

# Diabetes and musculoskeletal disorders-a review

## Abstract

Diabetes mellitus comprises of metabolic diseases that are characterized by elevated levels of blood glucose or hyperglycaemia, which is a result of insulin deficiency, insulin resistance or both. Marked hyperglycaemia causes an increase in morbidity and mortality that are related to macrovascular and microvascular complications. Musculoskeletal disorders seem to occur often in patients who have diabetes. Musculoskeletal pain is a usual occurrence in patients who have diabetes compared to the general population. The aim of this review was to explore and musculoskeletal disorders in diabetes. Diabetes causes significant morbidity and mortality and has been found to have an association with musculoskeletal disorders. A number of studies have found that diabetes has an association with musculoskeletal disorders such as osteoarthritis, rheumatoid arthritis, osteoporosis, fibromyalgia and carpal tunnel syndrome however the reasons underlying them are unclear. This review looks at the effects of diabetes on musculoskeletal disorders and the mechanisms through which diabetes contributes to them, so as to have a better understanding of the impact they may have in patients with diabetes. Further studies are necessary to understand how diabetes correlates with connective tissue metabolism, cytokines and obesity, for better patient care, treatment and prevention.

**Keywords:** diabetes mellitus, hyperglycaemia, osteoarthritis, fibromyalgia, carpal tunnel syndrome, musculoskeletal disorder

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**Abbreviations:** DM, diabetes mellitus; WHO, World health organization; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; PWD, patients with diabetes; IR, insulin resistance; OA, osteoarthritis; RA, rheumatoid arthritis; CF, charcot foot; AC, adhesive capsulitis, LJM, limited joint mobility; FMS, fibromyalgia syndrome; DC, Dupuytren contracture; TF, trigger finger; CTS, carpal tunnel syndrome; ORs, odds ratios; COA, charcot osteoarthropathy; HR, hazard ratio; FMS, fibromyalgia syndrome; DISH, diffuse idiopathic skeletal hyperostosis; FS, frozen shoulder; RR, relative risk; AGEs, advanced glycation end products; RAGE, receptor for advanced glycation end products; TNF, tumor necrosis factor; IL, interleukin; QoL, quality of life

## Introduction

Diabetes mellitus (DM) comprises of metabolic disorders that are chronic and characterized by hyperglycaemia, which is a result of insulin deficiency, insulin resistance or both.<sup>1</sup> Marked hyperglycaemia causes increased morbidity and mortality, which are mostly associated with macrovascular and microvascular complications.<sup>2</sup> The World Health Organization (WHO) estimated that globally about 422 million people currently have diabetes.<sup>3</sup> The number of adults with diabetes globally has been estimated to increase to 592 million by 2035.<sup>4</sup> In the United States (US), diabetes affects about 10% of the general population.<sup>5</sup> In 2009 2.6 million people were diagnosed with diabetes in the UK.<sup>6</sup> Diabetes can be grouped into two main categories. The autoimmune destruction of beta-cells of the pancreas causes Type 1 diabetes mellitus (T1DM), which starts in the young.<sup>7</sup> The most common form is Type 2 diabetes mellitus (T2DM) that is characterized by insulin resistance (IR) and comprises about 90–95% of patients with diabetes (PWD).<sup>6</sup> Evidence suggests that a number of musculoskeletal disorders are linked with diabetes, which may cause significant pain and disability.<sup>8–10</sup> While musculoskeletal disorders in PWD have been reported in previous studies,<sup>11–13</sup> the causes underlying

them are unclear. This review discusses some of the musculoskeletal disorders associated with diabetes.

## Diabetes and musculoskeletal disorders

Musculoskeletal disorders are common and the prevalence is raised in PWD.<sup>14</sup> About 20–33% of people globally and about one in two adults were found to have a musculoskeletal disorder in the US.<sup>15</sup> Worldwide, in 2017, musculoskeletal disorders were about 16% of global disabilities.<sup>16</sup> The common musculoskeletal disorders include osteoarthritis (OA), rheumatoid arthritis (RA), Charcot's foot (CF), adhesive capsulitis (AC), osteoporosis, limited joint mobility (LJM), fibromyalgia syndrome (FMS), Dupuytren's contracture (DC), trigger finger (TF) and carpal tunnel syndrome (CTS).<sup>17</sup> Musculoskeletal pain and loss of function can be caused due to restricted movement, flexibility and abilities.<sup>18</sup> In PWD, musculoskeletal pain may have negative consequences, which includes inadequate glycaemic control and a reduction in being physically active.<sup>19</sup>

## Diabetes and musculoskeletal pain

In PWD, several musculoskeletal disorders have been related, that have an impact on all age groups. There is evidence that musculoskeletal pain is a frequent problem in PWD.<sup>20</sup> In the UK, about 9.3 million working days are lost as a result of pain in the back, hips or knees.<sup>21</sup> Diabetes has been found to have significant associations with back/lower back pain, pain in the limbs, OA, osteoporosis, RA and shoulder/neck pain, with odds ratios (ORs) ranging between 1.2 to 1.6 ( $p < 0.01$ ).<sup>22</sup> In a previous study on 950 patients with T2DM, musculoskeletal pain was 1.7 to 2.1 times as frequent ( $p < 0.001$ ) to age and gender matched controls and the pain was more frequent in females ( $p < 0.001$ ).<sup>20</sup> Another study found that there was a significant rise in the pain intensity ( $p < 0.001$ ) of PWD with knee OA and raised synovitis scores were found ( $p = 0.024$ ) compared to patients without diabetes.<sup>23</sup>

## Diabetic neuropathy

Diabetic neuropathy has been found to affect over 90% of PWD<sup>24</sup> and is a common complication of both T1DM and T2DM. It has been observed in those who have had the disease for 10 years or longer. One of the main symptoms of diabetic neuropathy is pain.<sup>22</sup> Peripheral neuropathy, retinopathy, autonomic neuropathy or renal failure may be due to the long-term complications of diabetes.<sup>2</sup> Limited joint mobility (LJM) has been found to be more prevalent in patients with diabetic neuropathy. The blood vessels may be affected by autonomic neuropathy, which leads to increased blood flow and cause inflammation and damage to the bones. Autonomic neuropathy has been found in patients with Adhesive capsulitis (AC) often compared to other PWD, which could be an underlying mechanism.<sup>25</sup> Sharp pains, numbness, cramps, burning, tingling or sensory loss have been observed in peripheral neuropathy,<sup>26</sup> which may increase the risk of some forms of OA in PWD.<sup>1</sup>

## Charcot osteoarthropathy

Charcot osteoarthropathy (COA) or neuropathic arthropathy is also known as Charcot's Joint, and is a result of diabetic peripheral neuropathy.<sup>27</sup> In PWD, it causes damage and deformities of joints along with symptoms such as tingling, numbness or sensory loss.<sup>27</sup> COA is a progressive and degenerative disease and pain/discomfort may be observed in the acute stages. Joints such as the knees, ankles and feet, which are the weight-bearing joints, are mostly affected<sup>28</sup> and people of both genders are equally affected. The incidence of arthropathy was found to be about 10% in the foot and ankle, with an increase in prevalence of 1/680 in PWD, which increased with the duration of diabetes.<sup>18,29</sup> COA is mostly found in people above 50 years<sup>18</sup> and has been found in 0.1–5% of PWD. It is caused due to a lowering of the afferent neural impulses, which leads to abnormal vasomotor regulation.<sup>30</sup> T2DM was found in about two-thirds of people with COA.<sup>30,31</sup>

## Osteoarthritis

Osteoarthritis (OA) is caused due to degradation of the cartilage in one or more joints, which make them stiff and painful.<sup>1,32</sup> OA affects around 8 million people in the UK<sup>32</sup> and is the most common form of arthritis.<sup>22,33</sup> OA commonly affects the knees, hips and joints in the hands and musculoskeletal pain may arise in PWD.<sup>1</sup> The prevalence of OA amongst PWD was 29.5±1.2% and diabetes amongst patients with OA was 14.4±0.1%.<sup>34</sup> In PWD, the overall risk of OA as reported in a systematic review was 1.46 (95% confidence interval (CI) 1.08, 1.96;  $p=0.01$ ) and diabetes in patients with OA was 1.41 (CI 1.21, 1.65;  $p<0.001$ ).<sup>34</sup> T2DM has been significantly associated with OA (OR 1.21, 95% CI 1.02, 1.41).<sup>35</sup> A cohort study showed that in men with T2DM and knee OA, joint space narrowing was significantly higher than controls.<sup>36</sup> These results were supported by a few animal studies, which also found a negative effect of diabetes on OA.<sup>37</sup> In contrast, no association was found between OA and T2DM in those who had knee or hip joint replacement (OR 1.0, 95% CI 0.5, 1.9).<sup>38</sup> The researchers concluded that diabetes could be a risk factor for hip and knee OA.<sup>38</sup> Studies have suggested that T2DM may have a pathogenic effect on OA through major pathways involving inflammation and oxidative stress, caused by persistent hyperglycemia and IR.<sup>39</sup>

## Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic, inflammatory and autoimmune disease.<sup>32,40</sup> It affects the synovial membranes of joints and may lead to joint deformities.<sup>41</sup> Peripheral and symmetric polyarthritis observed in RA<sup>41</sup> are likely to cause destruction of

cartilage by the immune system.<sup>42</sup> Inflammation, pain, and decreased function of the affected joints are the common symptoms of RA.<sup>43</sup> RA has an estimated global prevalence of 0.24% and females are twice as likely to have RA as males.<sup>44</sup> Approximately 400,000 people are affected by RA in the UK.<sup>32,42</sup> An increased prevalence of diabetes has been observed in patients with RA.<sup>45,46</sup> Diabetes was associated with 55% elevated odds of having RA in a Danish study.<sup>22</sup> In contrast, some studies have found no evidence that RA occurs often in PWD.<sup>47,48</sup> Some studies have shown that T2DM increases the risk for developing RA and conversely, having RA increases the risk for developing T2DM. Patients with RA may be at an increased risk for IR and T2DM.<sup>49</sup> However, others have suggested that people with T1DM are likely to have a higher chance of developing RA,<sup>42</sup> as they share some common genetic characteristics such as the chromosomes HLA-DR9, 4q27, PTPN22 and the regions IDDM8 and IDDM5.<sup>50</sup>

## Gout

Gout is an inflammatory arthritis and commonly affects adult males.<sup>18</sup> The collection of monosodium urate crystals leads to inflamed and painful joints along with acute inflammatory attacks.<sup>32</sup> Gout had an association with an increased risk of diabetes (hazard ratio [HR] 1.45, 95% CI 1.37, 1.54) and the risk of incident diabetes was more in females (HR 1.77, 95% CI 1.51, 2.09) than males (HR 1.41, 95% CI 1.33, 1.50).<sup>51</sup> The incidence rates of diabetes were 9.5 in males and 10.1 in females per 1000 person-years in people with gout in a population-based study and 7.2 in males and 5.6 in females per 1000 person-years in controls.<sup>52</sup> A recent prospective study in the UK found that diabetes was related to a lower risk of incident gout<sup>53</sup> whereas a Chinese study found no significant relationship.<sup>54</sup> Some studies have found that people with gout are significantly more likely to develop T2DM than controls.<sup>55</sup> The prevalence of gout in T2DM patients was 22%.<sup>56</sup> In gout, serum uric acid levels have been related with the risk of developing diabetes.<sup>57</sup> Diabetes was strongly related with serum urate concentrations, abdominal obesity and gout,<sup>18</sup> while others found gout related with diabetes when hyperlipidaemia and obesity were present.<sup>47</sup>

## Diabetic muscle infarction

Diabetic Muscle Infarction is an uncommon complication of long-standing diabetes,<sup>58,59</sup> with established vasculopathy. The symptoms include sudden pain and inflammation in the lower limbs and it mostly affects the adductor muscles, quadriceps femoris and calf muscles.<sup>18</sup> Out of 114 PWD, it was found to be more common in females (61.53%), 59.1% had T1DM and 23.8% had T2DM.<sup>59</sup> The underlying factors such as vascular endothelial damage and diffuse diabetic microangiopathy may cause diabetic muscle infarction.<sup>60</sup>

## Diabetic amyotrophy

Diabetic Amyotrophy (Diabetic Cachexia) is a disabling and different form of diabetic neuropathy,<sup>61</sup> with an estimated incidence of about 1% amongst PWD.<sup>62</sup> The symptoms commonly include loss of tendon reflexes, pain, muscle wasting and weakness.<sup>18</sup> Diabetic amyotrophy has been found to often occur in older males with T2DM and is linked with weight loss.<sup>62</sup> The underlying factors may be due to a combination of metabolic imbalances, autoimmunity, microvascular inadequacy and oxidative stress.<sup>18</sup>

## Fibromyalgia syndrome

Fibromyalgia or Fibromyalgia syndrome (FMS) is a chronic condition that affects about 2–4% of adult females.<sup>63</sup> The symptoms consist of extensive musculoskeletal pain, stiffness and tenderness

along with functional and cognitive impairments, headaches and tiredness.<sup>64</sup> Diabetes may have a role in the development of FMS as it was found to be more common in FMS patients than controls.<sup>64</sup> Peripheral neuropathy has been linked with FMS as it was found in 61.9% of T2DM patients with FMS compared to only 2.5% of T2DM patients without FMS.<sup>64</sup> Other than endocrine and neurological factors, research indicates that environmental and genetic factors may also play a role in the development of FMS.<sup>64</sup>

### Diffuse idiopathic skeletal hyperostosis

Diffuse idiopathic skeletal hyperostosis (DISH), Forestier disease or ankylosing hyperostosis mostly affects the neck or spine.<sup>65</sup> In DISH, the tendons and ligaments harden along with the formation of new bones. Stiffness or a decrease in movement has been observed in PWD.<sup>65</sup> DISH commonly occurs in PWD (13–49%) compared to controls (1.6–13%),<sup>18</sup> and another study reported that it was present in 25% amongst 428 PWD.<sup>7</sup> DISH is mostly found in T2DM compared to T1DM and mainly occurs in the elderly.<sup>7,66</sup> DISH affects more males than females and in those with dyslipidaemia, hyperuricaemia or obesity.<sup>66</sup>

### Dupuytren's contracture

Dupuytren's contracture (DC) is a disorder that causes hardening, thickening, tethering and contraction of the fingers, with limited joint movements.<sup>67</sup> It is associated with peripheral neuropathy and diabetes was found to be a significant risk factor (mainly T1DM) for DC.<sup>68</sup> DC occurs more in PWD than in the general population<sup>69,70</sup> and has been reported in 16–42% of PWD.<sup>7,70</sup> A systematic review found an association between DC and diabetes (OR 3.06, 95% CI, 2.69, 3.48).<sup>71</sup> DC is common in patients who have long-standing diabetes and may increase with age and the duration of diabetes.<sup>72</sup> A study reported that the prevalence increased in both T1DM and T2DM compared to controls (35.0 and 30.0% versus 6.7 and 10.0%), both  $p < 0.01$  and had a correlation with age ( $p < 0.05$ ).<sup>73</sup>

### Adhesive capsulitis

Frozen shoulder (FS) or adhesive capsulitis (AC), is a disabling and common musculoskeletal disorder. The symptoms include restricted and painful shoulder movements, mainly with abduction and external rotation that causes acute pain, tightening and stiffness in PWD.<sup>22</sup> The prevalence of AC was estimated to be 11–30% in PWD and 2–10% in controls.<sup>74</sup> Another study reported that the estimated prevalence was 10–20% in T1DM, 7–32% in T2DM and 0–10% in controls.<sup>75</sup> In AC, a lower BMD was found in T1DM, whereas patients with T2DM and hyperinsulinaemia were found to have a normal/high BMD.<sup>65</sup> In T1DM, AC was found to be related with age and duration of diabetes whereas in T2DM, it was related only with age.<sup>75</sup>

### Osteoporosis

Osteoporosis is a disorder that causes bone damage and deterioration, making them prone to fracture.<sup>26</sup> Osteoporosis affects around 3 million people in the UK.<sup>76</sup> Diabetes has been associated with an increased risk of fracture. Studies suggest that diabetes could be a risk factor for fracture.<sup>26</sup> Osteoporosis can cause musculoskeletal pain and bone loss is greater in patients with inadequately controlled diabetes than those with good control.<sup>77</sup> T1DM and T2DM have different effects on BMD but share common pathways, which cause bones to become fragile.<sup>26</sup> In the Nurses' Health Study, 1,398 females had a hip fracture during 2.22 million person-years of follow-up and in T1DM, the risk of hip fracture was found to be six-fold higher than

those without diabetes.<sup>77</sup> The age-adjusted relative risk (RR) of hip fracture in T1DM was 7.1 (95% CI 4.4, 11.4) and 1.7 (CI 1.4, 2.0) in T2DM compared with females without diabetes.<sup>77</sup> Researchers have suggested that people with T1DM may have an increased risk of osteoporosis because they tend to have a lower BMD.<sup>76</sup>

### Diabetic cheiroarthropathy

Diabetic cheiroarthropathy, Diabetic Hand Syndrome or Limited joint mobility (LJM) is a disabling condition that may occur due to vascular insufficiency.<sup>64</sup> In LJM, limitations occur in joint movements due to contractures and skin of the hands become thick, tight and waxy, with deformities and pain in the joints.<sup>78</sup> The prevalence of LJM was found to vary from about 8 to 58% in T1DM, 25 to 76% in T2DM and 1 to 20% in controls.<sup>65</sup> LJM is associated with age and duration of diabetes.<sup>71</sup> Researchers have suggested that the differences in the prevalence estimates in LJM may be due to differences in glycaemic control.<sup>79</sup> The prevalence of LJM in T1DM was found to be related to age ( $p < 0.05$ ) and with duration of diabetes<sup>73</sup> and some studies have suggested that genetic factors could have a role in the development of LJM.<sup>65</sup> A study showed that the prevalence of LJM was 8% in T1DM, 9% in their siblings without diabetes and 2% in controls who were not siblings.<sup>80</sup> In contrast, another study found that genetic factors did not have a role in LJM in patients with T1DM and their first-degree relatives.<sup>81</sup>

### Carpal tunnel syndrome

Carpal tunnel syndrome (CTS) is a neuropathic disorder, which may occur due to diabetic neuropathy and/or compression of the median nerve in the carpal tunnel.<sup>7</sup> CTS causes pain, tingling and numbness in the hands. The prevalence of CTS in adults ranges from about 2.7% to 5.8%<sup>82</sup> while the incidence is about 125 per 100,000 person-years.<sup>61</sup> CTS is more common in females<sup>82</sup> with an incidence of 8% compared to 0.6% in males.<sup>18</sup> Diabetes is commonly associated with CTS and studies have found about 11% in T1DM, 12% in T2DM and 8% in controls.<sup>7</sup> CTS is associated with age and the duration of diabetes. A meta-analysis suggested that both T1DM and T2DM are risk factors for CTS.<sup>83</sup> A study found that the prevalence increased in both T1DM and T2DM compared to controls (26.7 and 15.0% versus 3.3 and 5%,  $p < 0.01$  and non-significant).<sup>73</sup>

### Flexor tenosynovitis

Flexor tenosynovitis is also known as stenosing tenosynovitis or trigger finger.<sup>84</sup> It is caused due to fibrous proliferation in the tendon sheath, which leads to limited movement around the fingers and hands.<sup>84</sup> In PWD, the incidence of flexor tenosynovitis ranges from 10 to 20%<sup>84</sup> and is linked with age and the duration of diabetes. A study observed an increased incidence in those with impaired glucose tolerance.<sup>85</sup> In both T1DM and T2DM, the prevalence increased compared to controls (23.3 and 16.7% versus 0.0 and 3.3%),  $p < 0.01$  and  $p < 0.05$ <sup>73</sup> and in T2DM, the prevalence also increased with age ( $p < 0.05$ ).<sup>73</sup>

### Causes of musculoskeletal disorders and pain in diabetes

The prevalence of musculoskeletal disorders of all types was 58.15% (95% CI 41.4, 73.9), as reported in a systematic review.<sup>86</sup> PWD commonly have an increased risk of having musculoskeletal pain,<sup>22</sup> which may be related to neuropathy, connective tissue disorders,<sup>64</sup> osteoporosis, reduced insulin-like growth factor 1, vasculopathy, obesity, sedentary lifestyle or due to these factors combined.<sup>87</sup> LJM



is associated with microvascular complications of diabetes in patients with T1DM.<sup>81,88,89</sup> In people with T2DM, musculoskeletal pain is especially common.<sup>87</sup> A population-based retrospective cohort study demonstrated a significantly higher 10-year cumulative incidence of musculoskeletal pain in T2DM in both genders and in all age groups compared to controls ( $p < 0.05$ ).<sup>87</sup> The relative risk (RR) for all age groups and genders was  $> 1$  and was increased in females compared to males.<sup>87</sup> Similarly, a previous study also found musculoskeletal pain in patients with T2DM, which was 1.7-2.1 times more than controls.<sup>20</sup> Researchers have suggested that pain can also be due to osteoporosis, which has also been associated with T2DM.<sup>90</sup> An earlier study had also reported that pain in the arms, hands, knees and/or hips and low-back pain had a significant relation with BMI ( $p < 0.005$ ).<sup>20</sup> Impaired QoL, a sedentary lifestyle and reduced physical function ( $p < 0.05$ ) were related with low back pain, which was found less in males compared to females ( $p < 0.001$ ).<sup>20</sup>

### Hyperglycaemia

Several studies have suggested that hyperglycaemia may play a vital role in musculoskeletal disorders and pain.<sup>24</sup> Diabetes causes a disturbance in insulin metabolism that leads to hyperglycaemia, which commonly leads to other complications.<sup>91</sup> Impaired insulin action on target tissues can be a result of faults in insulin secretion and/or decreased tissue responses to insulin, which may cause abnormalities in carbohydrate, fat and protein metabolism.<sup>2</sup> Hyperglycaemia may induce chronic inflammation that can lead to systemic changes in body organs.<sup>92</sup> Studies have reported association of diabetes and hyperglycaemia with OA.<sup>93,94</sup> OA was found to have correlations with inadequate glycaemic control and longer duration of diabetes.<sup>11-13</sup> Moderate hyperglycaemia has been linked with higher uric acid levels in individuals with gout.<sup>95</sup> Chronic hyperglycaemia may also cause impaired growth and susceptibility to certain infections, such as feet and hand infections, in PWD.<sup>2</sup>

### Advanced glycation end-stage products

Advanced glycation end products (AGEs) are harmful compounds and can be produced as a result of hyperglycaemia that can affect cartilage and bone health.<sup>65</sup> A combination of protein or fat with glucose may lead to the formation of AGEs, which are linked with diabetic microvascular complications.<sup>96</sup> AGEs can collect in the joints and surrounding areas, and cause increase the fragility of bones, cartilage stiffness and cause pain.<sup>97</sup> They can alter the structure of proteins and may damage the intracellular and extracellular structural proteins, such as collagen. AGEs may also act through specific receptors. Studies have reported that they can alter cellular functions by attaching to RAGE (receptor for advanced glycation end products) and produce cellular signalling outcomes such as activation of some signalling mechanisms that may cause cell stress, cellular dysfunction and damage.<sup>65</sup>

### Inflammation

Inflammation of a low-grade has been found that exists in diabetes<sup>98</sup> and also in OA.<sup>99</sup> Inflammatory arthritis such as RA and psoriatic arthritis have both been linked with diabetes.<sup>100</sup> In PWD, inflammatory markers are also found, that are also high in people who have inflammatory arthritis.<sup>100</sup> Diabetes may trigger inflammation which causes progressive joint damage, stiffness and pain, such as in RA. A study reported that diabetes was associated with 55% elevated odds of having RA however, in this study RA was reported by 15.1% and 7.6% of the participants with and without diabetes.<sup>101</sup>

In RA, inflammation of joints and other tissues have been associated with nociceptive pain.<sup>102</sup> Inflammation in RA can cause damage to the joints and more inflammation as in RA can increase IR and promote T2DM. Studies have suggested that inflammation may increase the risks of T2DM and OA and may also be a result of dyslipidaemia and visceral obesity.<sup>97,103</sup>

### Connective tissue

Diabetes has major effects on connective tissues, which significantly impacts tendons, ligaments, bones and cartilage.<sup>104</sup> An increased prevalence of connective tissue and musculoskeletal disorders has been observed in PWD.<sup>1</sup> The alterations observed in connective tissue in PWD have suggested that various factors can lead to musculoskeletal pain.<sup>1</sup> The cartilage extracellular matrix can alter due to metabolic abnormalities linked with diabetes.<sup>37</sup> The periarticular and skeletal systems may also get altered due to diabetes.<sup>64</sup> Abnormal deposition of collagen in the periarticular connective tissues can alter the extracellular matrix and cause damage.<sup>10,105</sup> Some studies in animal models of diabetes have shown a decrease in collagen production<sup>58</sup> and increased catabolism of proteoglycans,<sup>106</sup> which supports these findings. Faults related to disturbed glucose metabolism, such as increased non-enzymatic glycosylation of collagen,<sup>107,108</sup> cross-linking of collagen and resistance to enzymatic degradation, increased hydration of collagen<sup>109</sup> and changed collagen synthesis, may contribute to some musculoskeletal disorders and pain in PWD.<sup>65</sup>

### Inflammatory cytokines

Certain pro-inflammatory cytokines such as tumor necrosis factor alpha [TNF- $\alpha$ ], interleukin-6 [IL-6] and interleukin-1 beta (IL-1 $\beta$ ) have been found to be involved in musculoskeletal pain. TNF- $\alpha$ , a pleiotropic cytokine, is known to facilitate pathological conditions such as inflammation, arthritis, IR, immunomodulation, autoimmune diseases and apoptosis.<sup>18</sup> Bone resorption and osteoclastogenesis are increased by TNF- $\alpha$  when the receptor activator of nuclear factor kappa B ligand (RANKL) is present.<sup>18</sup> Inflammatory response is increased by IL-6, which activates the immune system. A number of studies have shown that some immunoregulatory components such as IL-6 and TNF- $\alpha$  are linked in musculoskeletal disorders such as RA, IR and T2DM.<sup>110,111</sup> They play an important role through intracellular pathways of signal transduction for producing cytokines, some enzymes and other inflammatory compounds.<sup>112</sup> The intracellular pathways get activated and causes inflammation and catabolism to increase in joint tissues,<sup>113,114</sup> which causes a loss of metabolic homeostasis.<sup>112</sup> A study reported higher synovitis scores ( $p = 0.024$ ) and a significant increase in the levels of IL-6 ( $p = 0.003$ ) in the synovial fluid of knee joints of PWD, in comparison with patients without diabetes.<sup>115</sup>

### Obesity

In recent years, diabetes and obesity have increased at an alarming rate globally.<sup>7</sup> The risk of T2DM as well as forms of arthritis such as OA, gout and RA may be increased due to obesity.<sup>32</sup> Musculoskeletal pain had an association with raised BMI, decreased quality of life (QoL), lower physical function and being physically active, in a previous study on 940 patients with T2DM.<sup>20</sup> Associations between OA and T2DM have also been found which were linked with the underlying risk factors of obesity and age.<sup>99</sup> In OA, damage to the joints may be due to excess pressure on the joints caused by obesity and joint injury.<sup>29</sup> A higher incidence of RA found in a study was likely to be driven by obesity, comorbidities and lifestyle factors.<sup>116</sup>

Dyslipidemia, hyperuricaemia, obesity and increased levels of serum insulin were found to be increased in patients with DISH compared to controls.<sup>18</sup> An increased production of TNF- $\alpha$ , IL-6, leptin and resistin has been found in obesity, which may contribute to IR.<sup>117</sup> Conversely, there is a decrease in the plasma levels and expression of the insulin-sensitizing effector, adiponectin, in obesity.<sup>117</sup>

## Discussion

This review looked at how diabetes affects musculoskeletal disorders, for a better understanding of the impact it can have on PWD. Musculoskeletal disorders are common in T1DM and T2DM and several studies have reported that PWD have an elevated risk of having musculoskeletal pain.<sup>118</sup> Diabetes has also been associated with elevated odds of OA, RA and osteoporosis.<sup>22</sup> A cross-sectional study reported that long duration of diabetes and dyslipidaemia were associated with raised prevalence of hand abnormalities ( $p=0.017$ ;  $p=0.019$ ).<sup>8</sup> Moreover, an increase was observed in the prevalence of soft tissue hand lesions in both T1DM and T2DM, compared to controls.<sup>73</sup> Researchers have suggested that disorders such as AC may have other complications of diabetes such as LJM, than controls. Changes in connective tissue could be the underlying mechanism that causes disorders such as LJM, DC and AC.<sup>65</sup> Insufficient control of diabetes can damage nerves, muscles and bones and cause musculoskeletal pain over time.<sup>119</sup> In PWD, musculoskeletal pain can occur due to a number of reasons, such as vasculopathy, connective tissue disorders, neuropathy or a combination of them. Neuropathy may be the underlying cause of the increased incidence of musculoskeletal disorders with associated pain in PWD.<sup>65</sup> The harmful effects of hyperglycaemia can cause diabetic neuropathy.<sup>120</sup> Neuropathic joints are complications of diabetes and are commonly found mainly in the foot and ankle of PWD.<sup>121</sup> A number of studies have found that RA has an association with neuropathic pain.<sup>122-124</sup> The pain may also be a consequence of the complications of diabetic polyneuropathy.<sup>22</sup> Neuropathic pain can increase due to central sensitization.<sup>43</sup> Although a study found a significant increase in the prevalence of musculoskeletal pain in patients with T2DM, only a weak correlation was found between the intensity of pain and peripheral inflammation.<sup>29</sup>

Studies have shown that hyperglycaemia can cause cell damage and induce inflammation by various mechanisms. A loss of BMD in PWD may be due to an increase in bone resorption and decrease in bone formation when diabetes is not controlled effectively.<sup>125</sup> Chronic inflammation due to diabetes has been found to lead to RA. An increased risk for diabetes associated with RA was found in a population-based study<sup>126</sup> and another study showed that RA increased the risk for diabetes by about 50%.<sup>51</sup> Pain is frequently considered a marker of inflammation and in patients with RA it may be caused due to joint inflammation or secondary OA.<sup>127</sup> Low-grade inflammation has been found to be associated with diabetes<sup>98</sup> and OA.<sup>99</sup> However, other than inflammation, some studies emphasize that the association between diabetes and OA could be due to AGEs and oxidative stress.<sup>92,127</sup> The accumulation of AGEs may cause musculoskeletal pain in PWD in joints and their surrounding tissues.<sup>117</sup> Hyperglycaemia may also raise the levels of plasma insulin significantly. High levels of insulin or insulin-like growth factors (IGF-1, IGF-2) due to hyperglycaemia, can promote new bone growth or calcification of bones, especially in obese patients with T2DM, which may explain a normal/high BMD found in T2DM patients with hyperinsulinaemia.<sup>65</sup> High levels of insulin and IGF-1 can lead to calcification and ossification of ligaments and areas that are exposed to mechanical stress.<sup>128</sup> Mechanical stress

can cause oxidative damage, as indicated in previous studies.<sup>129</sup> Some studies have found that hyperglycaemia can lead to joint inflammation and cartilage degradation not only through AGEs and oxidative stress, but also inflammatory mediators.<sup>127</sup> A significant synovitis observed in OA may have been due to the increased levels of inflammatory cytokines, prostaglandins and adipokines found in diabetic tissues.<sup>37</sup>

There is evidence that there are links between inflammations, TNF- $\alpha$ , IL-6 and RANKL, which regulates osteoclastogenesis.<sup>19</sup> TNF $\alpha$  stimulates resorption, inhibits the synthesis of proteoglycan in cartilage and inhibits the synthesis of proteoglycans and type II collagen by chondrocytes.<sup>130,131</sup> This may lead to the death of chondrocytes and prevent cartilage regeneration. Increased concentrations of IL-6 ( $p=0.003$ ) found in the synovial fluid of PWD and knee OA was likely to have been the reason for a significant increase in the intensity of pain.<sup>115</sup> In another study, increased hand pain in erosive OA along with worsening of pain was probably due to diabetes and/or synovitis.<sup>23</sup> In contrast, a Finnish self-reported study did not find diabetes to be associated with pain intensity in older males or females.<sup>132</sup> However, they did not measure cytokine levels, and this was a cross-sectional study, a cause-effect relationship cannot be assumed. Moreover, self-reported data may have certain inaccuracies and additionally, the study population was only from one area and therefore the results may not be generalizable to a larger population. Chronic hyperglycaemia may also cause susceptibility to certain infections in PWD, which may be caused due to arterial disease, diabetic neuropathy or obesity.<sup>12</sup> Other than associations with inadequate glycaemic control, raised BMI, age and duration of diabetes, musculoskeletal conditions and pain in diabetes have been found to be associated with reductions in QoL, physical function and being physically active.<sup>20</sup> Pain in the hands, arms, knees, hips and low-back pain have been associated with BMI ( $p<0.005$ ).<sup>20</sup> Studies have confirmed that in RA, diabetes occurred more often with increasing BMI and age.<sup>119</sup>

## Future implications

Future studies are needed to clarify the links between body composition, TNF- $\alpha$ , inflammation, musculoskeletal pain and IR. Studies have indicated that an optimal glycaemic control, control of inflammation and insulin sensitivity may decrease the risk of developing diabetes and musculoskeletal disorders associated with diabetes. Moreover, blockade of TNF- $\alpha$  may improve IR and lipid profiles and additionally, cytokines could be important targets for therapies. An improved understanding of the abnormalities of connective tissue metabolism in diabetes is needed. The underlying mechanisms that underlie diabetic neuropathic pain can lead to new or improved therapies to optimize pain control and may lead to significant improvements in clinical care of PWD.

## Conclusion

In conclusion, musculoskeletal disorders and pain are common in PWD. Diabetes is associated with musculoskeletal disorders like OA, RA, and osteoporosis and fibromyalgia syndrome along with pain. Insufficient glycaemic control can lead to worsening of these disorders in PWD, which clearly needs attention in clinical practice. This review suggests having an increased focus on musculoskeletal disorders in PWD in clinical practice. Early management of musculoskeletal problems in PWD and maintaining good glycaemic control can prevent or improve musculoskeletal disorders, pain, morbidity, mortality and improve QoL. Future studies to understand how diabetes relates with connective tissue metabolism, cytokines

and obesity for better patient care, prevention or management and treatment, are desirable.

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## Conflicts of interest

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