by activating  $\mu$ -opioid receptors peripherally and centrally, respectively (reviewed in Bender et al<sup>18</sup>). The hypothalamus, through its projections on the periaqueductal gray, has the capacity to activate descending nociceptive inhibitory mechanisms.

A systematic literature review showed that no conclusions can be made about the effect of exercise therapy on pain, on pain-modulatory substances (eg, serotonin, norepinephrine, and opioids), or on its effects on altering brain activity of areas involved in pain processing in patients with musculoskeletal pain.<sup>55</sup> Moreover, a dysfunctional response of some patients with chronic musculoskeletal pain to exercise has been shown.

### Dysfunction of Exercise-induced EA in Chronic Musculoskeletal Pain

On the basis of a review of the relevant literature, it was concluded that muscle contractions activate generalized EA in healthy, pain-free humans and patients with either OA or rheumatoid arthritis, but result in increased generalized pain sensitivity in FM patients.<sup>47</sup> In patients having local muscular pain (eg, shoulder myalgia), exercising nonpainful muscles activates generalized EA.<sup>47</sup> However, exercising painful muscles does not change pain sensitivity either in the exercising muscle or at distant locations.<sup>47</sup> We are unaware of studies examining exercise-induced EA in patients with migraine and tension-type headache.

Several populations of CP patients are unable to activate central descending nociceptive inhibition (EA) during aerobic exercise,<sup>24,25,38</sup> a dysfunction partly explaining symptom flares following exercise.<sup>38</sup> Remarkably, in the studies outlined above the various types of aerobic exercise

did activate EA in healthy sedentary controls<sup>21–23,53</sup> and patients with CLBP.<sup>25</sup> The latter confirms an earlier study in CLBP patients.<sup>17</sup> Thus, the mechanism of EA in patients with CLBP responds normally to aerobic exercise. It is concluded that the dysfunctional EA during aerobic exercise is not characteristic for all CP patients but rather limited to those with clear evidence of central sensitization (eg, CWAD, FM, ME/CFS).<sup>47</sup> There is a dearth of studies that examine the mechanisms behind dysfunctional EA during both aerobic exercise and local muscle contractions in patients with CP, with only few (unsuccessful) attempts so far.<sup>25,56</sup>

The dysfunctional EA during exercise might explain the low compliance with exercise interventions in CP patients. Typically the early stages of exercise therapy programs are prone to dropouts. Lack of exercise-induced analgesia implies a decreased pain threshold following exercise. This makes patients vulnerable for new nociceptive input. Exercise is typically associated with myofiber damage,<sup>57</sup> and substances released in response to exercise (eg, oxidative stress, lactate) potentially provide increased nociceptive input in response to exercise.<sup>57</sup> Hence, the dysfunctional EA during exercise increases the risk of severe symptom flares following exercise sessions.

### Guidelines for Applying Exercise in Patients With Dysfunctional EA

Clinicians should account for the dysfunctional EA during exercise in certain CP conditions. This might be achieved by applying the following guidelines: prefer aerobic exercise over eccentric or isometric muscle work, as the latter 2 are likely to increase the hyperexcitability of the central nervous system.<sup>58</sup> Exercising preferably nonpainful parts of the body could have pain-relieving effects in myalgia patients by reducing pain sensitivity in painful muscles, whereas low-intensity training regimes would be expected to be favorable in FM to avoid unnecessary exacerbations of pain.<sup>59</sup> In addition, it seems rational to combine centrally acting drugs with exercise therapy,<sup>47</sup> but direct evidence supporting this notion is lacking.

Besides dysfunctional exercise-induced analgesia, there is evidence of abnormal stress responses involving alterations in the hypothalamo-pituitary-adrenal axis and hyperactivity of the sympathetic branch of the autonomic nervous system in patients with CP.<sup>60</sup> Because of the ongoing pain, patients are exposed to stress continuously, referring to an important issue, especially because exercise is known to be a stressor as well. This highlights the need for focusing on and monitoring adequate recovery periods and optimizing the balance between exercise and recovery when patients with CP are exposed to exercise therapy.

### EXERCISE-INDUCED ACTIVATION OF THE STRESS RESPONSE SYSTEM

Exercise is known to activate stress responses within the neuroendocrine system provoking diverse changes in the concentration of many hormones (eg, growth hormone, testosterone, cortisol, epinephrine, norepinephrine),<sup>61–65</sup> which is likely to be closely related to EA in response to exercise. This helps the body accommodate and adjust to the stressor, thereby maintaining a homeostatic control. The level of stress it provokes is influenced by the intensity and duration of the exercise. Stress in small amounts with optimal scattered rest-recovery periods enables the sympathetic nervous system and adrenal-hypothalamo-pituitary

axis to respond adequately and reestablish the homeostatic equilibrium.

However, excessive exposure to stress can lead to inappropriate neuroendocrine responses resulting in an ongoing sensitization of nociceptive neurons and, hence, an increased pain sensitivity.<sup>66</sup> CP has been associated with ongoing exposure to stress. There is evidence of dysfunctional reactivity of the adrenal-hypothalamo-pituitary axis in patients with CP such as FM, low back pain, and rheumatoid arthritis.<sup>67,68</sup> The blunted reactivity of the adrenal-hypothalamo-pituitary axis may contribute to the exercise intolerance and exercise-induced symptom exacerbation that is so characteristic for some CP syndromes such as FM.

These results highlight the fact that clinicians should be careful when exposing patients with CP to physical stressors (eg, exercise). Exercise can benefit patients with CP when implemented without detrimental effects on the underlying pathophysiological mechanisms, symptom perception, and patient's functional status. Therefore, it is important to optimize the balance between recovery and stress (eg, due to exercise). Cycling between stress and recovery is crucial to prevent stress-related problems and achieve functional goals in patients with CP. Furthermore, we recommend that the stress-recovery relationship will be continuously monitored.

### RECOVERY FROM STRESS (INCLUDING EXERCISE)

Research into stress and recovery states is gaining increasing attention. Although it has been established that the quality and quantity of stress plays a key role in individual coping modes, the effective use of periods of recovery (eg, breaks during the day, weekends, vacations) and enjoyable activities (eg, exercise, social contact, sleep, reading) to compensate stress seems to be often overlooked. One way to address stress-associated problems (eg, burnout, increase in pain) is to focus on recovery activities in an effort to create buffers to help individuals to better deal with the demands of life.

Central to recovery is the principal of homeostasis.<sup>69</sup> A return to homeostatic balance is achieved when a deficit organism state (eg, fatigue) reestablishes the initial state. This simplistic view of recovery does not capture the complexity of the recovery construct. Kellmann and Kallus<sup>70</sup> describe the complex processes and propose characteristics of a general psychophysiological concept of recovery:

- Recovery is a process in time.
- Recovery is related to the type of and duration of stress.
- Recovery depends on a reduction of, a change of, or a break from stress.
- Recovery is individually specific and depends on individual appraisal.
- Recovery ends when a psychophysical state of restored efficiency and homeostatic balance is reached.
- Recovery includes purposeful action (proactive recovery), as well as automated psychological and biological processes restoring the initial state (passive recovery).
- Recovery can be described on various levels (eg, physiological level, psychological level, social level, sociocultural level, and environmental level).
- Recovery processes can be displayed in various organismic subsystems.
- Various subprocesses of recovery can be dissociated.

- Recovery is closely tied to boundary conditions (eg, sleep, social contact).

They define recovery as “an inter- and intra-individual multilevel (eg, psychological, physiological, social) process in time for the re-establishment of performance abilities. Recovery includes an action-oriented component, and these self-initiated activities (proactive recovery) can be systematically used to optimize situational conditions to build up and refill personal resources and buffers.”<sup>70</sup> Furthermore, Kellmann has proposed a general model describing the interrelationship between stress states and recovery demands.

In short, Kellmann's<sup>69</sup> model suggests that high stress levels are not detrimental, as long as the person engages sufficiently in recovery activities. The basic assumption of this model is that with increased stress, increased recovery is necessary to prevent any further rise in stress. However, limited resources (eg, time) can initiate a vicious cycle, wherein increased stress and an inability to meet increased recovery demands can result in a person experiencing more stress. Recovery demands are defined as the quality and/or quantity of recovery activities needed to balance the current recovery-stress state. People may be stressed to the point that they fail to find or make time to recover adequately, or fail to consider better ways of coping with the situation. The model proposes that with intermediate levels of stress, one can find a level of optimal performance and thus a level of adequate recovery. Beyond this point, however, it is argued that one cannot meet recovery demands without additional recovery activities. Stress will then accumulate, and without intervention symptoms of underrecovery (eg, burnout, overtraining) are likely to develop.

For the clinical application, another aspect seems to be relevant. If the requirements of adequate recovery are met, but the person is confronted with an emotional discussion, noise, or lack of or wrong debriefing of performance,<sup>71</sup> it can nevertheless result in *disturbed recovery*. In laboratory experiments, Kallus and Krauth<sup>71</sup> found that during the regeneration pause, there is a considerable increase in the amount of sensitivity toward disturbances, annoyances, and irritations. Thus, slight interruptions in the normal situation during the break may have great effects on performance.

Not only strategies of recovery have to be applied individually, but it is also recommended that each individual have >1 recovery strategy available. Probably the most important aspect about recovery is that recovery is a proactive self-initiated process to re-establish psychological and physiological resources. For example, going to a movie, visiting close friends, and going for a run can be self-initiated and proactively puts a person in charge. Hanin<sup>72</sup> points out that each individual emphasizes specific recovery strategies, which match the personal situation and preferences. However, sometimes the first choice cannot be used or does not work because of external or internal circumstances. For example, a person's number-one recovery strategy of “going for a run” may work perfectly in a familiar environment, but in the first few days after traveling overseas and crossing 7 time zones, the same recovery activity may stress the organic systems while the individual is still suffering from jet lag. The result is likely to be more stress instead of recovery. A second, third, or fourth backup recovery strategy should be available and applied, depending on current personal and situational factors, as it is not always possible to use the number-one recovery strategy. It becomes clear that it is not bad to be high on stress as long as the person knows how to recover.

Herein, we propose that clinicians applying exercise interventions for people with CP account for the dysfunctional stress response system as often seen in patients with CP. Indeed, the dysfunctional stress response system implies that recovery following exercise is delayed, as evidenced in patients with ME/CFS<sup>73</sup> and FM.<sup>74</sup> This calls for applying the above outlined reasoning and practice guidelines in exercise interventions for patients with CP. Research efforts are required to establish the most effective recovery strategies for patients with CP.

## CONCLUSIONS

Given the body of evidence demonstrating the beneficial clinical effects of exercise in many different CP disorders, exercise therapy is regarded as the cornerstone of conservative management in those with chronic musculoskeletal pain. The main goals of exercise in these patient groups are to reduce pain, improve physical fitness, and optimize participation in social, professional, and domestic activities. Improved physical fitness allows that daily activities can be performed at a lower percentage of maximum capacity and, possibly, with less likelihood of increasing symptoms.

Exercise has also been shown to be effective in the treatment of patients with chronic tension-type headache and migraine. However, it is still not clear how exercise should be applied in patients with headache. Aerobic exercise on a submaximal level may be the best option in migraine prophylaxis, whereas specific neck and shoulder exercises may be a better choice in treating chronic tension-type headache. The training should be tailored appropriately and individually. Symptom flares may occur during the initial exercise stage, but should cease after a few weeks when exercise routine is established. Therefore, exercise should preferably be performed over a couple of weeks and patients should persist.

Besides the consensus that exercise therapy is beneficial in the treatment of CP, the lack of EA in some chronic pain disorders should not be ignored. Exercise leads to normal EA in patients with OA and rheumatoid arthritis, whereas it results in increased generalized pain sensitivity in patients with FM, ME/CFS, and CWAD. In addition, disturbances in the reactivity of the stress response system have been observed in some CP disorders. This makes these patients vulnerable for new nociceptive input and increases the risk of severe symptom flares following physical stressors (ie, exercise therapy). These results highlight the fact that care must be taken when applying exercise therapy to patients with CP. Aerobic exercises like cycling and walking, starting at a low and tolerable level preventing postexertional malaise, over eccentric or isometric muscle work are suggested to avert exercise-related pain and disability. However, further studies are needed to clarify the biology of dysfunctional EA following exercise in some CP disorders and to examine how these findings should be applied in clinical practice.

Furthermore, optimizing the balance between exercise and recovery is of crucial merit to avoid stress-related detrimental effects due to exercise and to achieve optimal functioning and performance in patients with CP. The present paper represents a general model describing the interrelationship between stress states and recovery demands rather than discuss specific characteristics, demands, and strategies of adequate recovery to compensate stress and return to homeostatic balance in patients with chronic pain.

The basic assumption of the model is that with increased stress, increased recovery is necessary to prevent further rise in stress. If not, a vicious circle of increased stress and an inability to meet increased recovery demands can be initiated, resulting in accumulating stress. Further work is required to establish how this recovery model can be applied to patients with CP.

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