# Title:

# Physical Activity to reduce systemic inflammation associated with chronic pain and obesity

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**<H1>Abstract**

***Introduction***

The increasing prevalence of chronic pain and obesity has significant health and cost implications for economies in the developed and developing world. Evidence suggests that there is a positive correlation between obesity and chronic pain and the link between them is thought to be systemic inflammation.

***Objectives***

The aim of this narrative review was to explore the physiological links between chronic musculoskeletal pain and obesity and to consider the potential role of regular physical activity in providing a means of managing obesity-related chronic pain.

***Discussion***

Systemic inflammation, mechanical overload and autonomic dysfunction are associated with increased prevalence and severity of chronic pain in individuals with obesity. It has been proposed, therefore, that interventions which target systemic inflammation could help to reduce chronic pain in obese individuals. Reduction in abdominal fat has been shown to alleviate pain and reduce the systemic markers of inflammation that contribute to chronic pain. Interventions which include exercise prescription have been shown to reduce both abdominal fat and systemic inflammation. Furthermore, exercise is also known to reduce pain perception and improve mental health and quality of life which also improves pain outcomes. However, adherence to formal exercise prescription is poor and therefore exercise programmes should be tailored to the interests, needs and abilities of individuals in order to reduce attrition.

## <H1>Introduction

The increasing prevalence of chronic pain and obesity has significant health and cost implications for economies in the developed and developing world. Evidence suggests that there is a positive correlation between obesity and chronic pain (for review see [1]). A reduction in body fat can improve the symptoms and disability associated with chronic musculoskeletal pain including knee osteoarthritis, low back pain, hip and ankle pain, headaches, and chronic widespread pain and fibromyalgia syndrome [1-5]. Evidence suggests that improvement in pain outcomes associated with weight reduction is mediated by a decrease in load on weight bearing joints [6] improvement in joint alignment [7] and improvement in posture (see [5] for review). However, individuals with headaches and chronic widespread pain experience pain in both weight bearing and non-weight bearing parts of the body and therefore it cannot be attributed to mechanical overloading [2, 8-10].

The presence of proinflammatory cytokines in the systemic circulation may provide a common link between obesity and hronic musculoskeletal pain [4, 5]. It has been suggested that interventions, such as physical activity, which target both systemic inflammation and obesity could reduce pain [1]. The aim of this review is to explore the links between chronic musculoskeletal pain and obesity and to consider the potential role of regular physical activity in providing a means of managing obesity-related chronic pain.



## <H2>Chronic Musculoskeletal Pain and Obesity

Chronic pain is defined as a persistent and disabling pain lasting for 12 weeks or more (or for longer than the time normal healing would have been expected to take place) [10]. Studies

have shown that chronic pain affects approximately 25-35% of adults worldwide depending on the definition used [11]. In the United States an estimated prevalence of 30% has been reported with more females than males affected [12] and worldwide the prevalence is estimated to be over 20% of all adults, with 10% newly diagnosed each year [13, 14]. Chronic pain is now regarded as a disease entity in its own right [15] impacting on individuals, their families and their communities [16]. The cost to national economies in terms of lost work days, benefit claims and healthcare is estimated to be billions of pounds [17].

Chronic musculoskeletal pain affects muscles, ligaments, tendons and bones and may be localised or widespread. Chronic musculoskeletal pain is associated with reduced physical activity, reduced sleep quality, fatigue and mood disturbance, giving a reduced quality of life. The causes of chronic musculoskeletal pain are still not fully understood and are likely to be complex and multifactorial involving both physiological and psychological mechanisms. Chronic musculoskeletal pain often exists in the absence of any apparent pathology although hyper-excitability, or sensitisation, of the central and peripheral nervous systems is usually a factor [18, 19]. There is evidence that this sensitisation may be associated with systemic inflammation and dysfunction of the descending pain modulatory network [20]. It has been proposed that functional changes in the central nervous system can be reversed with appropriate and effective interventions, with earlier intervention being most significant [15, 21, 22].

Obesity has been described as a global pandemic [23, 24]. Obesity is a leading risk factor for death globally [9, 25] and it is projected that around 50% of adults will be obese by 2030 [26]. Worldwide, an estimated 4 billion adults are overweight or obese [25]. The cost to the

UK economy of the overweight and obese population was estimated at £15.8 billion per year in 2007; a figure which includes £4.2 billion in costs to the NHS, [27] and continues to increase each year. An individual is defined as being obese if their BMI is ≥ 30.0 kg/$m^2$ and overweight if their body mass index (BMI) is between 25.0 kg/$m^2$ and 29.9 kg/$m^2$. However, BMI should only be taken as a rough guide to whether an individual is overweight or obese because metabolic (central) obesity can occur in normal weight individuals due to the presence of visceral fat [1, 28]. It is therefore generally accepted that waist circumference [29] or waist:hip ratio [30] are better indicators of abdominal fat than BMI [31, 32].

A survey of >1 million individuals in the United States found that pain rates were 68% to 254% higher in those classified as obese compared with non-obese groups [33]. Obesity has consistently been identified as a factor contributing to a variety of pain conditions [2], including chronic widespread pain [34], fibromyalgia syndrome [4], neck, back and shoulder pain [35, 36], sciatica [37] and chronic daily headache [9]. Obesity has also been found to be positively correlated with the incidence and severity of pain [1, 4, 5, 26, 35, 36, 38, 39]. Evidence suggests that obese individuals have heightened responses to stimuli that produce pain [5]. Studies using functional magnetic resonance imaging (fMRI) have provided evidence that there is cortical or subcortical augmentation of pain processing in individuals with fibromyalgia syndrome. This results in a heightened pain perception when compared with pain-free individuals [20, 40]. The available evidence suggests that the relationship between obesity and chronic pain is complex and multifactorial [5] and is likely to involve a combination of systemic inflammation, musculoskeletal overload, and autonomic dysregulation [4, 5, 38]. In addition, psychosocial factors cannot be ignored as contributing to the problem [41, 42].

The presence of pro-inflammatory cytokines may provide a common link between obesity and increased chronic musculoskeletal pain [4, 5]. Adiposopathy ('sick fat') occurs with excessive body weight, resulting in dysfunctional fat tissue due to enlargement of fat cells. Adiposopathy results in elevated concentrations of pro-inflammatory biomarkers in the systemic circulation which are secreted by adipose tissue. These include prostaglandins, C-reactive protein (CRP) and cytokines such as interleukins (e.g. interleukin-6 (IL-6)), tumour necrosis factor alpha (TNF-α) and leptin [4, 26]. These biomarkers sensitise nociceptors lowering their thresholds of activation resulting in an amplified nociceptive input to the central nervous system. Hence, adiposopathy may contribute to non-resolving systemic inflammation and states of persistent pain [1, 12, 34, 43]. Furthermore, unresolving systemic inflammation may contribute to continued sensitisation of the nociceptive system and may also prevent the healing of tissue in the periphery [44]. This chronic inflammation is compounded by repetitive acute inflammation due to the consumption of food and a corresponding post-prandial rise in blood glucose.

It has been discovered that adipose tissue hypoxia occurs in obesity possibly due to decreased angiogenesis and blood flow. It is likely that this triggers an increase in the ratio of inflammatory to anti-inflammatory macrophages within adipose tissue, leading to increased local and systemic inflammation [45].

Given the links between obesity and systemic inflammation it is therefore unsurprising that studies have shown that pain can be reduced secondary to weight loss [3, 46]. Weight loss has been found to be associated with reduced levels of systemic pro-inflammatory markers in pain conditions including fibromyalgia syndrome [47], low back pain [48, 49] and osteoarthritis of the knee [6, 7, 46, 50]. It has also been found that bariatric surgery has a

positive effect on musculoskeletal pain outcomes by reducing the long-term risk of developing work-restricting musculoskeletal pain and increasing the likelihood of recovering from such pain. [46]. The precise links between weight reduction and decreases in pain have yet to be established; nevertheless, because metabolic syndrome and adiposopathy drive disease expression, it is likely that interventions targeting systemic inflammation will have a positive effect on chronic pain.

Obesity also results in increased levels of physical fatigue and pain resulting from mechanical overload on the musculoskeletal system and particularly the weight-bearing joints such as the knees, hips and the spine. Biomechanical abnormalities in the musculoskeletal system occur due to the malalignment of joints as a result of excessive body weight and the abnormal distribution of fat [6, 7]. An example of this can be observed readily when increased in abdominal fat results in a forward shift of the centre of gravity forcing the adoption of an exaggerated lumbar lordosis. A similar phenomenon occurs in pregnant women[51]. This malalignment can cause a disruption and magnification of the normal forces through weight bearing joints resulting in pain due to joint degeneration, muscle fatigue and tendinopathies [6, 7]. There is also an increased risk of lumbar disk herniation resulting in pain and disability from sciatica [37]. Excessive stress on joint tissue causes breakdown of joint cartilage leading to mechanical disruption and local inflammation which contributes to pain by augmenting systemic inflammation [26].

Dysregulation of the hypothalamic-pituitary-adrenal axis is also known to contribute to pain, altered mood, sleep disturbance and fatigue and has been observed in obese individuals both with and without pain. This has also been observed in individuals with chronic musculoskeletal pain including fibromyalgia syndrome [52, 53]. The hypothalamic-pituitary-

adrenal axis regulates the secretion of cortisol in response to psychological and physiological stimuli including 'fight or flight' situations.

Obesity also has psychological effects which can contribute to the magnification of pain. It can lead to an increase in depressive illness and decrease in self-esteem and well-being which result in further decreases in levels of physical activity, thus compounding the problem [54, 55]. Even a modest weight loss can reduce the mental health risks associated with obesity and improve pain outcomes [46, 55]. Interestingly, exercise has been shown to improve both mental health and physical health even if no weight is lost [56, 57].

**<H2> The role of physical activity in reducing obesity-related chronic pain**

A number of studies have shown that weight loss reduces the levels of pro-inflammatory markers and that even a modest weight loss will have benefits in terms of decreased pain and pain-related problems such as depression, sleep disturbance, fatigue and mechanical overload [7, 47, 49, 50, 58, 59].

Aside from promoting weight loss, physical activity has been shown to have an independent anti-inflammatory effect. In a review by Wärnberg [60] various studies were found to have observed that systemic inflammation decreased when using physical activity as an intervention [61-63]. Further reviews by You [45] and Nicklas [64] suggest that exercise training reduces chronic inflammation independently of weight loss. One of the mechanisms suggested is a reduction in adipose tissue hypoxia which occurs due to increased angiogenesis and an increase in blood flow as a result of exercise training [45]. Evidence for this has been gathered from large population cohort studies which observed the

relationships between plasma CRP and the level of physical activity, and illustrated that this relationship was independent of obesity as measured by body mass index [64]. However, not all studies illustrate this independent relationship [65] and there is clearly more scope for research in this area.

There are a number of other advantages to regular aerobic exercise which either directly or indirectly affect pain outcomes. Mork and Vasseljen [4] claimed that that exercise itself has a prophylactic effect on the development of some pain conditions such as fibromyalgia syndrome, and neck, shoulder and back pain. They claim that being overweight and sedentary is a greater risk factor for fibromyalgia pain than being overweight and active; possibly due to enhancement of pain inhibitory capacity. A review by Koltyn [66] provided evidence that physical activity increases pain threshold and decreases pain perception with a cumulative effect in people with an enhanced aerobic capacity although the mechanisms for this analgesia are still poorly understood [66]. Physical activity, irrespective of weight reduction has been found to increase lean body mass by initiating skeletal muscle growth, with consequent short term increases in resting metabolic rate for over 24 hours post medium or high intensity exercise, which helps weight control [67]. The findings of a Cochrane systematic review provided evidence that the use of physical activity as a weight loss intervention improves general health status even if no weight is lost because physical activity improves plasma lipoprotein profile [56]. There is also strong evidence that physical activity has a positive effect on mood and sense of well-being by reducing depression, improving sleep and sense of well-being which improves the quality of life and lessens the psychological impact of chronic pain [46, 54, 55]. For example, Knapen et al [68] found that aerobic physical activity carried out at 40-60% of VO2max was associated with improvements in state anxiety and subjective well-being. These effects of exercise on the

obese population were summarised by Zdziarski [42] who identified three mechanisms of action contributing to the reduction of pain: a reduction in inflammation, a decrease in mechanical loading and an improvement in psychological state. The greatest anti-inflammatory benefit was found to be achieved through multimodal exercise (aerobic combined with resistance exercise). It is suggested, therefore, that regular physical activity will help to reduce chronic pain by reducing systemic inflammation and indirectly by promoting a sense of well-being even where no weight is lost.

Ideally, physical activity must be incorporated into daily life, although compliance is known to be poor [69]. Attrition rates can be as high as 50% for adults engaging in exercise programmes [70]. Exercise prescriptions which require individuals to do moderate amounts of pleasant regular aerobic exercise, might overcome the problems associated with poor compliance whilst producing better pain outcomes and promoting improvements in body composition. High-impact physical activity is poorly tolerated in individuals suffering from chronic pain and therefore low impact activities initiated at a very gradual pace (e.g. 5 minutes daily) should be considered to help promote compliance [71]. Other modifications to exercise programmes have been suggested to improve compliance, such as breaking up exercise sessions into shorter bouts or combining impact exercise with non-impact exercise, but the main objective should be to tailor the exercise programme to the needs and abilities of the individual [42].

There are no guidelines for exercise prescription specifically designed to reduce systemic inflammation, and until further research is conducted it is suggested that guidance is taken from studies investigating the effect of physical activity on body fat. McTiernan found a reduction in intra-abdominal fat in men and women when facility and home-based aerobic activity was performed for at least 250 minutes per week compared with non-intervention

sedentary controls [72]. The American College of Sports Medicine Position Stand on appropriate strategies for weight loss and the prevention of weight regain suggest that moderate-intensity physical activity between 150 and 250 minutes per week is effective to prevent weight gain. Wareham, et al [73] suggested that there is a requirement for a minimum of 45-60 minutes per day of moderate intensity physical activity to prevent the development of obesity but Slentz et al [74] have suggested that as little as 30 minutes of moderate physical activity per day would be sufficient for weight control. The consensus appears to be that an additional 3000 walking steps per day (equivalent to approximately 30 minutes of activity) over and above normal daily activity is necessary for a healthy lifestyle [75-77]. This goal could be achieved simply by increasing the activities of daily living rather than a formalised exercise prescription which might be difficult for individuals to adhere to.

**<H2> Summary and Future Directions**

Systemic inflammation, mechanical overload and autonomic dysfunction are associated with an increased prevalence and severity of chronic pain in individuals with obesity. In particular, reduction of abdominal fat has been shown to reduce systemic markers of inflammation which contribute to chronic pain. Interventions which include exercise prescription have been shown to specifically reduce abdominal fat, which consequently reduces systemic inflammation. Significantly, reductions in inflammatory biomarkers through exercise programmes have been shown to be independent of weight loss. Furthermore, exercise is also known to reduce pain perception and improve mental health and quality of life, which in themselves affect pain outcomes. Unfortunately, adherence to self-administered exercise prescription is poor and it is therefore more likely that lifestyle-

based pleasurable physical activity would be easier to maintain than a prescriptive formal programme of exercise.

There are currently no evidence based guidelines for exercise prescription specifically to reduce obesity-related systemic inflammation associated with chronic pain conditions, although exercise interventions are commonly used in the management of many chronic pain conditions [42]. Additional research is necessary to establish appropriate exercise guidance for chronic pain relief in overweight and obese patients, which should include comparisons of exercise type, intensity and frequency [42].

In conclusion, it is suggested that the key to managing obesity-related chronic pain is to reduce systemic inflammation by encouraging regular physical activity, with or without weight loss. This notion requires further investigation because to date there is a dearth of studies specifically investigating the systemic effects of programmes of physical activity on chronic pain in obese and overweight populations.

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