Title:

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

Authors:

Paley C.A. [1, 2, 3] PhD

Johnson M.I. [2,3} PhD

Affiliations:

1. Airedale NHS Foundation Trust
2. Faculty of Health and Social Sciences, Leeds Beckett University
3. Leeds Pallium Research Group www.leeds.ac.uk/pallium

Address for correspondence:

Dr Carole A Paley
Head of Research and Innovation
Airedale NHS Foundation Trust
Skipton Road
Steeton, Keighley
West Yorkshire
BD20 6TD
carole.paley@anhst.nhs.uk
Tel: +44(0)1535 292278

<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.

REFERENCES

1. Bonakdar RA. Targeting systemic inflammation in patients with obesity-related pain: Obesity- related pain: time for a new approach that targets systemic inflammation. *The Journal Of Family Practice*. 2013;62(9 Suppl CHPP):S22-S9.
2. Wright LJ, Schur E, Noonan C, et al. Chronic pain, overweight, and obesity: findings from a community-based twin registry. *The Journal Of Pain: Official Journal Of The American Pain Society*. 2010;11(7):628-35.
3. McGoey BV, Deitel M, Saplys RJ, et al. Effect of weight loss on musculoskeletal pain in the morbidly obese. *The Journal Of Bone And Joint Surgery British Volume*. 1990;72(2):322-3.
4. Mork PJ, Vasseljen O, Nilsen TIL. Association between physical exercise, body mass index, and risk of fibromyalgia: longitudinal data from the Norwegian Nord-Trøndelag Health Study. *Arthritis Care & Research*. 2010;62(5):611-7.
5. Janke EA, Collins A, Kozak AT. Overview of the relationship between pain and obesity: What do we know? Where do we go next? *Journal Of Rehabilitation Research And Development*. 2007;44(2):245-62.
6. Messier SP, Mihalko SL, Legault C, et al. Effects of intensive diet and exercise on knee joint loads, inflammation, and clinical outcomes among overweight and obese adults with knee osteoarthritis: the IDEA randomized clinical trial. *JAMA*. 2013;310(12):1263-73.
7. Felson DT, Zhang Y, Anthony JM, et al. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. *Annals Of Internal Medicine*. 1992;116(7):535-9.
8. Bigal ME, Gironda M, Tepper SJ, et al. Headache prevention outcome and body mass index. *Cephalalgia: An International Journal Of Headache*. 2006;26(4):445-50.
9. Bigal ME, Rapoport AM. Obesity and chronic daily headache. *Current Pain And Headache Reports*. 2012;16(1):101-9.
10. McCarthy LH, Bigal ME, Katz M, et al. Chronic pain and obesity in elderly people: results from the Einstein aging study. *Journal Of The American Geriatrics Society*. 2009;57(1):115-9.
11. Breivik H, Eisenberg E, O'Brien T. The individual and societal burden of chronic pain in Europe: the case for strategic prioritisation and action to improve knowledge and availability of appropriate care. *BMC Public Health*. 2013;13:1229-.
12. Arranz L-I, Rafecas M, Alegre C. Effects of obesity on function and quality of life in chronic pain conditions. *Current rheumatology reports*. 2014;16(1):390-.
13. Elzahaf RA, Tashani OA, Unsworth BA, et al. The prevalence of chronic pain with an analysis of countries with a Human Development Index less than 0.9: a systematic review without meta-analysis. *Current Medical Research And Opinion*. 2012;28(7):1221-9.
14. Goldberg D, McGee S. Pain as a global public health priority. *BMC Public Health*. 2011;11(1):770.
15. van Hecke O, Torrance N, Smith BH. Chronic pain epidemiology and its clinical relevance. *British journal of anaesthesia*. 2013 July 1, 2013;111(1):13-8.
16. Colvin LA, Stein A, Smith BH. IV. Managing chronic pain: a clinical challenge: new SIGN guidelines provide a practical evidence-based approach and identify research gaps. *British journal of anaesthesia*. 2014 January 1, 2014;112(1):9-12.
17. Lee J, Ellis B, Price C, et al. Chronic widespread pain, including fibromyalgia: a pathway for care developed by the British Pain Society. *British journal of anaesthesia*. 2014 January 1, 2014;112(1):16-24.
18. Dieppe P. *Chronic Musculoskeletal Pain*2013.
19. Shipley M. Chronic widespread pain and fibromyalgia syndrome. *Medicine*. 2010;38(4):202-4.
20. Jensen KB, Loitoile R, Kosek E, et al. Patients with fibromyalgia display less functional connectivity in the brain's pain inhibitory network. *Mol Pain*. 2012;8:32-.

21. Gwilym SE, Filippini N, Douaud G, et al. Thalamic atrophy associated with painful osteoarthritis of the hip is reversible after arthroplasty: a longitudinal voxel-based morphometric study. *Arthritis and rheumatism*. 2010;62(10):2930-40.
22. Rodriguez-Raecke R, Niemeier A, Ihle K, et al. Brain gray matter decrease in chronic pain is the consequence and not the cause of pain. *The Journal Of Neuroscience: The Official Journal Of The Society For Neuroscience*. 2009;29(44):13746-50.
23. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384(9945):766-81.
24. Roth J, Qiang X, Marbán SL, et al. The obesity pandemic: where have we been and where are we going? *Obesity research*. 2004;12 Suppl 2:88S-101S.
25. WHO. Obesity and overweight. WHO; 2014; Available from: http://www.who.int/mediacentre/factsheets/fs311/en/.
26. McVinnie DS. Obesity and pain. *British Journal of Pain*. 2013 November 1, 2013;7(4):163-70.
27. PHE. Obesity and Health. Public Health England; 2014; Available from: http://www.noo.org.uk/NOO_about_obesity/obesity_and_health.
28. Rothman KJ. BMI-related errors in the measurement of obesity. *International Journal Of Obesity (2005)*. 2008;32 Suppl 3:S56-S9.
29. Bener A, Yousafzai MT, Darwish S, et al. Obesity index that better predict metabolic syndrome: body mass index, waist circumference, waist hip ratio, or waist height ratio. *Journal of obesity*. 2013;2013:269038-.
30. Kartheuser AH, Leonard DF, Penninckx F, et al. Waist circumference and waist/hip ratio are better predictive risk factors for mortality and morbidity after colorectal surgery than body mass index and body surface area. *Annals of surgery*. 2013;258(5):722-30.
31. Kissebah AH, Vydelingum N, Murray R, et al. Relation of body fat distribution to metabolic complications of obesity. *The Journal Of Clinical Endocrinology And Metabolism*. 1982;54(2):254-60.
32. Olivier M. Body fat distribution, lipoprotein metabolism, and insulin resistance: a lifetime of research on the pathophysiology of the human metabolic syndrome. *Journal Of Clinical Lipidology*. 2012;6(6):601-3.
33. Stone AA, Broderick JE. Obesity and Pain Are Associated in the United States. *Obesity*. 2012;20(7):1491-5.
34. Seaman DR. Body mass index and musculoskeletal pain: is there a connection? *Chiropractic & Manual Therapies*. 2013;21(1):15-.
35. Nilsen TIL, Holtermann A, Mork PJ. Physical exercise, body mass index, and risk of chronic pain in the low back and neck/shoulders: longitudinal data from the Nord-Trondelag Health Study. *American journal of epidemiology*. 2011;174(3):267-73.
36. Smuck M, Kao M-CJ, Brar N, et al. Does physical activity influence the relationship between low back pain and obesity? *The Spine Journal: Official Journal Of The North American Spine Society*. 2014;14(2):209-16.
37. Shiri R, Lallukka T, Karppinen J, et al. Obesity as a Risk Factor for Sciatica: A Meta-Analysis. *American journal of epidemiology*. 2014 April 15, 2014;179(8):929-37.
38. Janke EA, Fritz M, Hopkins C, et al. A randomized clinical trial of an integrated behavioral self-management intervention Simultaneously Targeting Obesity and Pain: the STOP trial. *BMC Public Health*. 2014;14:621-.
39. Ray L, Lipton RB, Zimmerman ME, et al. Mechanisms of association between obesity and chronic pain in the elderly. *Pain*. 2011;152(1):53-9.
40. Gracely RH, Petzke F, Wolf JM, et al. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis and rheumatism*. 2002;46(5):1333-43.
41. Janke EA, Kozak AT. "The more pain I have, the more I want to eat": obesity in the context of chronic pain. *Obesity (Silver Spring, Md)*. 2012;20(10):2027-34.

42. Zdziarski LA, Wasser JG, Vincent HK. Chronic pain management in the obese patient: a focused review of key challenges and potential exercise solutions. *Journal Of Pain Research*. 2015;8:63-77.
43. Bays HE, González-Campoy JM, Henry RR, et al. Is adiposopathy (sick fat) an endocrine disease? *International Journal Of Clinical Practice*. 2008;62(10):1474-83.
44. Nijs J, Van Houdenhove B, Oostendorp RAB. Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice. *Manual therapy*. 2010;15(2):135-41.
45. You T, Arsenis NC, Disanzo BL, et al. Effects of exercise training on chronic inflammation in obesity : current evidence and potential mechanisms. *Sports Medicine (Auckland, NZ)*. 2013;43(4):243-56.
46. Peltonen M, Lindroos AK, Torgerson JS. Musculoskeletal pain in the obese: a comparison with a general population and long-term changes after conventional and surgical obesity treatment. *Pain*. 2003;104(3):549-57.
47. Senna MK, Sallam RA-ER, Ashour HS, et al. Effect of weight reduction on the quality of life in obese patients with fibromyalgia syndrome: a randomized controlled trial. *Clinical rheumatology*. 2012;31(11):1591-7.
48. Melissas J, Volakakis E, Hadjipavlou A. Low-back pain in morbidly obese patients and the effect of weight loss following surgery. *Obesity surgery*. 2003;13(3):389-93.
49. Roffey DM, Ashdown LC, Dornan HD, et al. Pilot evaluation of a multidisciplinary, medically supervised, nonsurgical weight loss program on the severity of low back pain in obese adults. *The Spine Journal: Official Journal Of The North American Spine Society*. 2011;11(3):197-204.
50. Vincent HK, Heywood K, Connelly J, et al. Obesity and weight loss in the treatment and prevention of osteoarthritis. *PM & R: The Journal Of Injury, Function, And Rehabilitation*. 2012;4(5 Suppl):S59-S67.
51. Betsch M, Wehrle R, Dor L, et al. Spinal posture and pelvic position during pregnancy: a prospective rasterstereographic pilot study. *European Spine Journal: Official Publication Of The European Spine Society, The European Spinal Deformity Society, And The European Section Of The Cervical Spine Research Society*. 2014.
52. Crofford LJ, Demitrack MA. EVIDENCE THAT ABNORMALITIES OF CENTRAL NEUROHORMONAL SYSTEMS ARE KEY TO UNDERSTANDING FIBROMYALGIA AND CHRONIC FATIGUE SYNDROME. *Rheumatic diseases clinics of North America*. 1996;22(2):267-84.
53. Björntorp P, Rosmond R. Obesity and cortisol. *Nutrition (Burbank, Los Angeles County, Calif)*. 2000;16(10):924-36.
54. Karlsson J, Taft C, Rydén A, et al. Ten-year trends in health-related quality of life after surgical and conventional treatment for severe obesity: the SOS intervention study. *International Journal Of Obesity (2005)*. 2007;31(8):1248-61.
55. Larsson U, Karlsson J, Sullivan M. Impact of overweight and obesity on health-related quality of life--a Swedish population study. *International Journal Of Obesity And Related Metabolic Disorders: Journal Of The International Association For The Study Of Obesity*. 2002;26(3):417-24.
56. Shaw K, Gennat H, O'Rourke P, et al. Exercise for overweight or obesity. *The Cochrane Database Of Systematic Reviews*. 2009(4):CD003817.
57. Hayward LM, Sullivan AC, Libonati JR. Group exercise reduces depression in obese women without weight loss. *Perceptual And Motor Skills*. 2000;90(1):204-8.
58. Henriksen M, Klokker L, Graven-Nielsen T, et al. Association of exercise therapy and reduction of pain sensitivity in patients with knee osteoarthritis: a randomized controlled trial. *Arthritis Care & Research*. 2014;66(12):1836-43.
59. Heffner KL, France CR, Trost Z, et al. Chronic low back pain, sleep disturbance, and interleukin-6. *The Clinical Journal Of Pain*. 2011;27(1):35-41.
60. Wärnberg J, Cunningham K, Romeo J, et al. Physical activity, exercise and low-grade systemic inflammation. *The Proceedings Of The Nutrition Society*. 2010;69(3):400-6.

61. Jennersjö P, Ludvigsson J, Länne T, et al. Pedometer-determined physical activity is linked to low systemic inflammation and low arterial stiffness in Type 2 diabetes. *Diabetic Medicine: A Journal Of The British Diabetic Association*. 2012;29(9):1119-25.
62. Mora S, Cook N, Buring JE, et al. Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. *Circulation*. 2007;116(19):2110-8.
63. Bergström G, Behre CJ, Schmidt C. Moderate intensities of leisure-time physical activity are associated with lower levels of high-sensitivity C-reactive protein in healthy middle-aged men. *Angiology*. 2012;63(6):412-5.
64. Nicklas BJ, You T, Pahor M. Behavioural treatments for chronic systemic inflammation: effects of dietary weight loss and exercise training. *CMAJ: Canadian Medical Association Journal = Journal De L'association Medicale Canadienne*. 2005;172(9):1199-209.
65. Christiansen T, Paulsen SK, Bruun JM, et al. Exercise training versus diet-induced weight-loss on metabolic risk factors and inflammatory markers in obese subjects: a 12-week randomized intervention study. *American Journal Of Physiology Endocrinology And Metabolism*. 2010;298(4):E824-E31.
66. Koltyn KF. Analgesia following exercise: a review. *Sports Medicine (Auckland, NZ)*. 2000;29(2):85-98.
67. Stiegler P, Cunliffe A. The role of diet and exercise for the maintenance of fat-free mass and resting metabolic rate during weight loss. *Sports Medicine (Auckland, NZ)*. 2006;36(3):239-62.
68. Knapen J, Sommerijns E, Vancampfort D, et al. State anxiety and subjective well-being responses to acute bouts of aerobic exercise in patients with depressive and anxiety disorders. *British Journal Of Sports Medicine*. 2009;43(10):756-9.
69. Loveman E, Frampton GK, Shepherd J, et al. The clinical effectiveness and cost-effectiveness of long-term weight management schemes for adults: a systematic review. *Health Technology Assessment (Winchester, England)*. 2011;15(2):1-182.
70. Annesi JJ, Whitaker AC. Weight loss and psychologic gain in obese women-participants in a supported exercise intervention. *The Permanente Journal*. 2008;12(3):36-45.
71. Clauw DJ, Crofford LJ. Chronic widespread pain and fibromyalgia: what we know, and what we need to know. *Best Practice & Research Clinical Rheumatology*. 2003;17(4):685-701.
72. McTiernan A, Sorensen B, Irwin ML, et al. Exercise effect on weight and body fat in men and women. *Obesity (Silver Spring, Md)*. 2007;15(6):1496-512.
73. Wareham N, van Sluijs E, Ekelund U. Physical Activity and Obesity Prevention: a review. *Proceedings of the Nutrition Society*. 2005;64:229-47.
74. Slentz CA, Duscha BD, Johnson JL, et al. Effects of the amount of exercise on body weight, body composition, and measures of central obesity: STRRIDE--a randomized controlled study. *Archives Of Internal Medicine*. 2004;164(1):31-9.
75. Tudor-Locke C, Bassett DR, Jr. How many steps/day are enough? Preliminary pedometer indices for public health. *Sports Medicine (Auckland, NZ)*. 2004;34(1):1-8.
76. Tudor-Locke C, Bassett DR, Jr., Rutherford WJ, et al. BMI-referenced cut points for pedometer-determined steps per day in adults. *Journal Of Physical Activity & Health*. 2008;5 Suppl 1:S126-S39.
77. Tudor-Locke C, Craig CL, Brown WJ, et al. How many steps/day are enough? For adults. *The International Journal Of Behavioral Nutrition And Physical Activity*. 2011;8:79.