Upper extremity musculoskeletal disorders in patients with type 2 diabetes in general practice

Summary and general discussion

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This dissertation focuses on the awareness among general practitioners (GPs) and nurse practitioners (NPs) of upper extremity musculoskeletal disorders (MSDs) in patients with type 2 diabetes mellitus (T2DM) in general practice, as well as their prevalence, and the diagnoses of those suffering from shoulder pain. This chapter is divided into two parts: first, a summary of the main results is reported, after which these results are discussed in a broader context.

Main results

MSDs are not incorporated in the Dutch T2DM guidelines for GPs as a complication of diabetes mellitus (DM), which means it is possible that GPs are unaware of their association with T2DM. In **chapter 2**, an online survey was conducted among Dutch GPs and NPs to investigate their awareness of the association between MSDs of the upper extremity and T2DM. In addition, opinions regarding the question of who should screen for MSDs of the upper extremity if this is done in the near future were assessed [1]. We found that the majority of GPs and NPs are aware of the common T2DM complications, which they check for during the regular DM check-up in practice. However, most GPs are not aware that MSDs are a T2DM complication, with an unawareness for specific upper extremity disorders ranging from 59% to 73%, nor is 76% of the NPs. When asked to decide which treatment they would start in a patient with T2DM having a carpal tunnel syndrome (CTS), only 41% of GPs advised the most optimal treatment; most of them were experienced GPs. Finally, only 25% of the GPs believed that screening for MSDs of the upper extremity should be performed during the regular T2DM check-up compared to 63% of the NPs. In contrast to NPs, most GPs do not believe that screening for MSDs should be performed during the regular T2DM check-up.

To our best knowledge, prior to this thesis, no studies had been conducted that assessed the prevalence of MSD of the upper extremity in the Netherlands, a country with a well-organized healthcare system including care for patients with T2DM. Therefore, in **chapter 3**, the prevalence of MSDs of the upper extremity was investigated by using two approaches, a questionnaire study among patients with T2DM in general practice and a medical database study representative of the Dutch population (the database of the Research Network Family Medicine of Maastricht University) [2]. In the questionnaire study, 200 patients with T2DM were included who reported a lifetime prevalence of painful upper extremity body sites for at least four weeks of 67.3%. In the database study, 2669 patients with T2DM and 2669

patients without DM were included. MSDs were observed in 16.3% of patients with T2DM compared to 11.2% of patients without DM ($p < 0.001$, OR 1.53, 95% CI 1.31–1.80).

Patients with T2DM have a higher risk of developing shoulder pathology. However, only adhesive capsulitis is addressed in shoulder pain guidelines for GPs as a disorder associated with DM even though patients with T2DM are at risk of having several other shoulder disorders, including focal neuropathy. Therefore, in **chapter 4**, a cross-sectional study was conducted, which included 66 patients with T2DM suffering from shoulder pain who were enrolled in the questionnaire study of chapter 3, to quantify the presence of shoulder disorders using physical exam and musculoskeletal ultrasound (US) imaging [3]. Subacromial pain syndrome was most frequently diagnosed by physical exam (66.6%, 95% CI 51.6–72.0%; $p < 0.0001$), while US imaging showed that subacromial disorders were statistically significantly most prevalent (90.3%, 95% CI 81.9–95.2%), with calcific tendinopathy most commonly observed (80.6%, 95% CI 70.8–87.8%). Only two patients (3%) were diagnosed with neuropathic shoulder pain.

To diagnose neuropathic shoulder pain, only findings from history taking and physical exam were used. It is assumed that in patients with diabetic neuropathy, muscle denervation can result in shoulder disorders. This muscle denervation will lead to changes in muscle architecture as healthy muscle tissue is replaced by fat and fibrosis, which can be assessed by qualitative muscle ultrasound (QMUS). To get a better insight into the question of whether focal diabetic neuropathy is present in patients with T2DM suffering from shoulder pain, a QMUS study was conducted and presented in **chapter 5**. In this cross-sectional study, including the same 66 patients with T2DM who had shoulder pain in chapter 4, the echogenicity of the biceps brachii, deltoid, supra- and infraspinatus muscles was assessed, and compared to 23 patients without DM suffering from shoulder pain. In the painful shoulders of patients with T2DM and those without DM, the mean echogenicity z-score of the four muscles was significantly increased over reference values. Two-thirds of the total number of painful shoulders in patients with T2DM and those without DM had at least one muscle with a z-score exceeding ≥ 2.0. No significant differences between patients with T2DM and those without DM were observed. These findings indicate that patients with painful shoulders seem to have abnormal muscles. The final common pathway that leads to shoulder pain, irrespective of having T2DM, might be muscle denervation. We did not include any assessment to diagnose underlying neurological disorders, as screening for muscle denervation was the main goal of this study.

In this thesis, two different umbrella terms are used for musculoskeletal complaints of the upper extremity in patients with T2DM, MSDs and limited joint mobility (LJM). LJM was

used to describe the variety of shoulder and hand disorders only in chapter 2. The reason for dropping LJM was that it can be misleading as this term is also used for the stiff hand syndrome, also known as cheiroarthropathy, a specific hand disorder in patients with DM [4].

Screening for upper extremity musculoskeletal disorders in patients with type 2 diabetes

Awareness of the association between DM and MSDs

The study in chapter 2 investigated the awareness of GPs and NPs of the association between T2DM and MSDs of the upper extremity using an online survey. It was noticeable that only a few experienced GPs were aware of the association between adhesive capsulitis and T2DM. Those experienced GPs were the ones who chose the correct treatment option in the medical vignette for a case of CTS. Most probably, this knowledge was gained over the years by observing these complaints in clinical practice, where they also found that corticosteroid injections rarely led to glucose level disruption. This unawareness could be explained by the fact the MSDs complications are not mentioned in any (inter)national diabetes guidelines [5-7]. In the literature, it is reported that more than 50% of patients with DM suffer from musculoskeletal pain [8], and patients with T2DM suffer from mobility impairments which might influence their daily living activities [9]. Taking all this into account, screening for MSDs of the upper extremity in patients with T2DM should be considered.

Screening for upper extremity MSDs

It has been suggested that MSDs should be included in the periodic check-ups of patients with T2DM [10]. Currently, all patients with DM are screened for vascular complications as well as nephropathy, retinopathy and neuropathy, but not for MSDs. Interestingly, despite the high prevalence of MSDs in international studies, their evaluation is still not part of national or international diabetes guidelines, like British and Dutch guidelines, and therefore, not incorporated in the regular check-ups in general practice [5, 6]. That is the reason why no screening for MSDs is done in practice.

We define screening in this thesis as a systematic application, during a regular T2DM check-up, of a simple question and brief physical exam to identify patients at risk of having a specific disorder which needs further investigation [11]. More than 50 years ago, Wilson and Jungner developed criteria for screening composed of 10 points that are still upheld today as the "reference standard of screening assessment" [12]. Based in part on the results

from this thesis and the fact that the Wilson and Jungner criteria are applicable, it seems advisable to start screening for MSDs of the upper extremity. A brief overview of these points, discussing some in conjunction, and how they fit for MSDs is given below.

Are MSDs an important health problem?

The study presented in chapter 3 that investigated the prevalence of MSDs showed that upper extremity MSDs have a high prevalence in Dutch patients with T2DM presenting in general practice in the Netherlands. In the database study, MSDs were prevalent in patients with T2DM, and their prevalence was statistically significant compared to patients without DM. In the questionnaire study, we found that upper extremity MSDs have a high prevalence in patients with T2DM presenting in general practice. The prevalence ranged from 16% based on GP registered disorders and complaints, to 67% based on self-reported diagnosis and pain. When MSDs of the upper extremity are not recognized and are causing pain, this will lead to a more inactive lifestyle or might progress to disability, which will negatively influence self-control. This may lead to an earlier development of other DM complications and reduce the patient's quality of life [10, 13]. On the other hand, it can aggravate MSD, creating a vicious circle. That is why it is important to screen for MSDs in patients with T2DM specially if they are suffering from pain [4, 14]. Stiff hand syndrome in particular, is reported to be associated with an incidence of hospitalization with infection and a useful indicator to assess the risk of hospitalization in patients with T2DM [15]. Early detection and treatment of these disorders may play a role in preventing the development of chronic MSDs and thus decrease its burden.

Are the natural history and pathophysiology of MSDs in patients with DM adequately understood?

In the general population, most MSDs have an unfavorable natural course; this has not been specifically studied in people with DM [16, 17]. Yet the pathophysiological mechanism of MSDs in patients with DM is still not fully understood, but mainly seems related to advanced glycation end-products (AGEs); the evidence suggests that in patients with DM, there is an increased accumulation of AGEs [18, 19]. AGEs are formed by the non-enzymatic condensation of metabolic intermediates and glucose, and this process is increased or stimulated in chronic hyperglycemia. A key characteristic of this event is the construction of covalent cross-links within collagen fibres. Furthermore, AGEs also attract inflammatory cells like macrophages and monocytes, releasing cytokines leading to a pro-inflammatory state. It is hypothesized that these collagen disturbances and low-grade inflammation are responsible for damaging joint capsules, tendons and nerves [19-22]. Remarkably, AGEs are also believed to play a role in vascular complications [23].

Are the symptoms recognizable, easily tested and acceptable to the population?

Symptoms of all types of MSDs of the upper extremity are recognizable; they usually start with pain followed by stiffness. Asking for these symptoms is easy. In the Netherlands, T2DM is mainly managed in primary care, and care groups have been established to provide this care. Care groups consist of groups of associated care providers, often exclusively GPs, who are responsible for coordinating and ensuring the delivery of care for patients with T2DM [24, 25]. In practice, GPs delegate most T2DM care to NPs, who are often employed by these care groups [24]. This T2DM care is delivered in conformity with the Dutch Diabetes Federation Health Care and guidelines of the Dutch College of General Practitioners (DM guidelines) [26, 27]. During periodic T2DM check-ups, GPs and NPs together closely monitor blood glucose levels and related complications of patients with T2DM. Including MSDs of upper extremity screening in the periodic health checks with, for example, a question about musculoskeletal pain followed by a brief physical exam of the hands performed by the NP seems acceptable to the DM population. In a hospital-based study performed in Japan, concerning the association with MSD of the hand in patients with T2DM, MSD of the hand was significantly associated with the hospitalization [15]. The authors concluded that a brief physical exam of the hands to check for the presence of a positive tabletop sign or prayer sign as a manifestation of a stiff hand syndrome (also known as LJM or cheiroarthropathy) might be useful in assessing the risk of hospitalization for these patients.

One section of our survey questionnaire included MSD screening of upper extremity in patients with T2DM. Unlike the GPs, most NPs thought screening should be incorporated in the annual check-up during T2DM care visits. One of the possible reasons for this discrepancy is that NPs spend more time with the patients during these checks. Another explanation could be that GPs question the prevalence and severity of MSDs compared to other harmful complications like cardiovascular disorders and nephropathy. Also, they may believe the prevalence of MSD of upper extremity is rather low, so that screening for it would not be cost-effective. To get a better insight into the difference in opinions of GPs and NPs, and to evaluate the GPs' reasons for not being interested in screening for MSDs, one option for future research would be a qualitative study with interviews or focus groups with GPs and NPs. Consensus has to be reached on who should perform this screening. If the guideline committees recommend screening for MSDs, NPs could be good the appropriate profession to start to perform screening.

Are there acceptable treatments and facilities available to diagnose MSDs of the upper extremity?

Treatments that are non-invasive and not harmful are available for all MSDs including a better control of glucose levels and corticosteroid injections for specific MSDs, as well as physiotherapy of the hand or shoulder [4]. All these treatments can be initiated and performed in primary care.

What about the cost effectiveness for MSDs of upper extremity screening?

Costs seem low for the above explained approach, since periodic check-ups are part of regular care and asking questions and physical exam is cheap, as this only requires limited time. According to the Dutch guidelines, additional imaging is normally not required in early phases of MSDs [16, 17]. Also, corticosteroid injections and physiotherapy treatment are rather cheap interventions. However, policy makers might insist on a cost-effectiveness study before implementing this screening [28].

Could MSDs of upper extremity screening be a continuing process?

The screening can be easily implemented annually in the routine check-up and followed up annually for each patient with T2DM. This creates a continuous process of screening for every patient. The overall conclusion when using the criteria of Wilson and Jungner that it seems possible and feasible to screen for MSDs although the economic evaluation is not yet done [4].

Is screening for MSDs of upper extremity advisable in Saudi Arabia?

Two MSD prevalence studies were conducted in Saudi Arabia, with one being retrospectively performed in all National Guard Hospitals and primary health clinics in the Kingdom, using the patients' medical data from electronic files [29]. The data came from all registered diagnoses of MSDs that were entered as "visit diagnosis" of all patients with T2DM between 2015 and 2019. The second study was a hospital-based study that evaluated patients with DM presenting in the Endocrinology clinic and diagnosed with MSD, by a physical exam during a one-year period between 2010 and 2011 [30]. The highest prevalences reported in the medical data study were for osteoarthritis of the upper extremity (4.8%), followed by CTS (10%) and trigger finger (7.2%). In the hospital-based study, the highest prevalence was reported for CTS and adhesive capsulitis (6.7% each). When comparing these numbers to our two studies presented in chapter 3, it is most noticeable that these disorders were less prevalent in the Research Network Family Medicine (RNFM) database study and our questionnaire study. From the two studies in Saudi Arabia, it is concluded that MSDs are also prevalent in Saudi Arabia.

The primary care system in Saudi Arabia provides sufficient medical care and plays a relevant role in the prevention and management of health conditions. Patients are referred to secondary care when more complex care is needed. DM care usually takes place in primary care, and nurses and GPs screen for known DM complications using a set form for each patient. Therefore, also in Saudi Arabia it seems possible and feasible to implement screening in the routine check-ups for the early detection of these disorders in patients with T2DM.

Diagnosing shoulder pain

As shoulder disorders are the most prevalent upper extremity MSD, chapter 4 focused more on the shoulder diagnosis using physical exam and US imaging. Dutch GPs are advised to start with a non-specific diagnosis based on history taking and a physical exam, and proceed to a specific diagnosis using US imaging when symptoms persist [17]. The two most important outcomes presented in chapter 4 were: the subacromial region is most frequently affected in patients with T2DM suffering from shoulder pain, and instead of adhesive capsulitis, which is believed to be frequently diagnosed in patients with T2DM suffering from shoulder pain [17, 31, 32], calcific tendinopathy, a subacromial pain disorder, was the most commonly observed specific shoulder disorder present.

Diagnosis based on physical exam

The most frequently diagnosed disorder found by physical exam was the subacromial pain syndrome (SAPS). To establish shoulder disorders based on physical exam, we used the diagnostic criteria described in the shoulder pain guidelines of the Dutch College of General Practitioners prevailing at the time of conducting the study [33]. In this guideline, three diagnostic groups are distinguished, all three included in our study by using a mutually exclusive method: a glenohumeral disorder defined by an external rotation range of motion of less than 45 degrees; SAPS defined by either a painful abduction with or without a limited range of motion during abduction, or positive Hawkins–Kennedy and Neer tests. And finally, "other disorder" defined as not being either of the two previous disorders. It is notable that the Hawkins-Kennedy and Neer tests are not incorporated in the guidelines. Although debatable, we added them because the clinical performance of single tests is limited [34, 35]. In our analysis, when both tests were positive, we considered it an indication of SAPS. The "other disorder" group contains several diagnoses such as acromioclavicular (AC) disorders and shoulder instability. Recently, a revised version of the guidelines was published [17], in which palpation of the AC joint was added to the

physical exam. Unfortunately, diagnosing AC disorders by physical exam was not possible in our study. However, the US exams showed that AC osteoarthritis was present in almost 6 out of 10 patients. Therefore, it is possible that patients with AC disorders are hidden in the SAPS or "other disorder" group. AC disorders can mimic findings of SAPS, like a painful abduction. Moreover, it is reported in some cases of SAPS that the origin of the pain is underlying pathology of the AC joint [36]. However, it is not known if all these US observed AC disorders were symptomatic.

Diagnosis based on musculoskeletal ultrasound imaging

In this thesis (chapter 4), US imaging was used to diagnose specific shoulder disorders [37]. It was found that subacromial disorders were diagnosed most frequently in both symptomatic and asymptomatic shoulders (90% and 77%, respectively). It is known that asymptomatic shoulder pathology is common, e.g. calcific tendinopathy and rotator cuff tears [38, 39]. Therefore, it is important to consider the US findings in the clinical context to avoid unnecessary treatment of asymptomatic disorders or targeting the wrong disorders when multiple disorders are present. In symptomatic shoulders, rotator cuff disorders (90.3%) were most frequently observed, while calcific tendinopathy was present in 4 out of 5 patients.

Two other US imaging studies conducted in general practice in the Netherlands also showed that calcific tendinopathy was the most prevalent disorder, with percentages ranging from 29% to 50% [38, 39]. The pathophysiological pathway might be the reason why the prevalence of calcific tendinopathy is higher in patients with T2DM [40]. Although the exact pathophysiology of tendon disorders in patients with DM remains uncertain, there is evidence that abnormal tendon collagen disposition alters the structural matrix and the mechanical properties of the tendons [41]. Through this process, the continuum of tendon pathology might be initiated, in which a normal tendon changes into a degenerative tendon (called tendinopathy, for which different stages are described) and can ultimately tear [42]. Part of this process seems reversible through healing responses, but in patients with DM and other endocrine disorders, this healing process can fail; calcium deposits then arise due to a mechanism that has not yet been elucidated [40].

Diabetic neuropathy

Diabetic neuropathy is the most prevalent complication of DM and affects approximately 50% of all patients with DM [43]. This heterogeneous group of conditions affects somatic and autonomic nerves and presents with diverse clinical forms [44]. The American Diabetic Association advises classifying neuropathy in patients with DM as either diffuse neuropathy

(e.g. distal symmetric polyneuropathy), mononeuropathy or (poly)radiculopathy [44]. Distal symmetric polyneuropathy is the most studied and prevalent presentation in patients with DM [44]. Diabetic radiculoplexus neuropathy, also known as diabetic amyotrophy, has been mainly observed in the proximal thigh nerves (femoral, sciatic, and obturator nerves and lumbosacral plexus) [45], and those patients typically have T2DM [46]. Involvement of the brachial plexus or nerves innervating the shoulder muscles is considered rare [47-49].

This seems confirmed in the study presented in chapter 4, with only 3% (two patients) of the patients with T2DM suffering from shoulder pain being diagnosed with neuropathic shoulder pain. It is remarkable that these two patients were also diagnosed with distal symmetric polyneuropathy and did not have a glenohumeral disorder based on physical exam, or adhesive capsulitis based on US imaging findings. Any form of polyneuropathy (clinical or subclinical) was most prevalent in patients diagnosed with a glenohumeral disorders. We do know that diabetic neuropathy increases the risk of developing adhesive capsulitis of the shoulder, a glenohumeral disorder [50]. Overall, the prevalence of polyneuropathy ranged from 39% to 56% depending on the clinical level. This is broadly consistent with a cross-sectional study performed in a hospital showing that 38% of patients with T2DM and musculoskeletal disorders had polyneuropathy [50].

To diagnose neuropathic shoulder pain, we used both parts of the DN4 questionnaire: history taking and physical exam. Currently, another validated questionnaire is available in Dutch to diagnose neuropathic shoulder pain: the modified painDETECT (REF). A Dutch study performed in an Orthopedic surgery outpatient clinic evaluated the modified painDETECT in patients with SAPS, and concluded that it is valid for distinguishing neuropathic pain from nociceptive shoulder pain. A UK study using the painDETECT showed that central sensitization, which is an augmented pain transmission, is present in a proportion of patients with shoulder pain and impingement [51].

There is an overlap between the questions from the painDETECT and DN4 questionnaire, but there are also differences. An important difference is that the painDETECT asks for more details about the nature of the pain, i.e. radiating pain [52]. Although the question about radiating pain is covered by us through assessing this during the physical exam of the neck, the additional questions would give us more insight into the nature of the pain. During our research period, the painDETECT was not yet available in Dutch.

Identifying patients with neuropathic shoulder pain helps in choosing the optimal and effective treatment. For example, patients with SAPS and neuropathic pain might benefit more from treatment targeted to the neuropathic pain [52]. This seems important especially in patients with T2DM, as shoulder pain might negatively influence physical activity, which

is considered to be the cornerstone of DM treatment. Therefore, inadequate treatment of shoulder pain might negatively influence DM treatment, eventually leading to the above mentioned vicious circle [10, 13].

Muscle denervation in shoulder disorders

In chapter 4, we used only the DN4 questionnaire to test for neuropathic pain and concluded that neuropathic shoulder pain seems rare in patients with T2DM. It is known that the reference diagnostic test to assess neuropathy involves nerve conduction studies. However, QMUS is considered a reliable alternative and has the advantage of being non-invasive [53]. Therefore, it is used in chapter 5 of this thesis to assess whether shoulder pain in T2DM might be caused by neuropathy.

It has been postulated that in patients with diabetic neuropathy, muscle denervation results in shoulder disorders [45]. Muscle denervation will lead to changes in muscle architecture as healthy muscle fibres become atrophied and muscle tissue is replaced by fat and fibrosis. These changes are visible on ultrasound [54] as a brighter appearance of the muscle on the screen, known as a higher muscle echogenicity. QMUS is a reliable and patient-friendly ultrasound technique to assess changes in echogenicity. These changes, resulting from neurological denervation, have been studied successfully with QMUS [55]. Gray-scale analysis has been developed and validated clinically to optimize sensitivity. It requires minimal training and increases diagnostic sensitivity to 92% [53, 55]. Therefore, it can be used as a screening tool for the presence of neuromuscular disorders [56]. While normal musculoskeletal US imaging is highly dependent on the radiologist and the interpretation is subjective, quantified analysis is more objective and less observer-dependent. By using a constant standardized muscle ultrasound protocol, an influence of the ultrasound system setting can be ruled out [57].

In chapter 5, the same patients with T2DM who had a painful shoulder in chapter 4 underwent QMUS of the supraspinatus, infraspinatus, deltoid, and biceps muscle of both shoulders. Patients without DM were also included in this study, as insulin resistance is positively associated with increased intermuscular adipose tissue in muscles [58], and we did not want to include two possible etiological factors for increased echogenicity. Healthy participants were used to establish reference values. We found that in painful shoulders of patients with T2DM and those without, the mean echogenicity z-score of the four investigated muscles was significantly increased compared to the reference values. Interestingly, the mean echogenicity values in patients with T2DM were higher than in patients without DM, yet did not achieve statistical significance, which might be explained

by a low sample size of patients without DM. Also, patients with T2DM tend to have abnormally high z-scores (≥ 2) more frequently compared to patients without DM, but still this was not statistically significant. In chapter 4, it was reported that subacromial pain disorders are the most frequently observed disorders in patients with T2DM suffering from shoulder pain, and only 3% of all patients had neuropathic shoulder pain [3]. These results were based on findings from a physical exam only. The results presented in chapter 5 indicate that muscle denervation, as a sign of neuropathy, is present in many patients. In painful shoulders of patients with T2DM, 64.5% had at least one muscle with an abnormal high z-score as did 69.2% of patients without DM. The final common pathway that leads to shoulder pain, irrespective of having T2DM, might be muscle denervation.

In this thesis, we did not include any assessment to diagnose underlying neurological disorders. Any disorder originating from the central nervous system to the peripheral nerves can cause muscle denervation. The differential diagnosis could include focal motor neuron atrophy, cervical radiculopathy, brachial plexus lesions, focal entrapment neuropathy (e.g. of the suprascapular nerve), or infarction of the peripheral nerves.

QMUS is a highly reliable method and sensitive for detecting neuromuscular disorders [53]. It was thought that the fatty degeneration of muscles increases with age and weight [59], yet in this study the observed increased mean echogenicity is unlikely to be due to age or obesity, since the calculated echogenicity was corrected for age and BMI. The mechanism behind fatty degeneration of the supra- and infraspinatus muscles due to tendon tears is not well known. Mean echogenicity values were corrected for rotator cuff tendon tears in this study, and there did not seem to be any association between them.

One of the challenging points for using QMUS in daily practice is that it is very time consuming to establish reference values for every ultrasound machine. Also, muscle ultrasound is not yet part of the neuromuscular teaching curricula, yet an international consensus-based guideline statement for neuromuscular ultrasound was recently published to help in establishing a core curriculum [60].

This problem can be avoided by using qualitative muscle ultrasound to get an indication of the diseased shoulder muscles. The visual evaluation using a four-point visual grading Heckmatt scale seems an option for this qualitative analysis. In this scale, the muscles' gray-scale level is compared to that of the overlying subcutaneous fat layer. The sensitivity is around 71%–76%, depending on the subject and the observer's experience [53]. A promising study performed in the USA of patients with muscle spasticity, in which they compared the Heckmatt scale with quantitative gray-scale analysis, concluded that there is a good correlation between both methods, indicating a high validity [61]. Therefore, for

the near future it might be feasible to investigate the inter-rater reliability for using the Heckmatt scale in order to implement it in practice.

Distal symmetric polyneuropathy was significantly associated with increased echogenicity z-scores of all muscles except for the infraspinatus muscle only in patients with T2DM. This may indicate that the cause of muscle denervation in patients with T2DM is systematic in nature, which might lead to abnormal muscle functions and ultimately result in shoulder disorders. The high number of patients with T2DM with bilateral shoulder pain seems to support this idea. Looking at the results presented in chapters 4 and 5, as both studies included the same patients, there may be a causal relationship between muscle denervation and the diagnoses found by physical exam and US imaging. In other word, an ongoing muscle denervation in the muscles of the shoulder might lead to abnormal muscle movement, and other muscles of the shoulder girdle may start to compensate the influence of denervation, causing tension in different parts, e.g. tendons or bursa, which might eventually result in subacromial disorders, which are the most frequently observed disorders.

Recruitment of patients with T2DM and other limitations of the thesis studies

Recruitment of patients

During the recruitment of patients for the study presented in chapter 3, several obstacles were encountered. For the questionnaire study, we aimed to include 900 patients. Over a period of four months, consecutive patients with T2DM were asked by NPs during their routine check-up visit to participate in our study and fill in a questionnaire addressing MSDs. During these four months, we realised we needed to increase the recruitment by matter of other methods, because the total number of patients participating fell short of expectations; Finally, this strategy yielded 182 patients with T2DM. Therefore, we placed an announcement to recruit participants in the national diabetes magazine (Diabc); this yielded 18 more patients. This total of 200 patients was far below expectation. No formal evaluation of the reasons for the lack of inclusion has been carried out. However, NPs told us that they often did not get around to recruiting patients due to busyness. Although this study was carried out with the consent of the Meditta diabetes care group, there were also GPs who did not give their NPs permission to make time for this.

Of the 200 patients from the questionnaire study, 38 met the inclusion criteria for the studies presented in chapters 4 and 5. In order to increase this number participating, we distributed flyers and posters to general practices and physiotherapy centers in the Meditta

region, inviting patients with T2DM suffering from shoulder pain to participate in the study. This yielded 27 more patients. Additionally, we placed an announcement on the national diabetes association website (Diabetesvereniging Nederland, DVN), which yielded only one patient more.

Other limitations of the thesis studies

There are few limitations of the studies in this thesis that can be addressed. In chapter 3, each of the two prevalence studies had different study methods; a medical database and questionnaire approach. There might be an underestimation in the database of the real prevalence, while in the questionnaire approach there might be an overestimation. The medical database study only contained data of people with DM who sought medical attention for their MSDs, so only the registered MSDs. On the other hand, patients with T2DM suffering from pain might be more eager to participate in the questionnaire study; in this approach, half of the patients reported experiencing pain at the time of filling in the questionnaire. The prevalence results presented in chapter 3 are therefore composed of registered (database study) and non-registered MSDs (questionnaire study).

Patients from the questionnaire study were invited to participate in the next study in chapter 4, but the total number of participants remained small. A larger number in this study would have resulted in narrower 95% confidence intervals. In this study the US diagnostic criteria for glenohumeral disorders such as adhesive capsulitis were questioned as more features are mentioned in the literature, e.g. thickening of the coracohumeral ligament and restriction of external rotation on dynamic scanning [62]. These features are not detected during scanning positions according to the standardized protocol of the European Society of Musculoskeletal Radiology. For practical purposes, we did not incorporate the additional scanning positions necessary to detect these features. This may have introduced an underestimation of the presence of adhesive capsulitis. Last but not least, in the final study, presented in chapter 5, a selection bias might have been developed from our recruitment strategies (invitation from the questionnaire study), which might have hampered the generalizability of the study results to the entire population of patients with T2DM having shoulder pain. It is possible that patients with higher pain levels or a longer duration of pain might be even more eager to participate, which might be an indication of more severe shoulder pathology. This could explain why the mean echogenicity that we found was higher compared to healthy participants and the majority of patients has at least one abnormal z-score.

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