Not a Painless Condition: Rheumatological and Musculoskeletal Symptoms in Type 2 Diabetes, and the Implications for Exercise Participation

Emily R Cox^{1*}, Jeff S Coombes¹, Shelley E Keating¹, Nicola W Burton² & Brooke K Coombes³

¹School of Human Movement and Nutrition Sciences, The University of Queensland, St Lucia, Queensland, Australia

²School of Applied Psychology, Griffith University, Mt Gravatt, Queensland, Australia

³School of Allied Health Sciences, Griffith University, Nathan, Queensland, Australia

*Address correspondence and reprint requests to this author at the School of Human Movement and Nutrition Sciences, University of Queensland, St Lucia, Australia; Tel: +61 7 3365 6767; E-mail: emily.cox@uq.net.au

Abstract

Objectives: People with type 2 diabetes (T2D) are more likely to develop a range of rheumatological and musculoskeletal symptoms (RMS), and experience both chronic and widespread pain, compared with the general population. However, these symptoms are not commonly acknowledged by researchers, which hampers our understanding of the impact on this population. Since exercise is a key lifestyle management strategy for T2D and participation levels are typically low, understanding the potential impact of RMS on exercise participation is critical. The aim of this review is to summarise the literature regarding the prevalence and pathophysiology of RMS in T2D, the evidence for the benefits and risks associated with exercise on RMS, and the currently available tools for the reporting of RMS in both research studies and community settings.

Methods: A narrative review.

Results: There are numerous exercise trials in T2D, but few have sufficiently reported pain-related adverse events and even fewer have investigated the effects of exercise on RMS and chronic pain.

Discussion: Recommendations for future research are provided.

Key words: Type 2 diabetes, chronic pain, musculoskeletal symptoms, exercise, self-report tools

1.0 Introduction

The macrovascular and microvascular complications associated with type 2 diabetes mellitus (T2D) such as peripheral vascular disease, ischaemic heart disease, retinopathy and nephropathy, are considered the major cause of morbidity and mortality. Rheumatological and musculoskeletal symptoms (RMS) in these individuals are often overlooked, despite their ability to adversely impact quality of life, independence and exercise participation. RMS may present alone or alongside other diabetic complications such as diabetic symmetrical polyneuropathy (DSPN), although the impact of this clustering of comorbidities is poorly understood. The aims of this review are to summarise the literature regarding the pathophysiology and prevalence of RMS and chronic pain in people with T2D. Second, evidence for the effects of exercise on RMS, focussing on people with T2D, will be reviewed.

Third, a review of currently available self-report tools to evaluate RMS and monitor the effects of exercise interventions on RMS, and recommendations for minimum reporting of information in clinical trials or community settings will be presented. There is much work to be done in this area, but it is hoped this review will draw greater attention to the burden of RMS and chronic pain in people with T2D and lead to more research to determine the benefits and risks of exercise training in these individuals.

2.0 Impact of RMS and chronic pain on physical health

Pain is “an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage” [1]. Two thirds of Australians aged 15 years and over report experiencing bodily pain, with around 1 in 10 describing severe or very severe levels [2]. Further, chronic pain contributed 12% of the total burden of disease and injury in Australia in 2011, which is a total of 521,286 disability-adjusted life years [3]. Chronic musculoskeletal pain is highly prevalent in people with T2D [4-8]. Based on a survey of 951 people with T2D and 2,923 matched people without T2D from the Danish population, the prevalence of RMS was 1.7-2.1 times more frequent in people with T2D than in the general population ($p < .001$) [9]. Another cross-sectional study, which aimed to determine the prevalence of pain and its association with glycaemic control and physical functioning in 11,689 people with T2D, found that 57.8% of participants had moderate to extreme pain [10].

Chronic pain is frequently associated with physical, psychological and social issues which may adversely impact a person’s ability to perform activities of daily living (ADLs) and consequently quality of life [11-13]. This includes sleep disturbances, fatigue [14, 15], lack of independence [16, 17], and reduced work productivity [18, 19]. For people with T2D, additional issues include poorer diabetes self-management, poor mental health, and an increase in the number of doctor visits [10, 20-22]. Of major importance, the presence of chronic pain significantly impacts an individual’s exercise

participation [2, 11, 23], which is the key lifestyle strategy recommended for people with T2D for glycaemic control and reduction of weight [20, 23]. In a general population based sample aged 45 years and over, adults with severe or very severe pain were more likely than those without pain to be overweight or obese (80% versus 67%) and to lead an inactive lifestyle (53% versus 37%) [2]. Avoidance of regular exercise may lead to a progressive decrease in strength and flexibility as well as an increase in body weight, which may exacerbate pain and disability [11].

3.0 Prevalence and pathophysiology of RMS and chronic pain in people with T2D

People with T2D have an increased risk of developing specific RMS such as adhesive capsulitis of the shoulder, tendinopathy, diffuse idiopathic skeletal hyperostosis (DISH), Dupuytren's disease and limited joint mobility syndrome (LJMS) [24]. There are a number of other musculoskeletal conditions such as osteoarthritis (OA), low back pain (LBP), carpal tunnel syndrome and gout [25], which are also common in people with T2D, although a causal relationship has not been established [24, 26]. It is believed that the high comorbidity may be a result of the shared risk factors between T2D and RMS, including obesity, hyperlipidaemia, inactive lifestyle, hypertension, chronic kidney disease, and older age [27, 28]. Psychosocial issues such as depression [29, 30], fear of injury [31] and impaired quality of life [32] have also been linked with RMS and chronic pain in T2D.

Multiple mechanisms have been suggested to underlie the development and persistence of chronic RMS and pain in people with T2D. T2D is thought to increase the expression of pro-inflammatory cytokines [33] and proliferation of fibroblasts [34], both of which also play a key role in painful processes [35]. Animal studies have also shown altered mechanical properties of tendons in animals with chemically-induced diabetes mellitus [36, 37]. It is believed chronic hyperglycaemia, via abnormal glucose regulation, affects the collagen cross-linking in the connective tissue due to the accumulation of advanced glycation end products [4, 9, 38, 39]. This may result in increased tissue stiffness, which may lead to microdamage, inflammation and inhibited soft tissue repair. Further, the high levels of

insulin and insulin-like growth factor seen in T2D stimulates bone formation and results in abnormal collagen deposition in the connective tissues [40]. With regards to neural damage, it has been suggested that insulin resistance promotes the production of reactive oxygen species, resulting in endothelial dysfunction and ultimately neuro-ischemia [41]. Detailed reviews of these mechanisms are found elsewhere [4, 39, 42].

3.1 Adhesive Capsulitis

Adhesive capsulitis, also known as frozen shoulder, is characterized by pain and increasing stiffness of the glenohumeral joint resulting in restricted movement, particularly with external rotation and abduction [43]. People with T2D are five times more likely (95% CI 3.2-7.7, $p < 0.001$) to develop adhesive capsulitis than non-T2D controls [43]. The estimated prevalence of adhesive capsulitis ranges from 10.5-31.8% in people with T2D compared with 2.5-10.3% in the general population [44, 45]. Nearly one third of cases occur bilaterally, with unilateral cases affecting the dominant side more often [45, 46]. Compared with the general population, adhesive capsulitis begins at an earlier age and is less painful in people with T2D, although it has a poorer prognosis and is less responsive to non-operative treatment [47].

3.2 Tendinopathy

A systematic review of 31 studies found that people with T2D are more than three times as likely (OR 3.67, 95% CI 2.71-4.97) to develop both painful disorders of the tendon and asymptomatic structural tendon pathology than age and sex matched non-T2D controls [48]. Risk factors for the development of tendinopathy in T2D include the increased tendon thickness present in T2D, age and the length of time the patient has had T2D [48-50]. The exact cause is not clear due to other contributing factors common in T2D such as increased adiposity and medical therapy (e.g. statins) also having an effect [51, 52].

In another large epidemiological study of 1,296 people with T2D and 5,159 age and sex matched non-T2D controls, a 44% greater risk of tendon rupture requiring hospitalisation was found in people with T2D (incident rate ratio 1.44 (95% CI 1.10-1.87; $p=0.005$). The rotator cuff was the most common site for a tear. Independent risk factors for any tendon rupture were greater body mass index (BMI) and alcohol consumption. After adjusting for these factors, the risk due to T2D was estimated to be as high as 1.84 [53].

3.3 *Diffuse Idiopathic Skeletal Hyperostosis (DISH)*

DISH has been found to occur in 12-49% of people with T2D, compared with 1.6-13% of the general population [54, 55]. With a prominent effect on the thoracolumbar spine, DISH is characterized by calcification of spinal ligaments, generalized ossification of ligaments and tendons (particularly the skull, pelvis, patellae and calcaneus) and new bone formation [54, 55]. Clinical manifestations of DISH include thoracic, cervical and lumbar pain and decreased range of motion. In more severe cases, this can also include dysphagia and neurological abnormalities [56].

3.4 *Dupuytren's Contracture*

Dupuytren's contracture is defined as chronic and idiopathic thickening of the palmar aponeurosis which leads to various degrees of flexion deformities of the fingers. Mustafa et al. (2016) completed a cross-sectional study on 1,000 people with T2D, with 19% reporting a diagnosis of Dupuytren's contracture [57]. Another study found that 42% of 206 participants with T2D were suffering from Dupuytren's contracture compared with 29% of 203 age, gender and occupation-matched participants [58]. Age, duration of diabetes, female gender and microangiopathy significantly increase the likelihood of developing this condition [57-59]. In the general population, Dupuytren's contracture typically effects the fifth finger, whilst participants with T2D are more so affected in the ring and middle fingers [60, 61].

3.5 Limited Joint Mobility Syndrome (LJMS)

LJMS of the hand, also known as cheiroarthropathy is caused by thickening of the skin over the dorsum of the hands resulting in reduced flexion of the metacarpophalangeal and interphalangeal joints [27]. Increased glycosylation of collagen in the skin and periarticular tissues, increased collagen degradation, diabetic microangiopathy, increased duration of diabetes and DSPN have been associated with this condition [62, 63]. Pal et al. (1986) examined 109 people with T2D and 75 non-T2D people, clinically diagnosing LJMS of the hand in 49% of participants with insulin-dependent T2D ($p<0.01$) and 52% of participants with non-insulin dependent T2D ($p<0.001$), compared with 20% of non-T2D participants [63]. LJMS can also effect the small joints in the foot, with long-term progression resulting in impairment of the shoulder, hip, ankle or spine [64].

3.6 Widespread Chronic Pain

People with T2D also have a greater risk of daily widespread chronic pain. In a community study of 480 adults aged 30-65 years, Mantyselka et al. (2008) reported 42% of people with T2D and chronic pain experienced pain daily or continuously for at least 3 months compared with 18% of people without T2D [4]. Moreover, 32% of people with T2D reported pain at more than three bodily sites [65]. In another study with 100 participants with type 1 diabetes and T2D, higher HbA_{1c} levels were observed in people with widespread chronic pain than those with no chronic pain ($9.2 \pm 1.1\%$ vs $6.4 \pm 1.5\%$) [66].

3.7 Low Back Pain

LBP is a common RMS with $11.9 \pm 2.0\%$ of people worldwide suffering from the condition [67]. A cross-sectional analysis of 2,096 Spanish twins demonstrated that T2D was associated with a higher prevalence of severe LBP (adjusted OR 1.63; 95% CI 1.00 to 2.64) than those without the disease [68]. A significant association was also seen between LBP and the risk of diabetes (RR 1.30; 95% CI 1.09 to 1.54, $p=0.003$) [69].

3.8 Osteoarthritis

OA is the most frequent RMS experienced in both the general and T2D population, causing joint pain, stiffness and disability. It is characterized by loss of cartilage, bone hypertrophy, sclerosis and synovial inflammation [70]. A recent systematic review and meta-analysis of 10 studies and 16,742 patients concluded that T2D was significantly associated with the presence of symptomatic OA (OR 1.21; 95% CI 1.02-1.41) [71]. These odds were increased when controlling for weight and BMI (OR 1.25; 95% CI 1.05-1.46). Another systematic review and meta-analysis of 49 studies showed a mean OA prevalence of $29.5 \pm 1.2\%$ in people with T2D. The risk of OA was again greater in people with T2D than those without (OR 1.46; 95% CI 1.08-1.96, $p=0.01$) [72].

3.9 Diabetic Symmetrical Polyneuropathy

DSPN, which is characterized by progressive sensory loss, is one of the most common long-term complications of T2D, affecting 16.3-50% of people with the disease [25, 73]. Approximately 1 in 4 people with DSPN also experience chronic pain described as burning, tingling, electric, sharp, shooting, and lancinating pain in the extremities [73]. Symptoms of DSPN respond poorly to conventional analgesics. Painful DSPN is known to affect physical functioning and quality of life [73] and if inadequately treated, is associated with increased anxiety, depression, and sleep disturbance [25]. While attention to symptoms of DSPN is more commonly considered in research studies, it is often under-recognized that RMS and DSPN often coexist. In their study of 255 people with painful DSPN, Gore et al. (2006) found nearly two-thirds (63%) had other chronic musculoskeletal pain conditions, with OA (34%) and nociceptive LBP (27%) being the most common. 1 in 4 people (26%) also had other chronic neuropathic pain conditions; carpal tunnel syndrome (14%) and LBP with neuropathic involvement (13%) were the most common [25].

4.0 Effect of exercise on RMS and chronic pain

Clinical guidelines advise exercise and diet modification be used for the management of T2D before initiation of medication [74, 75]. The benefits of exercise for prevention of diabetes-related complications such as cardiovascular disease, neuropathy and nephropathy are well documented [75-81]. Exercise improves insulin sensitivity and diabetes pathologies through a number of mechanisms including the activation of AMP-activated protein kinase (AMPK) [82]. In contrast to the large amounts of data showing the benefits of exercise on insulin sensitivity, there is little evidence on the specific effects of exercise on RMS or chronic pain in people with T2D, though pilot studies are promising [83-85]. Exercise is thought to be beneficial in managing RMS and chronic pain in the general population by reducing associated symptoms such as pain, poor sleep and subsequent fatigue, reduced functional capacity, inflammation, and depression and anxiety [86]. In people with T2D, improvements in cardiorespiratory fitness, strength and flexibility were associated with lower symptoms and better function of the limbs and spine following exercise, compared to a control intervention [85].

A recent overview of Cochrane reviews by Geneen and colleagues (2017) concluded that the quality of evidence surrounding the impact of exercise for chronic pain is low, mainly due to small sample sizes and short planned follow-up periods [87]. Based on the heterogeneity of doses, intensities and modalities of exercise investigated in research studies, there are no specific guidelines for exercise and chronic pain [87], although the beneficial effects of exercise are proposed to be volume dependent [85]. Laboratory-based research in healthy [88] and older [89] adults has shown that individuals who self-reported greater levels of vigorous and total physical activity exhibited enhanced pain modulatory function [88]. Aerobic exercise, strength training, flexibility training and movement therapies have been most often recommended as non-pharmacological treatment of chronic pain [86].

Low to moderate intensity aerobic exercise (50-60% maximum heart rate) has been demonstrated to improve chronic pain symptoms in meta-analyses of randomized controlled trials with people with fibromyalgia [90-92]. Another recent systematic review has shown that aerobic exercise may also reduce neuropathy-related symptoms in people with T2D, with minimal adverse events [93]. If tolerated, moderate to vigorous intensity aerobic exercise (60-80% maximum heart rate), which is the current recommended intensity for the general population for improvements in cardiorespiratory fitness, body weight and general health [94, 95], may also be done. Reduction in weight from aerobic exercise has been shown to reduce the loading on joints and provide relief from osteoarthritic pain [96].

Strength training is also well supported as a safe and effective management strategy for chronic pain [97-99]. Strength training increases muscles mass and strength, which aids in maintaining physical function and preventing the development of other health conditions such as sarcopenia, osteoporosis, cardiovascular disease and T2D [94].

With the main aim of improving joint range of motion and decreasing stiffness, flexibility training may also provide benefits in people with T2D, with or without chronic pain [87]. Movement therapies such as Tai Chi and yoga have also been investigated for use in chronic pain populations. As these therapies are of low intensity and address pain and physical function, as well as balance, joint mobility and cognitions related to pain, they are safe and well tolerated [100-102].

While evidence suggests regular exercise can reduce chronic pain, acute increases in physical loading, such as when commencing an exercise regime, may aggravate musculoskeletal symptoms. Johansen et al (2017) randomized 98 people with T2D into standard care (individualized counselling and medical therapy) or a lifestyle intervention (standard care as well as 5-6 exercise sessions per week and dietary plans for weight loss). One in five people in the lifestyle intervention group reported RMS or

discomfort resulting in an inability to exercise for 7 or more consecutive days [103]. The Italian Diabetes and Exercise Study, which was a randomized controlled trial investigating the efficacy of an intensive exercise intervention strategy in people with T2D (n=606), reported 34 exercise-related, musculoskeletal adverse events in the exercise group. This included rotator cuff tendinopathy, aggravation of LBP or OA of hip or knee joint, shin splints/lower limb pain, as well as other/generalized musculoskeletal discomfort [104]. Thirteen participants (4.3%) dropped out of the exercise intervention group (n=303) due to adverse events, though the nature of the events which lead to this was not stated. Praet et al (2008) compared 12-months of either brisk walking or a medical fitness programme in 92 people with T2D. Of the 40 participants (43%) who were no longer participating at 12-months, 19 (48%) reported orthopaedic-related comorbidities such as overuse injuries and/or subclinical OA of the lower extremities as their reason for dropping out [105]. Exercise training studies frequently exclude potential participants based on the presence of RMS [104, 106-109], hence estimates of adverse events related to exercise training may be underestimated.

5.0 Evaluation of Rheumatological and Musculoskeletal Symptoms and Chronic Pain

Systematic assessment of the risk versus benefit of exercise interventions on chronic pain in people with T2D is challenging for several reasons. Musculoskeletal symptoms are not commonly explored during exercise interventions. In the aforementioned Cochrane review, only 25% of the studies included actively reported adverse events [87]. Another systematic review of randomized controlled trials in people with T2D found only 1 of the 136 exercise trials evaluated pain at baseline, and no trials were designed to specifically target the chronic pain [110]. The Italian Diabetes and Exercise Study used tailored exercise programs to minimize the risk of injury and worsening of RMS so to improve exercise adherence [85]. A self-reported questionnaire was used at baseline to evaluate RMS, however this was not repeated following the 12-month intervention, although joint-specific symptoms and functional status of 5 main body areas were only evaluated in a smaller cohort of participants. From these they were able to determine correlations between symptom scores and functional status, and

exercise volume. Unfortunately, each of the 5 questionnaires used contains up to 50 items each, which is a significant participant burden and is unlikely to be replicated in future exercise studies.

Our review of the literature highlights a lack of validated instruments exist to capture the range of symptoms experienced by people with T2D, as well as the multidimensional characteristics of pain in this population. For example, questionnaires such as the Nordic Musculoskeletal Injury Questionnaire address only the prevalence of symptoms in multiple areas of the body without providing information regarding the severity or interference with ADLs. Other questionnaires such as the Brief Pain Inventory (BPI) and the Medical Outcomes Study 12-item Short-Form Health Survey (SF-12), lack the capacity to identify widespread chronic pain, which is common in people with T2D. Several questionnaires, such as the Neuropathy Total Symptom Score-6 (NTSS-6), focus on symptoms of DSPN, but do not consider symptoms which may overlap with non-neuropathic musculoskeletal conditions. A combination of these tools may be needed to fully capture the burden of RMS and chronic pain. Development of a self-report questionnaire that considers chronic widespread pain, region-specific RMS and DSPN, and evaluates their impact on ADLs, in this population is required.

6.0 Recommendations

In order to better understand and address chronic pain in people with T2D, there needs to be an improvement in the associated monitoring and reporting of adverse events in exercise trials, particularly those related to the exacerbation of RMS. We strongly recommend, as a standard requirement, reporting both the prevalence of acute injury during exercise and the prevalence of musculoskeletal pain or discomfort resulting in an inability to exercise for 7 or more consecutive days, as documented in a recent trial published in the Journal of the American Medical Association [103]. The combination of these two outcomes provides meaningful information about the impact of RMS and pain on exercise adherence and may provide insight into potential barriers of regular exercise in T2D populations. To improve the generalisability of study findings, we also recommend more explicit

description of participant eligibility and reasons for exclusion due to pre-existing musculoskeletal conditions and chronic pain. To determine the efficacy of exercise training on chronic pain, future studies need to evaluate the presence, severity and interference of RMS and chronic pain at baseline and at follow up in both intervention and control or usual care groups.

Prevalence and Impact	<ul style="list-style-type: none"> • 42% experience chronic pain daily or continuously, compared to 18% of the general population ^[4] • Up to 50% experience chronic neuropathic pain ^[25] • 2 fold increase in healthcare costs due to chronic pain or RMS ^[22]
Mechanisms	<ul style="list-style-type: none"> • Accumulation of advanced glycation end products affecting collagen cross-linking ^[4,9] • Increased expression of pro-inflammatory cytokines ^[33] • Insulin & insulin-like growth factor resulting in abnormal collagen deposition in connective tissue^[40]
Risk Factors	<ul style="list-style-type: none"> • Shared comorbidities such as obesity, hyperlipidaemia ^[4] • Psychosocial issues including depression, fear of injury ^[25]
Exercise Participation	<ul style="list-style-type: none"> • 1 in 5 report RMS causing cessation of exercise for 7 or more consecutive days ^[103] • 1 in 2 report RMS as the reason for no longer participating in regular exercise ^[105] • Effects of exercise on RMS and chronic pain is not clearly established
Research Issues	<ul style="list-style-type: none"> • Participants with chronic RMS are often excluded from exercise interventions • RMS are not commonly explored during exercise interventions • A lack of validated instruments to capture the multi-dimensional characteristics of RMS
Future Research Directions	<ul style="list-style-type: none"> • Prospective studies on the effect of exercise interventions on RMS presence, severity and interference on activities of daily living • Improved reporting of pain-related adverse events and exclusion criteria in exercise trials

Figure 1: Summary of Evidence Regarding Rheumatological and Musculoskeletal Symptoms in Type 2 Diabetes, and the Implications for Exercise Participation and Research

7.0 Conclusion

RMS and chronic pain are highly prevalent in people with T2D, inferring that T2D is not a painless condition. The impact of RMS and chronic pain on exercise, a key component of managing T2D, is not clearly understood, potentially hampering critical efforts to improve participation in this population. High quality research investigating the efficacy of exercise to improve RMS and chronic pain in people with T2D is urgently needed. There also needs to be an improvement in the reporting and monitoring of adverse events during exercise training studies. Greater attention toward RMS may help

researchers and practitioners to understand, prevent and treat RMS and chronic pain and ultimately improve exercise adherence in people with T2D.

Acknowledgements

No sources of funding were used to assist in the preparation of this article.

Conflicts of Interest

The authors declare that they have no conflicts of interest, financial or otherwise, relevant to the views shared in this article.

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