ABSTRACT
There is an unmet need in achieving better pain management to improve quality of life in diabetics. Acute pain, chronic pain and painful diabetic neuropathy (PDN) are very frequently reported by diabetics along with anger and frustration related to pain. Diabetes is also associated with widespread symptoms and complications related to joint health and there is a strong link between the two conditions. However, neuropathy is often neglected in diabetics as glucose and metabolic control always gains priority. It is very important to categorize the type of pain in diabetics and detailed history taking along with bedside examination are really crucial. Appropriate assessment is also necessary to determine if it requires immediate management or referral. Pain scales are very helpful to assess pain intensity and guide treatment selection and adjustment. Key goals of pain management include reduced pain and improved function with minimum acceptable side effects. Patients with severe or disabling pain requiring opioids may require referral to a specialist. Paracetamol should be the first-line analgesic agent for management of chronic pain due to its favorable side effect and safety profile. Non-steroidal anti-inflammatory drugs (NSAIDs) are however superior to paracetamol (combining both however increases efficacy) and COX-2 inhibitors (coxibs) offer safety advantages over non-selective NSAIDs. Non-opioid analgesics complement opioid analgesics for multimodal analgesia. Treatment of PDN necessitates use of specific therapeutic agents e.g. alpha-2-delta ligands (pregabalin, gabapentin), tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors.

Keywords:
Acute Pain; Chronic Pain; Painful Diabetic Neuropathy; Charcot's Joint; Diabetes Care

INTRODUCTION
Pain is one of the vital signs in clinical assessments and is a major determinant of poor health-related quality of life (HRQoL). Pain is however considered secondary to risk-factor control in chronic disease, such as in diabetes.

Although diabetes does not directly result in pain, its treatments and complications do inflict pain. There is an unmet need in achieving better pain management to improve HRQoL in diabetics. In Singapore, pain/discomfort is frequently reported by diabetics in primary-care settings. Pain/discomfort was the most common complaint among the five Euroqol 5-D domains (reported by 28.0% of the respondents) in a cross-sectional survey in adult diabetes patients under primary care in Singapore.1 In the Northern California ‘Diabetes & Aging Study’2 involving 13,171 adults with type 2 diabetes, acute pain, chronic pain, and painful neuropathy were reported by 41.8 percent, 39.7 percent, and 23.7 percent of diabetics, respectively.

TYPES AND CATEGORIES OF PAIN
If pain persists or recurs for longer than 3 months, it is termed as “chronic pain”. Such pain often becomes the sole or predominant clinical problem in some patients. Chronic pain is a frequent condition, affecting an estimated 20 percent of people worldwide and accounts for nearly one-fifth of physician visits. Patients with chronic primary pain often report pain-related disability, increased depressed and anxious mood, as well as anger and frustration. There are also two distinct categories of pain — nociceptive and neuropathic pain. Nociceptive pain is caused by an inflammatory response to an overt tissue-damaging stimulus. Neuropathic pain is initiated or caused by a primary lesion or dysfunction in the peripheral or central nervous system. Neuropathic pain is a clinical entity and often described as shooting, electric shock-like, burning — commonly associated with tingling or numbness. The painful region may not necessarily be the same as the site of injury. Pain occurs in the neurological territory of the affected structure (nerve, root, spinal cord, brain). It is almost always associated with a chronic condition (e.g. post-herpetic neuralgia, post-stroke pain, diabetic neuropathy, and responds poorly to conventional analgesics. Co-existence of nociceptive and neuropathic pain is termed as mixed pain. Examples of co-existing mixed pain include herniated disc (causing low back pain) and lumbar radicular pain. Effective management requires a broader therapeutic approach to relieve both the nociceptive and neuropathic pain components.

Appropriate assessment of patients presenting with pain is crucial in order to determine whether they are suffering from a condition that requires immediate management or referral. It can also help ensure optimal treatment of pain through identification of the underlying cause of the pain and recognition of the pathophysiologic mechanism behind the pain, which can help guide treatment selection. Finally, determining baseline pain intensity enables future assessment of treatment efficacy in order to guide titration and modification of the analgesic regimen.
EXAMINING A DIABETIC PATIENT WITH PAIN: TAKING A PAIN HISTORY

- Question the patient about his/her pain\textsuperscript{12-13}
  - Duration
  - Frequency
  - Quality
  - Intensity
  - Site of pain
    - a primary location: description ± body map diagram
    - radiation
- Be alert and ask for common verbal descriptors of neuropathic pain (e.g., tingling, electric shock-like, numbness, burning, shooting)\textsuperscript{12-14}
- Use analogue or numerical scales to quantify the pain\textsuperscript{15}
- Associated symptoms (e.g., nausea)\textsuperscript{13}
- Treatment received thus far:\textsuperscript{13}
  - Current and previous medications, including dose, frequency of use, efficacy and side effects
- Relevant medical history\textsuperscript{15}
  - Prior or coexisting pain conditions and treatment outcomes
  - Prior or coexisting medical conditions
- Factors influencing symptomatic treatment\textsuperscript{13}

Various pain scales\textsuperscript{16,17} have been developed to help assess pain intensity, which can help guide treatment selection and adjustment. “Simple Descriptive Pain Intensity Scale”, “0–10 Numeric Pain Intensity Scale” and “Faces Pain Scale — Revised” are 3 of the most common pain intensity scales. The selection of which scale to use may depend on the literacy, numeracy, and cognitive abilities of the patient. For instance, the more visual “Faces Pain Scale” may be the most useful in young children, especially those under 3 years of age, or in elderly patients suffering from cognitive decline.

Bedside examination of a diabetic patient with pain is aimed at identifying altered sensation in the painful area, and so responses should be compared with a non-painful or adjacent area. A painful response to lightly stroking the skin with a finger or cotton wool is a sign of allodynia, a common characteristic of neuropathic pain.\textsuperscript{12} Numbness (hypoalgesia) or an exaggerated painful response (hyperalgesia) to pinprick testing with a monofilament or sharp object confirms an altered pinprick threshold. Inability to distinguish warm from cold objects suggests an altered thermal threshold. A combination of characteristic painful symptoms in an area of altered sensation on bedside testing is usually enough to make a diagnosis of neuropathic pain.\textsuperscript{14,15} In diabetic neuropathy, there is usually a symmetrical sensory loss to all modalities in a stocking distribution on clinical examination. In severe cases, this may extend well above the ankle and also involve the hands. The ankle reflexes are usually reduced or absent, and the knee reflexes may also be absent in some cases. Motor weakness is unusual, although small muscle wasting in the feet and also the hands may also be seen in more advanced cases. Any pronounced motor signs should raise the possibility of a nondiabetic aetiology of the neuropathy, especially if asymmetrical.\textsuperscript{18}

GOALS IN PAIN MANAGEMENT

It is important to discuss and agree on realistic treatment goals before starting a treatment plan.\textsuperscript{14} In cases of neuropathic pain, for example, total pain relief is usually an unrealistic goal and will result in frustration for both patient and doctor. A reduction in pain of about 50 percent is more realistic, and is clinically important to patients.\textsuperscript{19} Sometimes to achieve greater pain relief, there may be increased side effects related with its treatment. With this in mind, patients’ expectation is moderated for reduced pain and improved function with minimum acceptable side effects as a goal of pain management.

Acute and Chronic Pain Management

Patients presenting with acute pain should be evaluated by obtaining a medical history and performing a physical examination. Factors that may influence choice and dose of analgesic should be evaluated, including comorbid medical conditions or laboratory anomalies and current medications with potential for drug interactions. Patients with severe or disabling pain requiring opioids may require referral to a specialist for treatment.\textsuperscript{20} Other patients should be treated with appropriate analgesics and educated about doses, expected time to response, possible side effects, etc. Clinicians should also stress the benefits of behavioural interventions such as exercise and relaxation. The presence of anxiety and/or depression should be evaluated and these conditions should be treated as necessary. Finally, pain severity and functional impairment should be re-assessed at regular intervals and the treatment adjusted based on assessment of response. Transcutaneous electrical nerve stimulation and acupuncture may be of benefit in some acute pain settings. Evidence regarding the benefits of massage, manual therapy, and heat and cold therapy is limited.\textsuperscript{15} There is a step-wise approach to the treatment of recurrent persistent pain in DM patients. Apart from medications, there are more advanced modalities of pain management such as spinal cord stimulation, nerve ablation and modulation, and intrathecal drug delivery system.

The overall concept underlying acute pain relief is multimodal or “balanced” analgesia, that is, the use of combinations of analgesics or analgesic techniques with different modes or sites of action. Acute pain model rests on the reduction of inflammatory mediators by rest, elevation, ice, and anti-inflammatory medication. There is good evidence to support the use of non-opioid analgesics to complement opioid analgesics for multimodal analgesia; non-steroidal anti-inflammatory drugs (NSAIDs) are superior to paracetamol (and combining both increases efficacy), and COX-2 inhibitors (coxibs) offer safety advantages over non-selective NSAIDs, in particular with regard to platelet dysfunction leading to blood loss.\textsuperscript{21} Opioids remain an adjunct component of systemic analgesia for the relief of severe pain despite the multiple opioid-sparing approaches.\textsuperscript{21} The use of opioids in pain management can be associated with a variety of adverse effects. Gastrointestinal side effects can include nausea, vomiting and constipation, while central nervous system effects may include cognitive impairment, sedation, lightheadedness, and dizziness. Respiratory depression, orthostatic hypotension, fainting, urticaria, miosis, sweating and urinary retention are among the other potential adverse effects of...
Paracetamol (acetaminophen) should be the first-line analgesic agent for management of chronic pain due to its favourable side effect and safety profile, however it is less effective in pain relief than anti-inflammatory drugs. NSAIDs are very effective drugs, but their use is associated with kidney, CV, skin, and GI side effects. Proton pump inhibitors (PPIs) are unable to prevent NSAID-associated lower GI damage and celecoxib significantly reduces toxicity in the lower GI tract. COX-2 selective NSAIDs and ns-NSAIDs have a similar incidence of CV adverse effects, with molecule-specific quantitative differences between the various drugs. Naproxen appears to be the least harmful, but this advantage has to be weighed against GI toxicity. Celecoxib is associated with fewer adverse events throughout the entire GI tract compared to ns-NSAIDs. International NSAID Consensus Group has provided some recommendations for safe prescribing of NSAIDs for chronic uses depending on CV and GI risk status of patients:

Patients with the following:
- Low GI and CV risks: any ns-NSAID;
- Low GI and high CV risk: naproxen may be preferred or celecoxib at the lowest approved dose (200 mg once daily) may also be acceptable;
- High GI risk and low CV risk: Celecoxib±PPI; or
- High GI and CV risks: avoid NSAID therapy, if possible, or low-dose celecoxib±PPI.

**Treatment of Painful Diabetic Neuropathy (PDN)**

Good glycaemic control is the first priority for both prevention and management of PDN. However, even with good glycaemic control, up to 20 percent of patients will develop PDN. Treatment of PDN therefore necessitates use of therapeutic agents specific to neuropathic pain, such as alpha-2-delta ligands (pregabalin, gabapentin), tricyclic antidepressants (TCAs), and serotonin-norepinephrine reuptake inhibitors (SNRIs). Given their presumed safety, non-pharmacological treatments should be considered whenever appropriate. In general, non-pharmacological treatment is complementary to drug therapy. Non-pharmacological treatment options include: physiotherapy, pain management programmes, acupuncture, and transcutaneous electrical nerve stimulation (TENS).

European Federation of Neurological Societies (EFNS) guidelines on pharmacological treatment of neuropathic pain recommend tricyclic antidepressants (TCAs), gabapentin, and pregabalin as first-line agents for most neuropathic pain conditions. The serotonin-norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine are also recommended as first-line agents for painful diabetic polyneuropathy (DPN). Second-line treatments include tramadol and strong opioids.

**MUSCULOSKELETAL DISORDERS IN DIABETES MELLITUS**

Diabetes and joint pain are considered to be independent conditions. Joint pain is usually a response to an illness, injury, or arthritis. Diabetes is associated with widespread symptoms and complications to joint health. According to the Centers for Disease Control and Prevention (Arthritis Program November 2016), 47 percent of people with arthritis also have diabetes. There is an undeniably strong link between the two conditions. These include stiff hand syndrome, Dupuytren’s contracture, trigger finger, frozen shoulder (adhesive capsulitis), calcific periartthritis of the shoulder, carpal tunnel syndrome, muscular infarction, diffuse idiopathic skeletal hyperostosis (DISH), and Charcot’s arthropathy. In addition, a higher prevalence of crystal arthropitides, infections, osteoporosis, and osteoarthritis has been reported. Biochemical abnormalities seem to be related to some of these complications: increase in the non-enzymatic glycosylation of collagen fibres and collagen crosslinking; increase in the hydration mediated by aldolase reductase pathway; and in the formation of advanced glycosylation end products (AGEs).

The pain of diabetic arthropathy, unlike pain caused by immediate trauma, happens over time. The greatest concern regarding diabetic joints would be Charcot’s joint. Charcot’s joint occurs when diabetic nerve damage causes a joint to break down. Also called neuropathic arthropathy, this condition is seen in the feet and ankles of people with diabetes. Nerve damage in the feet is common in diabetes, which may lead to Charcot’s joint. A loss of nerve function leads to numbness. Patients who walk on numb feet are more likely to twist and injure ligaments without knowing it. This places pressure on the joints, which can eventually cause them to wear down. Severe damage leads to deformities in the foot and other affected joints.

Bone deformities in Charcot’s joint may be prevented through early intervention. Signs of the condition include: painful joints, swelling or redness, numbness, an area that is hot to the touch and changes in the appearance of the feet. Once we suspect Charcot’s joint, it is important to limit use of the affected areas to prevent bone deformities by wearing orthotics for additional support.

The shoulder is one of the frequently affected sites and one of the common rheumatic conditions caused by diabetes is frozen shoulder, characterised by pain and severe limited range of motion. This disorder is a clinical diagnosis. Osteoarthritis being the most common rheumatic condition is an important differential diagnosis. There are many risk factors for shoulder osteoarthritis, including age, genetics, sex, weight, joint...
infection, history of shoulder dislocation, and previous injury, in older-age patients. Obesity could be a common factor to diabetes and osteoarthritis. However, there is no clear evidence implicating diabetes in early osteoarthritis although there are some studies attempting to implicate AGEs in cartilage degeneration. In the case of knee joint pain in diabetics, it may be caused or aggravated by excess weight, which is a common problem in those with type 2 diabetes, resulting in accelerated osteoarthritis (OA). Unlike Charcot’s joint, OA is not directly caused by diabetes. Instead, being overweight increases the risk of developing both type 2 diabetes and OA. The initial treatment of OA involves managing the weight of the patient. Excess weight puts more pressure on the bones. It also makes diabetes harder to control, so losing extra pounds can not only alleviate chronic joint pain, it may ease other diabetes symptoms. According to the Arthritis Foundation, losing 15 pounds may decrease knee pain by 50 percent. Regular exercise can do more than maintain weight. Physical movement also helps lubricate the joints, resulting in less pain. Pain medications may be used when joint discomfort from OA becomes unbearable. Surgery, such as knee replacement, may be required in severe late OA cases.

Fibromyalgia (FM) is also a common finding in patients with diabetes and its prevalence could also be related to control of the disease. As with other diabetes complications, FM might be prevented by improved control of blood glucose levels.

**CONCLUSION**

Diabetes care management should include not only good metabolic control, but also effective pain management across the disease course. Pain management should not be neglected in diabetics and more efforts should be made to help diabetic patients manage chronic pain.

**REFERENCES**

28. Corbett CF. Practical management of patients with painful


LEARNING POINTS

• There is an unmet need in achieving better pain management to improve quality of life in diabetics.

• If pain persists or recurs for longer than three months, it is termed as ‘Chronic pain’. Patients with chronic primary pain often report pain related disability, increased depressed and anxious mood, as well as anger and frustration.

• Neuropathic pain is often described as shooting, electric shock-like, burning – commonly associated with tingling or numbness. It is almost always associated with a chronic condition (e.g., post-herpetic neuralgia, post-stroke pain, diabetic neuropathy) and responds poorly to conventional analgesics. In diabetic neuropathy, there is usually a symmetrical sensory loss to all modalities in a stocking distribution on clinical examination.

• Diabetes is also associated with joint complications. The shoulder is one of the frequently affected sites and one of the common rheumatologic conditions caused by diabetes is frozen shoulder characterized by pain and severe limited range of motion. Osteoarthritis, the most common rheumatologic condition is an important differential diagnosis.

• Charcot’s joint or neuropathic arthropathy is commonly seen in the feet and ankles due to nerve damage in diabetes. Severe damage may lead to deformities in the foot and other affected joints. Bone deformities in Charcot’s joint may be prevented through early intervention. It is important to limit use of the affected areas in Charcot’s joint to prevent bone deformities by wearing orthotics for additional support.