Review Article

Diabetic peripheral neuropathy: pain management

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ABSTRACT

As diabetes mellitus continues to be a global health issue, more and more cases of macro-vascular and micro-vascular complications are being commonly observed amongst this category of patients. One micro-vascular complication often seen in diabetic patients is diabetic neuropathy as at least 50% of diabetic patients will experience some form of neuropathy following a diagnosis of diabetes for about 25 years. Even though diabetic patients are at risk for developing various types of neuropathies, polyneuropathies are most commonly observed and develop mainly develop due to hyperglycaemia, dyslipidemia and abnormal insulin signaling. Polyneuropathies are commonly accompanied by bilateral sensory loss in the distal limbs. Varying degrees of pain are also observed with this complication and pain management may serve to be very complicated. Therefore, this review discusses neuropathy focusing specifically on the effective management of the pain that commonly accompanies this diabetic complication.

Keywords: Diabetic peripheral neuropathy, Diabetes mellitus, Complications of diabetes mellitus

INTRODUCTION

It is observed worldwide that the prevalence of diabetes mellitus (DM) is increasing at alarming rates. This has brought a significant burden on the various healthcare systems across the globe as diabetes related complications such as cardiovascular and renal diseases are also becoming more common.[1] In 2015, the International Diabetes Federation (IDF) estimated that 415 million adults between the ages of 20-79 years were living with DM and it is projected that by 2040 this number will increase by at least 227 million.[2] In addition, what is quite concerning is that across the globe, about 232 million people are living with undiagnosed DM and are therefore at an increased risk for developing complications secondary to prolonged exposure to abnormally high blood glucose levels.[3]

DM is the leading cause of micro-vascular complications and one complication that is commonly observed in diabetics is neuropathy.[4] Approximately 50% of diabetic patients will develop some form of neuropathy after being diagnosed with the disease for about 25 years. There are different types of neuropathies; however, what is most commonly seen is polyneuropathies which involve bilateral sensory loss distally. Pain can occur along with polyneuropathies and one study demonstrated that lower extremity pain is experienced in 11.6% of type 1 diabetic (T1D) patients and 32.1% of type 2 diabetic (T2D) patients who suffer from this pathology.[5] Other types of neuropathies that may be observed as complications of

DM include: a) small-fibre predominant neuropathy b) autonomic neuropathy c) radiculoplexopathy (diabetic amyotrophy) d) radiculopathy e) mononeuritis multiplex f) mononeuropathy, and g) treatment-induced neuropathy.[6]

Since diabetic neuropathies are commonly observed in diabetic patients, it is important that clinicians not only be aware of its presentation but also be versed in its management and control. As a significant portion of diabetic patients presenting with diabetic neuropathy commonly presents with pain, this review serves to explore the management options available for controlling pain specifically in diabetic peripheral neuropathy (DPN).

PATHOGENESIS OF DIABETIC PERIPHERAL NEUROPATHY

Hyperglycaemia is considered a significant factor in the development of DPN. However, despite this fact, other factors have also been identified and highlighted for the role that they may play in the development of this pathology.[6] Dyslipidaemia is thought to play an essential role in the development of DPN in type 2 diabetics.[7] In type 1 diabetes mellitus (T1DM), it is observed that insulin and C-peptide levels are both decreased; however, in type 2 diabetes mellitus (T2DM), it is postulated that insulin sensitivity in neurons is severely reduced.[8,9] These findings demonstrate the importance of insulin signalling in the development of diabetic neuropathy.

HYPERGLYCAEMIA AND DIABETIC PERIPHERAL NEUROPATHY

When glucose enters the cell in excess it is channelled through different metabolic pathways as means of regulation and control. However, chronic hyperglycaemia can be toxic to cells and may lead to cellular damage through various mechanisms.

The presence of excess intracellular glucose potentially induces an increased activity of glycolysis which in turn overwhelms the electron transport chain, a pathway that functions within the mitochondria of a cell. When this occurs, it facilitates the excessive generation of reactive oxygen species (ROS) which has the potential to induce neuronal cell damage.[10]

Prolonged hyperglycaemia results in an increased activity of the hexosamine pathway which potentially induces cellular inflammatory damages.[11] In this pathway, an intermediate of glycolysis called fructose-6-phosphate is converted to uridine diphosphate-N-acetylglucosamine.[12] Uridine diphosphate-N-acetylglucosamine, potentially changes serine and threonine residues which are found in particular transcription factors. The modification of these transcription factors triggers an inflammatory cascade which subsequently damages the basement membranes of endothelial cells, thereby compromising neuronal blood flow, and also injuring beta-cells of the pancreas.[13]

Hyperglycaemia can induce cellular damage through the generation of advanced glycation end products (AGEs). AGEs are produced when reactive carbohydrate groups become attached to plasma components such as proteins, nucleic acids and lipids as part of a non-enzymatic modification process.[14] This process leads to diabetic neuropathy in one of two ways. AGEs impair the normal integrity of proteins thus affecting the normal functions or activities of neurons.[15] In addition, extracellular AGEs can also attach themselves to specific cell surface receptors called RAGE (receptor for AGE). This ligand to receptor interaction elicits an inflammatory response which causes damage to neurons through the activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and the induction of oxidative stress and injury.[16,17]

The polyol pathway uses an enzyme called aldose reductase (AR) to change glucose into sorbitol after which sorbitol is converted to fructose by sorbitol dehydrogenase (SDH).[18] The presence of prolonged hyperglycaemia, results in an increased conversion of glucose to sorbitol which in turn causes a depletion of NADPH as NADPH is utilized as a coenzyme during this process. Decreased NADPH levels affect the production of nitric oxide (NO) and results in a reduced capacity of the cell to generate reduced glutathione. These resulting effects compromises vascular integrity and support an increased generation of free radicals. The distribution of AR in Schwann cells explains the potential role that the pathological activation of this pathway may play in the development of nerve cell injury in the presence of hyperglycaemia.[19]

The protein kinase C (PKC) pathway is also described for its role in inducing tissue injury in the presence of hyperglycaemia. When hyperglycaemia occurs, diacylglycerol (DAG) is stimulated and stimulated DAG, activates PKC. It is theorized that the presence of PKC (especially PKC-β) promotes the increased expression of vascular endothelial growth factors (VEGFs), such as plasminogen activator inhibitor-1(PAI-1) and transforming growth factor beta (TGF-β). It also leads to the development of complications like diabetic retinopathy, diabetic nephropathy and cardiovascular diseases. It is believed that increased flux through the PKC pathway supports the development of diabetic neuropathy.[20-22] When the PKC pathway is activated, it functions in altering vasoconstriction and permeability in capillaries. This may lead to thickening of basement membranes, formation and development of new blood vessels, proliferation of endothelium and inadequate blood oxygenation.[23,24] These consequences are likely to explain the role that PKC plays in the development of diabetic neuropathy. A study carried out on streptozotocin (STZ) induced diabetic rats demonstrated the effects of the PKC pathway on the development of diabetic neuropathy. In this study, the inhibition of PKC potentially improved blood flow to the sciatic nerve with an increase in nerve function.[25] Furthermore different isoforms of PKC may be expressed promoting insulin resistance, which may lead to

the development of nephropathy through various mechanisms.[26,27]

DYSLIPIDAEMIA AND DIABETIC NEUROPATHY

Dyslipidaemia may be linked to diabetic neuropathy in different ways. The presence of free fatty acids has the potential to directly damage Schwann cells.[28] Additionally, systematically, free fatty acids can also induce the release of cytokines from cells such as adipocytes and macrophages thus supporting inflammation of peripheral nerves.[29] Through the process of glycation or oxidation, lipoproteins (especially low-density lipoproteins-LDL) in the blood can be changed or modified. These modified lipoproteins can then bind to various receptors (LDL receptor 1 (LOX1), Toll-like receptor 4 (TLR4) and RAGE) inducing signalling cascades (caspase 3 activation and degradation of nuclear DNA) that potentially results in the activation of NADPH oxidase and ultimately leads to increased oxidative stress and injury.[30] Furthermore, cholesterol can undergo oxidation to produce oxysterols. It has been demonstrated that oxysterol causes the death of neurons.[11,31]

Glycolysis, tricarboxylic acid (TCA) cycle and beta-oxidation in Schwann cells, dorsal root ganglions (DRGs) and axons produce both NADH and $FADH_2$ through the use of glucose and fatty acids. In Schwann cells, beta-oxidation of long chain fatty acids (LCFA) produce acetyl-CoA which is transported and used by the TCA cycle to form NADH and $FADH_2$. The presence of diabetes results in excess channelling of substrates through beta-oxidation, overwhelming the acetyl-CoA transport system and as a result, excess acetyl-CoA is then changed to acylcarnitines. The build-up of acylcarnitines in Schwann cells and DRG neurons has deleterious effects and this accumulation adds to nervous tissue injuries and subsequently diabetic neuropathy. Schwann cells may also release acylcarnitines which may cause axonal damage.[32]

NADH and $FADH_2$ are transported to the mitochondria where they go through oxidative phosphorylation to produce ATP. During the process of oxidative phosphorylation, reactive oxygen species are formed; however, these by-products are neutralized through the use of superoxide dismutase, glutathione and catalase. In the case of diabetes, substrate overload impairs oxidative phosphorylation, which ultimately results in ATP deficiency and increased levels of ROS. This in turn induces metabolic and oxidative stress which causes failure of the mitochondria, in addition to causing damage to Schwann cells and DRG neurons.[33] Decreased ATP levels also affect anterograde transport along axons further inducing damage and injury.[34]

Hyperlipidemia results in an increased catabolism of free fatty acids (FFA) through beta-oxidation. This can potentially lead to Schwann cell damage through an increased production of ROS. Damage may also ensue due to increased inflammation (local and systemic) through activation of macrophages which leads the – to production of inflammatory mediators such as cytokines and chemokines.[28,35]

IMPAIRED INSULIN SIGNALLING

Evidence from studies suggests that DRG neurons and axons (especially nodes of Ranvier) express insulin receptors.[36,37] Insulin does not promote the uptake of glucose into neurons; however, it has the potential to stimulate neuronal growth and support neuronal longevity.[38,39] Due to its growth factor-like effects, insulin demonstrates the potential to increase outgrowth of neuritis.[40] These potential neuronal effects of insulin are negatively affected by both insulin deficiency and resistance and these effects are therefore viewed as the major contributory factors to the development of diabetic neuropathy.[9] In T1DM patients, an observed decrease in C- peptide levels can result in neuronal damage through the reduced activities of endothelial nitric oxide synthase (eNOS) and sodium-potassium adenosine triphosphate (ATPase). In addition, endothelial neuronal blood flow may also be impaired, thus resulting in damage to neurons following ischemia.[8] In the liver and muscle tissues, free fatty acids induce insulin resistance. Free fatty acids also cause injury to the endoplasmic reticulum and support cellular inflammation. Therefore, it is postulated that peripheral nerve injury can occur following the accumulation of fatty acids which causes insulin resistance.[11]

MICRO-VASCULAR CONTRIBUTIONS TO THE DEVELOPMENT OF DIABETIC NEUROPATHY

Decreased blood flow to peripheral nerves is viewed as a contributory factor to the development of diabetic neuropathy. It is postulated that dysfunctions in the microcirculation are related to dysfunctions of peripheral nerves and persistent deficiencies in microcirculation leads to continuous damage of nervous tissues. In diabetic patients who have experienced nerve tissue damage, it is observed that corresponding blood vessels demonstrate thickening of their basement membranes.[41,42] Diabetic rats have demonstrated decreased vasodilation in epineurial arterioles prior to a loss of normal nerve function.[43] The levels of insulin growth factors, VEGF, nerve growth factor (NGF) and angiopoietins are decreased in the presence of DM. These factors are important as they promote the formation and development of blood vessels. VEGF given to diabetic rats demonstrated an improvement in nerve function and an increase density of the small vessels that supply peripheral nerves (vasa nervorsa).[44]

RISK FACTORS FOR PAIN IN DIABETIC NEUROPATHY

Diseases or damages to the somatosensory nervous system produce neuropathic pain. About 30%-50% of diabetic patients who suffer from diabetic neuropathy will complain of neuropathic pain.[45] Patients usually report

neuropathic pain as a burning sensation of the feet or they may also report brush-evoked allodynia. These presentations are often accompanied by a complaint of sensory loss.[33] Some patients present with diabetic neuropathy in the absence of pain, a phenomena which is not yet fully understood.[46] A few risk factors for developing pain with diabetic neuropathy have been identified. One risk factor is that of being a female (female gender). In addition, factors such as uncontrolled hyperglycaemia, abnormal renal function and a high body mass index (BMI) have also been identified as potential risks factors. Severe neuropathy, identified by the use of various scoring scales and quantitative sensory testing, is also associated with increased occurrence of pain.[33]

MANAGEMENT OF PAIN IN DIABETIC PERIPHERAL NEUROPATHY

Diabetic peripheral neuropathy may occur in isolation, or in conjunction with pain. However, it is indisputable the significance with which the subgroup with pain is impacted, making it worthwhile to explore this area as a form of study. As alluded to above, pain in diabetic peripheral neuropathy tends to be multifactorial in origin, and largely irreversible.[47] This makes it difficult to treat, as consideration must be given to all causative agents, but unfortunately addressing all causative agents may be an insurmountable problem. DPN is often described as severe, adversely impacting lives and leading to the creation of an imbalance within the complicated cycle of finances (days lost at work, increased health care burden to the individual and overall health system), increased emotional and mental symptom burdens, reduced or complete loss of social interactions, role reversals in the home, and other domains of the patients.[47] Often times, the caregivers and healthcare providers are also engulfed in the after-tide of the frustration created by this wave of not being able to effectively meet the needs of the patients. The end product is usually dejection and hopelessness, with increased vulnerability to anxiety, depressed emotions, sleep interruptions and other psychological pathologies.[47]

In keeping with the concept of total pain, this only serves to further complicate the pain, making this an indomitable feat.[48] All of these sum to affect the entire well-being and quality of life of the patients. The central theme underlying most treatment strategies seek to return the patient to a level of normalcy, gain control of the pain via application of intense measures – for tight blood glucose management and patient teaching.[47,49,50-52]

Treating parties must become more aware of the intricacies of treatment, and the limitations posed by this multifaceted condition. This in turn will make them more efficient in the formulation of decisions regarding treatment plans, and affording patients a better outcome. In an attempt to target most aspects of the pain, treatments are broadly lumped into pharmacological, non-pharmacological and surgical strategies.

PHARMACOLOGICAL AGENTS

Antidepressants

Antidepressants are often prioritized as a first-line choice in the pharmacological management of neuropathic pain. The factor giving them this advantage will be discussed below. This review will be limited to tricyclics (TCA's) and serotonin-norepinephrine reuptake inhibitors (SNRI) as examples of antidepressants that are commonly used in the management of DPN.[48]

TCA's,

TCA's in some cases, are considered first line therapy.[49] TCA's work by inhibiting the reuptake of the neurotransmitters noradrenaline and serotonin.[47] Therefore, there remains a higher concentration of these neurotransmitters available within the synaptic cleft. Commonly used examples include amitriptyline and imipramine. The side effect profile of both drugs remain relatively the same with sedation, confusion, constipation, dry mouth, blurred vision, urinary hesitancy, orthostatic dizziness.[47,49] On a cautionary note, this class of medication should be avoided in patients with glaucoma, prostate hypertrophy or cardiac conduction disturbances.[47]

Serotonin-norepinephrine reuptake inhibitors (SNRIs)

The exact mechanism of action of this drug largely remains unclear. The level of the body at which it works though is clear, and that is at the level of the spinal cord. Much like the TCA's, the SNRI's totally prevent or significantly reduce the reuptake of these neurotransmitters (serotonin and norepinephrine) within the synaptic cleft at the spinal cord. Particularly in the case of norepinephrine, higher quantities of this neurotransmitter become available for use, and working via the alpha 2-adrenergic receptors promote the activation and enhancement in performance of the pain inhibiting systems. These pain inhibiting systems make direct contact with the endogenous pain producing cells of the spinal cord (found in the dorsal horn), retarding their ability to produce pain. As part of this system, there is a region bilaterally in the brain which consists of a group of nerve cells called the locus coeruleus. Normally, this region functions predominantly in the production of endogenous pain by projecting directly onto the dorsal horn of the spinal cord. The cells of the locus coeruleus are endowed with norepinephrine receptors. By preventing the reuptake of norepinephrine, the now higher levels of norepinephrine within the synaptic cleft of the spinal cord will enter circulation and will bind to these receptors in the locus coeruleus. This culminates in an up-regulation of the function of the descending noradrenergic inhibitory system, and thereby inhibiting the pathway that produces pain.[50] A similar mechanism exists for serotonin.

SNRI's seem to have a more tolerable drug profile, thereby enhancing compliance and patient satisfaction. In comparison, the tolerability profile seems to be less so for

TCA's.[49] A widely used SNRI for DNP is Duloxetine. Duloxetine seems to have a better tolerability profile when compared to TCA's.[47,49] This is because SNRI's have less effect on muscarinic and histaminic receptors.[47] The recommended dosage is 60mg orally once daily and constipation was the most commonly reported side effect of this drug. Although not FDA approved for the treatment of DPN, another SNRI that has demonstrated promising results in DPN management is Venlafaxine. It inhibits serotonin, and at medium to high doses, inhibits the uptake of noradrenaline. It can precipitate nausea, headaches and insomnia.[47] There appears to be a potentiated effect when antidepressants are combined with the voltage dependent calcium channels alpha2delta subunit ligands such as pregabalin.[50]

ANTICONVULSANTS

Anticonvulsants that act on calcium channels tend to have a good outcome in the management of DPN, and as such tend to be recommended among this class of treatments.

Gabapentin

Gabapentin is usually touted as first-line for DPN. Following injuries to the nerves, the healing process results in damaged nerve and in turn the emission of haphazard signals. The ability to control the overactive transmission of pain signals from these damaged nerves is the basis of the strategy used to manage pain in this setting, making this category of DPN medication one that works on the pathogenesis of DPN. Others in this class include carbamazepine, lamotrigine and topiramate. There is often the complaint of an increase in the incidence of concentration disorders with gabapentin.[51]

Pregabalin

This is another anticonvulsant that is used in the treatment of DPN. Its mechanism of action involves the binding of the drug to voltage-gated calcium channels, particularly to the alpha 2-delta subunit, thereby reducing the amount of neurotransmitter in the synaptic cleft and also reducing the release of other particular neurotransmitters associated with pain production from the presynaptic cell.[47] Most common side effects include dizziness, excessive sleepiness, headaches, dried mouth, and weight gain.[51]

OPIOIDS

Opioids exhibit vulnerability to abuse.[47] Persons with DPN tend to have chronic symptoms, leading to an increased tendency for abuse in this subclass, and making this analgesic agent less favourable for use for the treatment and management of DPN. On these grounds, opioids as a class of analgesics are second line therapy for the management of DPN. However, there are studies that demonstrate that its usage in the management of this condition tend to be effective. Preferred opioids include oxycodone, morphine, methadone and tramadol.[47-51]

Tramadol

Tramadol can be used either by itself, or as a combination of tramadol/acetaminophen. The combination appears to be better tolerated as opposed to tramadol as a stand-alone option. Like the SNRI's, tramadol inhibits both noradrenaline and serotonin reuptake within the spinal cord.[53] Commonly reported side effects include nausea, constipation, misuse, confusion in the elderly.[51]

TOPICAL AGENTS

Capsaicin

This is an extract from chili pepper. It produces its analgesic effect by binding to TRPV1 receptors (also called capsaicin receptor) in the peripheral nerve, depleting the peripheral nerve of substance P.[54] Substance P is a pro-inflammatory neuropeptide.[55] It is often used in combination with cayenne pepper mixed in cold cream, and applied directly to the site of pain.[53] Side effects include pain and redness at application site.

Lidocaine

Lidocaine can be used in the form of a patch.[47] In this form, it works as an analgesic on the peripheral nervous system.[47] The recommendation is a 5% patch.[47] Advantages include minimal systemic absorption, as well as the fact that it can be used simultaneously with other analgesic agents.[47]

Vasodilators

As aforementioned, AGEs forms part of the pathogenesis of DPN.[56,57] AGEs tend to clog blood vessels, significantly reducing distal blood flow, and further worsening pain due to ischemic changes to the nerve fibres. Improved blood flow may help reduce the overall destruction to the nerve and thereby control pain. In a small randomized clinical trial of twenty-two (22) patients, isosorbide dinitrate spray has been used on the skin in the areas of the pain. Using a pain score, this method saw the documentation of an 18% reduction in pain in patients in the trial.[52] However, significantly more research is needed into this.

NON-PHARMACOLOGICAL MEASURES

It is believed that the management of blood glucose as well as lipids will add some sort of benefits to the retardation of the progress and severity of DPN.

Blood glucose control

The desire of the treating physician to maintain tight blood glucose levels must be balanced with the reality that the glucose levels can easily be shifted between extremes and leading to the unpleasant symptoms of hyper or hypoglycaemia. This point becomes even more salient as some studies suggest that in T2DM, tight blood glucose

control, even though it has been shown to slow down the disease progression, has minimal to no impact on the reduction in the severity of the pain experienced in these patients.[47,56] Such data was not available for T1DM. Whatever literature was examined in this review was not clear on acceptable recommendation ranges for maintaining blood glucose in either T1DM or T2DM patients.

Smoking cessation

Smoking is often associated with a worse outcome in persons with DPN. A direct correlation exists between early quitting and better pain control.[56] Steps should be taken to ensure that all the supportive measures are in place to achieve this process.

Anti-lipid treatment

As was explored above, unaddressed dyslipidaemia has a direct and negative effect on the integrity of blood vessels. A compromised flow to the peripheral nerves further complicates the pathogenesis, and worsens the pain experienced. Proper management of dyslipidaemia is strongly encouraged as part of the treatment of DPN.[56] The recommendation for lipid panel in diabetic patients with T2DM includes LDL cholesterol levels of 100 mg/dl or less, and this should be addressed with a statin. Triglyceride levels should be less than 150mg/dl and HDL cholesterol should be raised to 40 mg/dl or greater.[58] It may be that these figures can be used as a general guide for T2DM diabetic persons with DPN. No clear-cut data was seen for T1DM in the literature review.

Antioxidants

An abundance of ROS due to a constant state of hyperglycaemia produces oxidative stress.[53,56] This was expanded on above. Prolongation of hyperglycaemic states overwhelms the protective mechanisms that exist to combat the oxidative stress created. This results in destruction of the neurons, with marked neuronal inflammation. Antioxidants work by giving the neurons the ability to combat this high oxidative stress by increasing the enzymes that promote the removal of ROS molecules.[53,56] Vitamins B and E may be examples of vitamins that aid in reducing oxidative stress.[54] Alpha lipoic acid (ALA) is another antioxidant that has been suggested in the management of DPN.[47,56] A randomized clinical trial did show improvements with the use of ALA in comparison to placebo.[47] Despite this knowledge however, studies to this effect have not been able to demonstrate much evidence to support that antioxidants in general provide pain relief in DPN.

SURGICAL

This is usually the least popular method, for many reasons, but the incidence of a higher chance of complications is the greatest deterrent.

Nerve decompression surgery

Again, due to AGEs, nerves are susceptible to edema, making them easier to become entrapped in their course. This requires the use of decompression to bring about symptom relief. Studies show that decompression can relieve pain, and can even show success up to and including the restoration of sensory impairments.[57]

CONCLUSION

Due to the multifactorial causes, and the debilitating effects of diabetic peripheral neuropathy, pain control is difficult to achieve. The inability to achieve this often leaves both physicians and patients frustrated, suggesting that it is a rather important issue to be achieved. Most treatments are targeted to regaining some level of functionality, and not total absence of pain. It is hoped that this review would inform decision makers and inform decision making for clinical guidelines in the area of DPN.

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