

# **Prevalence and treatment of painful diabetic neuropathy**

**By**

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A thesis submitted in partial fulfilment of the requirements for the degree of MSc (by Research) at the University of Central Lancashire

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## **Declaration**

I declare that this thesis has been composed by myself and that, whilst registered as a candidate for the degree of Master of Science by Research, I have not been registered as a candidate for any other awarding body.

Amir Aslam

## **Abstract**

The prevalence of diabetes is rising globally and, as a result, its associated complications are also rising. Painful diabetic neuropathy (PDN) is a well-known complication of diabetes and the most common cause of all neuropathic pain. About one-third of all diabetes patients suffer from PDN. The reported prevalence of PDN varies from 11% in Rochester, Minnesota, USA to 53.7% in the Middle East. One UK study, published in 2011, reported that the prevalence of PDN was 21.5% in type 2 diabetes patients and 13.4% in type 1 diabetes patients, resulting in an overall prevalence of 21%. Numerous studies have found cardiovascular risk factors—including increased age, longer duration of diabetes, higher weight, smoking, poor glycaemic control, renal impairment and high cholesterol—to be associated with PDN. This disorder has a huge effect on people's daily lives both physically and mentally. Despite huge advances in medicine, the treatment of PDN is both challenging for physicians and distressing for patients. In this thesis, three studies were carried out on the following topics: *prevalence and characteristics of painful diabetic neuropathy, PDN patients' quality of life, and treatment employing lignocaine.*

This first study assessed the prevalence of painful diabetic neuropathy (PDN) and its relationship with various cardiovascular characteristics in diabetes subjects. This was done through an observational study of diabetes subjects in Northwest England, UK (n =204). The self-completed Leeds Assessment of Neuropathic Symptoms and Signs questionnaire was sent by post to the subjects and used to diagnose PDN. Consent for participation and access to blood results was given by the study participants. Ethical approval for the study was also granted by National Research Ethics Committee UK. The results of the study showed that the crude prevalence of PDN among subjects was 30.3%. The prevalence of type 2 diabetes subjects was higher (33.1 %) than that of type 1 diabetes

subjects (14.1%). There was a significant association of obesity, smoking and height in males with PDN compared to the non-PDN group ( $P < 0.05$ ). The results also showed a significant trend of increasing PDN prevalence with duration of diabetes, increasing HbA1c and increasing BMI ( $P < 0.05$ ). There was a trend of increasing prevalence with age as well ( $P > 0.05$ ); however, due to the small sample size, the data was not statistically significant. There was no relationship of PDN with systolic or diastolic blood pressure, nephropathy, alcohol intake or blood cholesterol ( $P > 0.05$ ). These results highlight the importance of better control of modifiable factors, including smoking, glycaemic control (HbA1c) and obesity.

The second study assessed the impact of painful diabetic neuropathy on quality of life (QoL), mood and anxiety by comparing patients suffering from painful diabetic neuropathy (PDN group) with diabetes patients not known to have PDN (control group, C). The study used short form (SF) 36 and Hospital Anxiety and Depression Scale (HADS Scale) questionnaires. For the PDN group, 25 adult subjects (mean age 56, standard deviation (SD) +/- 11 years, male 15, female 10) were randomly selected from patients attending the painful diabetes neuropathy clinic at Chorley Hospital. For the control group, 25 adult diabetic subjects (mean age 56, SD +/- 14 years, male 14, female 9) were randomly selected from patients undergoing General Practitioner Surgery. Both groups completed the HADS and SF36 questionnaires. Subjects in the PDN group had significantly lower SF36 summary scores in both the physical health ( $P < 0.0001$ ) and mental health domains ( $P = 0.026$ ) compared with the C group. HADS data showed that 56% subjects in the PDN group could be diagnosed anxiety compared to only 20% in the C group ( $P = 0.018$ ); and 60% of the PDN group received the diagnosis of depression compare to 44% in the C group ( $P = 0.396$ ). The results also show that PDN was significantly associated with impaired QoL, both physically ( $p < 0.0001$ ) and mentally

( $p < 0.026$ ). Anxiety was significantly associated with the PDN group compared to control ( $p < 0.018$ ), and depression was 16% more prevalent in PDN group than in the control group.

The final study assessed the efficacy of lignocaine infusion as a treatment for PDN in challenging cases where conventional treatment had not helped. A total 11 patients participated; 7 patients were referred from the pain clinic (non-PDN group), and 4 were referred from the foot clinic (PDN group). All were given lignocaine infusion as a treatment for chronic pain. Participants from both groups were on multiple pain medications with minimal results. All participants gave consent for participation and filled out a McGill short form (SF) questionnaire before and after lignocaine infusion. The results showed a 33% reduction in the visual analogue pain score after lignocaine infusion in PDN group compared to an 11% reduction in the non-PDN group. The data were statistically significant ( $P < 0.05$ ). Similarly, there was significant ( $p < 0.05$ ) reduction of affective pain score: 41% after lignocaine infusion in PDN group, compared to 21% in non-PDN group. In contrast, no significant difference was seen between groups for the sensory pain score reduction after lignocaine infusion: 23% in PDN group compared to 17% in non-PDN group ( $P > 0.05$ ). None of the 11 patients reported adverse effects from the treatment and their observations were within normal limits throughout the lignocaine infusion. Overall, the study showed that lignocaine infusion is effective and safe in reducing the chronic intractable pain when conventional treatments are intolerable or unhelpful. The treatment is also more effective for painful diabetic neuropathy than for other forms of chronic pain.

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## **Abbreviations**

A: After

ACE: Angiotensin converting enzyme inhibitor

ADA: American diabetes association

B: Before

C: Control

CVD: Cardiovascular disease

DM: Diabetes Mellitus

DN: Diabetic Neuropathy

HADS: Hospital anxiety and depression score

IV: Intravenous

McGill SF pain score: McGill Short form questionnaire

N= Total

NICE: National Institute for Health and Care Excellence

PDN : Painful diabetic neuropathy

QoL: Quality of life

S- LANSS questionnaire: Self report -Leeds assessment of neuropathic symptoms and signs questionnaire

SD: Standard deviation

SF 36: Short Form 36 questionnaire

SIGN: Scottish Intercollegiate Guidelines Network

VAS: Visual analogue score

## ***Chapter 1***

### ***Introduction: Diabetes Mellitus and Painful Diabetic Neuropathy***

## 1.1 Diabetes Mellitus

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycaemia due to either a lack of insulin or the presence of factors opposing insulin's actions (Harris & Zimmet, 1997). DM is a common health condition worldwide, and there are currently about 2.9 million people diagnosed with diabetes in the UK. Its prevalence is also rising; in the UK in 2006, prevalence of DM was 3.54% and currently the figure is at 4.6%. It has been estimated that by the end of 2025, about 4 million people in the UK will be suffering from diabetes (Diabetes.uk.org, 2013). DM has huge impact on conferring increased risk for macrovascular complications such as cardiovascular disease (myocardial infarction, peripheral vascular disease & stroke) and microvascular complications such as neuropathy, nephropathy, retinopathy and erectile dysfunction (Turner & Wass, 2009)

Diabetes was first described by Indian physicians in 1500 BC as “honey urine,” after they noted that ants were attracted by the urine of these patients. The name Diabetes Mellitus was given by Greek physician Apollonius of Memphis, with *diabetes* meaning ‘siphon’ (movement of fluid due to change in pressure) and *mellitus* meaning ‘sugar’. Together, these describe the hallmark symptoms of uncontrolled diabetes, including hyperglycaemia with osmotic symptoms of polyuria and polydipsia. Type 1 and type 2 diabetes were first identified as separate conditions in 400-500 CE by Indian physicians who noted the association of type 1 with young individuals and type 2 with middle aged obese (Poretsky, 2009). In the 18<sup>th</sup> century, Cawley linked diabetes with the pancreas (Cawley, 1788). In 1921, Banting and Best discovered insulin (Banting, 1942). After the discovery of insulin, the life expectancy of diabetes patients dramatically improved. Due to a better understanding of disease and advances in pharmacological treatments, diabetes

is now much better controlled. As a result people, are living longer with the long-term complications of diabetes, which include cardiovascular disease, nephropathy, retinopathy, erectile dysfunction and neuropathy.

### ***1.1.1 Type 1 and Type 2 Diabetes***

Type I, or Insulin-Dependent Diabetes Mellitus (IDDM), is caused by the deficiency of insulin. The onset of type 1 DM is typically during childhood and its pathogenesis involves environmental triggers that may activate autoimmune mechanisms in genetically susceptible individuals, leading to progressive loss of pancreatic islet  $\beta$  cells (Harrison *et al.*, 1999). Islet cell antibodies are present in most patients and are a diagnostic criterion of type 1 DM; however, these disappear over time. Other antibodies to specific proteins have recently been identified: these include antibodies to glutamic acid decarboxylase and tyrosine phosphatase. The presence of these antibodies in a non-diabetic individual indicates an 88% chance of developing diabetes within 10 years (Zimmet *et al.*, 2001).

Type 2, or Non-Insulin-Dependent Diabetes Mellitus (NIDDM), is associated with insulin resistance and obesity, in which target tissues fail to respond appropriately to insulin. Typically, the onset of this disease occurs in adulthood. In some patients, the insulin receptor is abnormal, while in others, one or more aspects of insulin signalling are defective. And in another group of DM patients, no defect has been identified. For most patients, insulin release is not usually impaired (at least initially) and insulin injections are therefore not useful for therapy. Rather, the disease is controlled through dietary therapy and hypoglycaemic agents (Harris & Zimmet, 1997; Moller, 2001; Zimmet *et al.*, 2001 ; Kumar & Clark, 2002).

### ***1.1.2 Sign and Symptoms***

The symptoms of diabetes mellitus are similar in both types of diabetes, including non-specific symptoms such as tiredness, fatigue, and as well as more specific osmotic symptoms such as polyuria, polydipsia, and blurred vision. Because of the total lack of insulin in type 1 DM, symptoms progress rapidly and more severely with the presence of diabetic ketoacidosis (DKA) (Alterman, 1997; Kumar & Clark, 2002). Longstanding undiagnosed diabetes sometime present with the complications of DM, such as a cardiovascular event (ischaemic heart disease, stroke), renal failure (chronic kidney disease), visual impairment (retinopathy), erectile dysfunction, foot ulcers & pain in legs (neuropathy) (Kumar & Clark, 2002 ; Bracken et al., 2003 ; Fallow& Singh, 2004).

### ***1.1.3 Diagnosis of diabetes***

Traditionally, a fasting blood glucose (FBG) level above 7 mmol/litre, random blood glucose (RBG) above 11 mmol/litre, or a two-hour oral glucose tolerance test (OGTT) above 11mmol/litre have been used to diagnose diabetes (NICE, 2009 & SIGN 2010). In 2011, the World Health Organization introduced HbA1c for the detection of DM, with a cut-off 48 mmol/mol. To confirm the diagnoses of diabetes, the physician needs any two abnormal readings of FBG, RBG or HbA1c 2 weeks apart, or any one abnormal reading with osmotic symptoms of polyuria, polydipsia and visual disturbance.

#### ***1.1.4 Macrovascular complications of diabetes***

Diabetes mellitus is a major risk factor for the formation of atherosclerosis, which causes the narrowing and hardening of blood vessels and leads to the development of cardiovascular disease (CVD) including myocardial infarction, stroke and peripheral vascular disease. As a result, people with diabetes have an increased risk of cardiovascular disease compared to the general population. CVD is a major cause of death and disability in people with diabetes, accounting for 44% of fatalities in people with type 1 diabetes and 52% of deaths in people with type 2 diabetes (Diabetes.uk.org, 2013). Stroke is twice as likely to occur if a person has diabetes, and myocardial infarction is 3–5 times as likely. Peripheral vascular disease can lead to gangrene and amputation, and is 50 times more likely in a person with diabetes (Kumar & Clark, 2002).

#### ***1.1.5 Chronic microvascular complications of diabetes***

Diabetes mellitus with chronic uncontrolled hyperglycaemia has a direct effect on small blood vessels. As a result, it causes microvascular complications with neuropathy, nephropathy, retinopathy and erectile dysfunction (Turner & Wass, 2009).

Diabetes nephropathy is a well-known microvascular complication of diabetes and is the most common cause of end-stage renal disease requiring dialysis (Satirapoj, 2012). The diagnosis of diabetic nephropathy relies on proteinuria. A urine spot albumin & creatinine ratio (ACR) above 2.5 mg/mmol in males and 3.5 mg/mmol in females classifies micro-albuminuria—the earliest sign of diabetic nephropathy. Urine proteinuria above 300 mg/day or urine spot ACR above 30 suggests a clear diagnosis of diabetic nephropathy (SIGN, 2010; CKS nephropathy, 2013). Research has shown a strong

correlation between micro-albuminuria and cardiovascular events (Viana et al., 2012). A Cochrane review by Strippoli et al. (2006) showed that the angiotensin converting enzyme (ACE) inhibitor are the drugs of choice for preventing the progression of diabetic kidney disease. These drugs are also recommended by Scottish Intercollegiate Guidelines Network (SIGN) and National Institute for Health and Care Excellence (NICE) even with normal creatinine levels and eGFR. If there is evidence of micro or macro albuminuria, the patient needs to commence treatment with an ACE inhibitor as soon as possible. Also, as there is a strong relationship between micro-albuminuria and cardiovascular events. Blood pressure needs to be optimized at target levels of 130/80 mm of Hg.

Diabetic retinopathy is another well-known microvascular complication of diabetes. It is estimated that, in England, there are 1,280 new cases of blindness every year, with 4,200 people are at risk for blindness caused by diabetic retinopathy (Diabetic eye screening UK, 2012). The United Kingdom Prospective Diabetes study (UKPDS) emphasized the importance of controlling both blood glucose and blood pressure in order to minimise the risk of developing sight-threatening retinopathy (Kohner, 2008).

Diabetic neuropathy affects 8.3% to 60% (Shaw & Hodge 1998, Boru et al., 2004) of all diabetic patients. It presents as a feeling of numbness in symmetrical stocking-glove pattern, with the involvement of distal peripheral nerves. Because of the lack of sensation, subjects are not aware of stepping on sharp objects, having a cut or blister, or touching something too hot or cold. Complications of diabetic neuropathy include pain, ulcers, infections and amputation (Tesfaye and Boulton, 2009). NICE (2009) and SIGN (2010) recommend feet examination upon diagnosis of diabetes and at least annually, including the 10-gram monofilament test for sensation, and searching for ulcers, calluses, deformities and pulses.

Erectile dysfunction is one of the microvascular complications that result from the neurovascular and autonomic neuropathy caused by diabetes. One study found that ED was three times more common in patients with diabetes mellitus. Erectile dysfunction in diabetes is strongly linked with macro-vascular diabetes complications (Watkins, 2003).

This thesis focuses mainly on painful diabetic neuropathy (PDN).

### ***1.1.6 Management of diabetes***

The management of diabetes from initial assessment to further review should include the following components:

1. Structured diabetes education
2. Diet and lifestyle modification
3. Glucose control
4. Blood pressure control
5. Assessment of need for lipid modification therapy
6. Consideration of whether the person should be taking antithrombotic therapy

#### *Structured diabetes education*

Structured diabetes education has been shown to lead to significant reduction in HbA1c and weight. The UK has in place a dedicated, well-structured programme called Diabetes Education and Self-Management for On-going and Newly-diagnosed Diabetes (DESMOND). Davies et al. (2008) demonstrated the DESMOND programme's effectiveness in a cluster randomised controlled trial of 824 adults with a diagnosis of diabetes. The structured six-hour education programme delivered by two trained health

professionals was compared with usual care. At the end of a 12-month follow-up period, HbA1c had decreased by 1.49% in the intervention group compared with 1.21% in the control group. The programme group also showed a weight reduction of 2.98 Kg, compared with 1.86 Kg for controls ( $P=0.027$ ). A positive association was also found between weight loss and a change in perceived personal responsibility at 12 months ( $P=0.008$ ). In sum, the DESMOND programme led to greater improvements in weight loss, beliefs about the illness, and reduction in glycated haemoglobin (HbA1c) levels in newly diagnosed type 2 diabetes patients up to 12 months after diagnosis.

Another structured educational programme for diabetes called “X-pert diabetes” consists of 6 sessions delivered weekly. The programme focuses on diabetes education, a patient-centred approach and self-empowerment. A randomized controlled trial showed significant improvement in clinical parameters, lifestyle and psychosocial well-being for programme participants with recent onset and long-term diabetes (Deakin et al., 2005).

Another programme, Dose Adjustment For Normal Eating (DAFNE) is a structured diabetes type 1 education programme focused mainly on carbohydrate intake control and injected insulin dosage, along with hypoglycaemia awareness and general diabetes education. A follow-up study showed significant reduction of HbA1c in program participants, as well as improved quality of life at 12-month follow-up (Speight et al., 2010).

#### *Diet and lifestyle modification*

Diet and lifestyle changes have been recommended by NICE (2009) and SIGN (2010) as the major element of diabetes management. Dyson et al. (2011) explained that lifestyle interventions are effective for weight loss, improving glycaemic control and reducing

cardiovascular risk in people with type 2 diabetes. Outside of pharmacological and surgical interventions, a combination of diet and physical activity is the standard and most successful route to achieving weight loss. NICE (2009) and SIGN (2010) recommend that people with type 2 DM should aim for 30 minutes of physical activity at least five days a week and be provided with the structured dietary advice that may help in the reduction of weight and better glycaemic control. Dietary options include simple caloric restriction, reducing fat intake, consumption of carbohydrates with low rather than high glycaemic index, and restricting the total amount of dietary carbohydrate (a maximum of 50 g per day appears safe for up to six months).

### *Glucose control*

Glucose control is paramount in the management of diabetes. In type 1 diabetes, the main form of glucose control is the commencement of insulin treatment upon diagnosis. In type 2 DM, the main treatment is oral medication or a combination of oral medications and insulin. When to initiate the treatment has been a controversial topic among national guidance organizations. NICE (2009) recommends diet and lifestyle modifications for the first 3 months, and if a target HbA1c of  $< 48$  mmol/mol is not achieved then the oral medication, metformin, would be started. However, SIGN (2010) suggests offering pharmacological treatment from the time of diagnosis, along with diet and lifestyle changes. A 10-year follow-up UKPDS looked at 5,102 type 2 DM patients who were randomly assigned to either conventional treatment (dietary restriction only) or intensive treatment (metformin or sulfonylurea, plus insulin). The HbA1c differences initially seen were lost after 1 year of follow-up. In the sulfonylurea-insulin group, relative reductions in risk for any diabetes-related end point (9%,  $P=0.04$ ) and microvascular disease (24%,  $P=0.001$ ) persisted at 10 years. Furthermore reductions in risk for myocardial infarction

(15%,  $P=0.01$ ) and death from any cause (13%,  $P=0.007$ ) emerged over time. In the metformin group, significant risk reductions persisted for all diabetes-related end points (21%,  $P=0.01$ ), myocardial infarction (33%,  $P=0.005$ ), and death from any cause (27%,  $P=0.002$ ). This study concluded that, despite an early loss of glycaemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during 10 years of post-trial follow-up. A continued benefit of metformin therapy was evident among patients (Holman et al., 2008). Therefore, better early control of glycaemia has a long-term effect in the prevention of micro- and macro-vascular disease.

#### *Blood pressure control*

Diabetes is itself a risk factor for cardiovascular events and the UKPDS risk calculator shows a direct relationship between hypertension and cardiovascular risks (Stevens et al., 2001; Kothari et al., 2002). The UKPD study of long term follow-up after tight control of blood pressure in type 2 diabetes showed significant relative risk reductions during the trial for all diabetes-related end points, diabetes-related death, microvascular disease, and stroke in the group receiving tighter blood-pressure control. However, the benefit of previous blood pressure control was lost when blood pressure improvements in both groups were not sustained during the post-trial follow-up. Thus, the study demonstrated the significance of good control of blood pressure in the long term for prevention cardiovascular events (Holman et al., 2008). There are several antihypertensive medications available to control BP. A Cochrane review showed the effectiveness of ACE inhibitors and angiotensin II receptor antagonists for the prevention and the progression of diabetic kidney disease alongside the control of blood pressure (Strippoli, 2006). Hence, ACE inhibitors are the drugs of choice for treating hypertension in diabetes.

### *Lipid lowering medication*

Hypercholesterolemia is one of the known risk factors for cardiovascular disease (Stevens et al., 2001; Kothari et al., 2002). Hence, lowering the cholesterol levels should lower the cardiovascular risk. Both NICE (2009) and SIGN (2010) advise the anti-lipid treatment simvastatin 40 mg for pre-existing cardiovascular disease. If the patient is on anti-lipid treatment, the target is a total serum cholesterol of <4.0 mmol/litre and LDL of <2.0 mmol/litre. According to SIGN (2010), for primary prevention, all diabetes patients above the age of 40 should be on statins.

### *Antiplatelet therapy in diabetes*

Anti-platelet therapy has been shown to have clear benefits in reducing cardiovascular risk. Traditionally, it has been used both for primary and secondary prevention in diabetes. However, recent randomized controlled trials showed benefits only in secondary prevention; for primary prevention, the trials did not show a reduction of cardiovascular death. At the same time, there is increasing evidence of GI bleeding caused by aspirin. It has thus been concluded that aspirin is not effective in the primary prevention of cardiovascular disease (De Berardis et al., 2009; Sacco et al., 2003). SIGN 2010 also suggests not to use Aspirin for primary prevention in diabetes.

As this thesis focuses mainly on PDN, the rest of this chapter will discuss the details of the pathogenesis and treatment of PDN.

## **1.2 Painful diabetic neuropathy (PDN)**

Diabetic Neuropathy (DN) is a well-known long-term complication of diabetes that can cause significant morbidity and mortality (Tapp and Shaw, 2009), and may affect up to 50% of diabetic population (Vinik et al., 1994). DN encompasses variety of clinical and sub clinical presentations depending on the involvement of sensory, motor or autonomic nerve fibres of the peripheral nerves. Thomas (1997) proposed the classification of DN into generalized, focal, and multifocal. Generalized DN includes diabetic peripheral neuropathy, painful neuropathy and autonomic neuropathy. Focal and multifocal neuropathies include mononeuritis multiplex, amyotrophy radiculopathy and entrapment of the median nerve causing carpal tunnel syndrome (Fonseca, 2006). This chapter focuses mainly on PDN.

Diabetes peripheral neuropathy is length dependent and manifests as a loss of sensation in a stocking pattern. Patients may present with the adverse consequences to the loss of sensation, such as plantar ulcers and arthropathy, mainly due to large fibre disease. One study on diabetic patients attending the diabetes clinic showed that 25% of patients exhibited symptoms of neuropathy and 50% were given a diagnosis of neuropathy after simple clinical tests such as the vibration perception test or ankle jerk (Larsen and Kronenberg, 2002).

PDN is a common presentation of diabetic neuropathy and the most common cause of neuropathic pain in Europe (Chong and Hester, 2007). The reported prevalence of PDN varied from 11% in Rochester, Minnesota, USA, (Dyck et al, 1993) to 53.7 % in the Middle East (Jambart et al, 2011). One UK study published in 2011 reported that the

prevalence of PDN was 21.5% in type 2 diabetes patients and 13.4% in type 1 diabetes patients, resulting in an overall prevalence of 21%. (Abbott et al, 2011). In the large, prospective EURODIAB study in 16 European countries, almost one-quarter of type 1 DM patients developed new onset PDN over a seven year period (Tesfaye et al. 1996). A prospective study in Finland followed newly diagnosed diabetes patients between the ages of 45 and 64 years for 10 years. It found a 6% prevalence at the time of diagnosis of diabetes and a 26.4% prevalence at the 10-year follow (Partanen et al, 1995). In a large UK-based community diabetic population, Abbot et al. (Abbott et al, 2011) observed that increasing age was directly related to painful symptoms of neuropathy. Most studies found no significant difference in genders, however, Abbot et al. (Abbott et al, 2011) reported a slightly higher prevalence of painful symptoms of neuropathy in females (38%) than males (31%). The same study also found a higher prevalence of painful symptoms in South Asians (38%) compared to Europeans (32%).

PDN symptoms exhibit a symmetrical “stocking and glove” distribution and are often associated with nocturnal exacerbation. It can present from a mild “pins and needles” sensation to stabbing, burning, unremitting or even unpleasant electric shock sensation. There can be allodynia in the form of cutaneous hypersensitivity leading to acute distress on contact with an external stimulus, such as clothing (Larsen and Kronenberg, 2002). The pain is often worse at night and disturbs sleep, causing tiredness during the day. Some patients present with distressing allodynia and severe pain in the legs. This may be so painful that it prevents them from performing their daily activities, thereby impacting their employment and social life. The constant, unremitting pain and withdrawal from social life often results in depression (Quattrini and Tesfaye, 1996). In extreme cases, patients lose their appetite and experience significant weight loss, which

is reported in the literature as “diabetic neuropathic cachexia” (Larsen and Kronenberg, 2002).

### **1.2.1 Physiology of pain**

Pain is the body’s perception of actual or potential damage to the nerve or tissue by noxious stimuli. The sensory afferent nerves carry sensations from the skin, joints and viscera via large and small fibres. Large fibres, such as A-alpha, are responsible for limb proprioception and A-beta fibres carry sensations of limb proprioception, pressure and vibration. Large A-delta myelinated fibres and small C unmyelinated fibres are mainly responsible for carrying nociceptive sensations. Superficial pain is often a sharp or pricking sensation and is transmitted by A-delta fibres. A deep seated, burning, itching, aching type of pain is often accompanied with hyper-algesia and allodynia and is transmitted via slow, unmyelinated C fibres. Tissue damage results in the release of inflammatory chemicals, such as prostaglandins, bradykinins and histamines, at the site of inflammation, which triggers the depolarization of nociceptors, thereby generating an action potential. The action potential transmits the nociceptive sensation, via the dorsal root ganglion (DRG), to the dorsal horn of the spinal cord. The release of glutamate and substance P results in the relay of nociceptive sensations to the spinothalamic tract, thalamus and, subsequently, the cortex, where pain is interpreted and perceived (Willis and Westlund, 1997).

Nociceptive pain is the normal response to noxious insult or injury of tissues such as skin, muscles, visceral organs, joints, etc. Nociceptive pain usually subsides upon the healing of the tissue injury. On the other hand, neuropathic pain arises as a direct consequence of

a lesion or disease affecting the somatosensory system without any noxious stimuli. Neuropathic pain is caused by damage or pathological change and is characterised by the activation of abnormal pathways of pain at the peripheral nerves and posterior roots (peripheral neuropathic pain) or spinal cord and brain (central pain) (Treed et al, 2008). Neuropathic pain manifestation can be focal, multifocal or generalized depending on the involvement of peripheral or central origin and cause of the disease. A few examples of neuropathic pain are listed in Table 1.1.

**Table: 1.1:** Examples of Neuropathic Pain

<b>Origin of Pain</b>	<b>Structures</b>	<b>Examples</b>
Peripheral Nervous System	Nerve	Diabetic painful neuropathy Neuroma Phantom limb pain Trigeminal Neuralgia Lumbosacral plexopathy
	Dorsal Root	Post-herpetic neuralgia Brachial plexus avulsion
Central Nervous System	Spinal Cord	Spinal cord injury Spinal cord infarction Multiple sclerosis
	Thalamus	Infarct Tumour Parkinson disease

## **1.2.2 Neuropathic pain generation pathogenesis**

The origin of pain in PDN is not fully understood. The abnormalities in the peripheral or central nervous system could be related to hyperglycaemia, as this is the key metabolic abnormality of diabetes. There are many other conditions that produce pain similar to that of PDN and they may also aid our understanding of the pathophysiology of PDN.

### ***1.2.2.1 Ectopic electrical impulses***

Chronic hyperglycaemic (HG) damage to the nerves can cause regeneration of nerve sprouts, called neuromas, at the stump. The sprouting of the new nerves in all directions cause collateral damage of otherwise undamaged nerves and expands the sensitized area (Devor et al, 1994). Hyper-excitability in the neuroma generates ectopic impulses that affect neighbouring intact afferents and the cell bodies of the DRG. It leads to spontaneous, exaggerated, abnormal hyper-excited responses, along with increased sensitivity to a given stimulus (Study and Kral, 1996). This phenomenon is called peripheral sensitization. Electrical impulses from the axons of small fibres at the dorsal horn of the spinal cord are increased and, hence, it alters the “gate” (described below) and causes the release of substance P and glutamate. This causes a relay of the impulses to the ascending track, which is perceived as pain (Campbell et al, 1988).

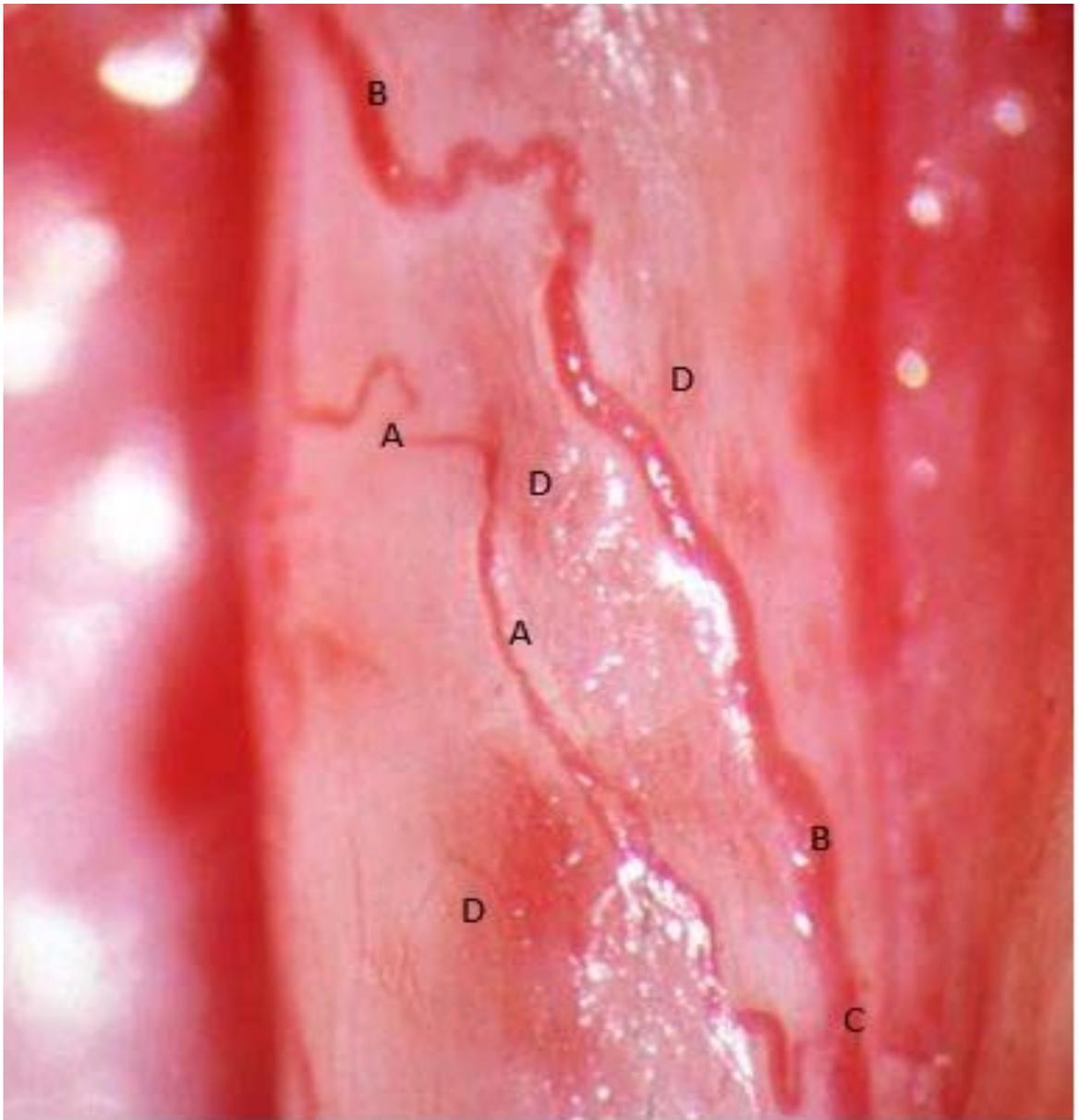
### ***1.2.2.2 Change in Glucose flux and pain***

Treatment induced acute painful neuropathy due to rapid glycaemic control in the first month of the initiation of insulin or oral hypoglycaemic agents has been reported in the literature as ‘insulin neuritis’. In 1933, Caravati first described the observation that acute

painful neuropathy might follow a sudden change in glycaemia control, suggesting that blood glucose flux could precipitate pain. This observation was experimentally tested in rats by Kihara et al, in 1994. In their study, they infused insulin under non-hypoglycaemic conditions and evaluated its effect on endoneurial oxygen tension, nerve blood flow, and the oxy-haemoglobin dissociation curve of peripheral nerves in normal and diabetic rats. Their results showed that insulin administration caused a reduction in nerve nutritive blood flow and an increase in arterio-venous shunt flow. When the arterio-venous shunts were obliterated by the infusion of 5-hydroxytryptamine, endo-neurial oxygen reverted to normal. Sudden changes in glycaemia may induce relative hypoxia in nerve fibres, which contributes to the generation of impulses, thereby indicating that it is the combination of structural and functional changes in peripheral nerves that cause the pain.

In 1996, Tesfaye et al observed neurovascular changes in vivo in five human diabetic patients with insulin neuritis. These patients presented with severe sensory symptoms but clinical examination and electrophysiological tests were normal, except in one subject who had severe autonomic neuropathy. On sural nerve exposure in vivo, epineural blood vessels showed severe structural abnormalities resembling the retinopathy changes normally seen in the retina, including arteriolar attenuation, tortuosity and arterio-venous shunting and the proliferation of newly formed vessels. They hypothesized that the structural abnormalities in epineural blood vessels, together with the formation of new vessels, caused a steal effect and, hence, resulted in hypoxia and neuropathic pain. It can now be postulated that a sudden change in glycaemic control can cause flux effects that result in structural and functional changes in the epineural blood vessels of nerves, which, in turn, can lead to neuropathic pain or “insulin neuritis” (Boulton, 1992; Tesfaye et al, 1996) (see Figure: 1.1). Symptoms can be mild and often go unreported, but may present with severe, excruciating neuropathic pain. Symptoms

usually last up to six months and respond to treatment that is usually needed for up to six months (Larsen and Kronenberg, 2002).



**Figure 1.1:** An image showing arteriolar attenuation (A), tortuosity (B), arterio-venous shunting (C) and proliferation of newly formed vessels (D) of the vasa nervosum seen in the sural nerve of a patient with insulin neuritis (Photo courtesy of Tesfaye and Boulton, 1996).

### ***1.2.2.3 Role of the dorsal root ganglion (DRG) in neuropathic pain***

The expression of voltage-gated sodium and calcium channels and voltage-independent potassium channels in the DRG has a significant role in the generation of nociceptive sensation and peripheral sensitization that leads to central sensitization. Hyper-excited ectopic impulses are generated by the expression of various voltage-gated sodium channels, such as Nav 1.3, Nav1.7 and Nav1.8 (Black et al, 2008). The voltage-gated sodium channel Nav1.3 probably plays a key role in the development of neuropathic pain (Cummins et al, 2001). Amir et al described after nerve injury, in the DRG, there is a sustained phasic discharge that results in repeated firing (Amir et al 1999). The voltage-dependent sodium channel alternates with a voltage-independent potassium leak to oscillate membrane potentials. When these oscillations reach the threshold amplitude, they result in the generation of ectopic impulses and, hence, lead to sustained peripheral sensitization (Amir et al 2002). In addition to the voltage-gated sodium channels, the expression of voltage-gated calcium channels were also found in neuropathic pain (Mathews et al, 2001), specifically subtype Cav 3.2 is highly expressed in DRG neurons and showed strong correlation with allodynia (Bourinet et al, 2005). Calcium entry through voltage-gated calcium channels causes the release of substance P and glutamate, which results in the modulation of pain at the dorsal horn (White and Zimmermann, 1988). The up-regulation of transient receptor potential expression is also found to be associated with neuropathic pain. Studies found a direct relationship between TRPV1 (transient receptor potential vanilloid 1) and neuropathic pain. A few animal studies suggest that hyper-algesia does not develop in TRPV1-deficient mice and TRPV1 antagonists reduce pain behaviour in mice (Caterina et al, 2000; Hudson et al, 2001).

#### ***1.2.2.4 Methylglyoxal (MGO) and pain***

Methylglyoxal (MGO) is a reactive intracellular by-product of several metabolic pathways. However, the most important source of MGO is glycolysis and hyperglycaemia (Inoue and Kimura, 1995). Studies found that PDN patients had significantly higher concentration of plasma MGO (> 600 nM) compared to healthy controls or diabetes patients without pain (Bierhaus et al, 2012; Han et al, 2007). MGO depolarizes the sensory neuron by activating TRPV1 in the DRG (Andersson et al, 2013) and also induces post-translational modification of the voltage-gated sodium channel Nav 1.8 (Bierhaus et al, 2012). These changes are associated with increased electrical excitability and facilitate firing of nociceptive neurons.

#### ***1.2.2.5 Sympathetic modulation of pain***

Nociceptive A-delta and C fibres are normally not directly connected to sympathetic nervous system. Several experiments using  $\alpha$ -adrenoreceptor agonists found that it did not activate sympathetic neurons at nociceptor fibres under normal conditions (Elam et al, 2004; Zahn et al, 2004). It is widely accepted that the sympathetic nervous system does not activate the sensory nervous system under normal conditions.

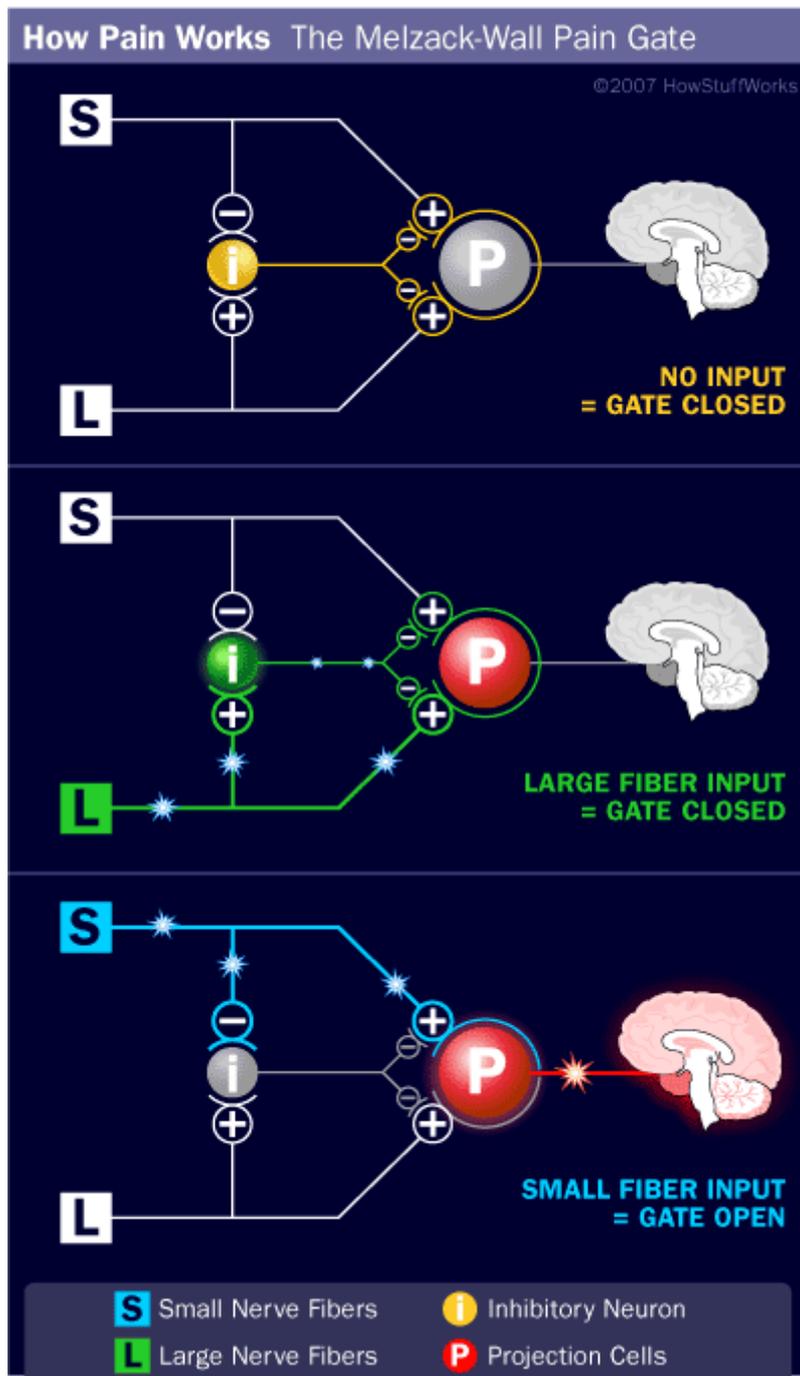
Neuropathy causes hypersensitivity in nerves as a result of an abnormal epinephrine-mediated transmission from one axon to another, this unusual connection is called ephaptic transmission or cross-talk (Janig et al, 1996). It was also noted that damaged nerves in the periphery also cause basket formation, called sympathetic sprouting in the DRG, which results in the release of noradrenaline (Kanno et al, 2010). Both sympathetic sprouting and ephaptic transmission release adrenaline and cause

sympathetic-sensory coupling. This leads to an increase in ectopic and spontaneous firing. This unusual connection is called sympathetically maintained pain.

Several studies proved this hypothesis and showed dramatic improvement in pain relief after sympathetic blockage (Yoo et al, 2011), sympathectomy (Sekiguchi et al, 2008) or temporary blockage with  $\alpha$ -adrenergic antagonists with intravenous phentolamine (Raja et al, 1991)

#### ***1.2.2.6 Gate control theory***

In 1965, Melzak and Wall described, for the first time, that nervous connections from the peripheral to central nervous system and to the brain is not a seamless transmission of information. They described the gate mechanism at the dorsal horn of the spinal cord, which inhibits or facilitates the flow of afferent impulses from peripheral nerves to the spinal cord before it evokes pain perception. The activity at the gate is primarily dependent on the transmission of impulses along small or large nerve fibres. Small nerve fibres, unmyelinated C fibres, and myelinated A-delta fibres tend to open the gate and large A-beta fibres tend to close the gate. Opening and closing of the gate depends on the number of input impulses. Thus, if nociceptive input from C- and A-delta fibres exceeds A-beta fibre input, then the gate is open and nociceptive impulses ascend to the spinal cord. On the other hand, if A-beta fibre input (touch, vibration and pressure) exceeds that of C- and A-delta fibre input (pain), then gate is closed; nociceptive impulses only pass through when the gate is open (see figure 1.2). The classic example of this phenomenon is the rubbing of an injured site immediately after suffering from trauma, which results in gate closure (Melzack and Wall, 1965).



**Figure 1.2:** Visual description of Gate control theory Freudenrich C. "How Pain Works" (2007). HowStuffWorks.com. <http://science.howstuffworks.com/life/inside-the-mind/human-brain/pain4.htm>. (Accessed on 06 August 2014)

### ***1.2.2.7 Central sensitization***

Central sensitization was first described by Woolf in 1983. Non-noxious stimuli transmitted from the periphery with A-beta fibres (touch) was perceived as painful by patients with allodynia (Woolf, 1983). A-delta fibres and C fibres are innervated in laminae I-II and A-delta fibres also innervated in lamina V of the dorsal horn. The majority of spinal cord neurons that express the substance P receptor are located in lamina I, or have their cell bodies in laminae III-IV, but extend their dendrites to lamina I. The pain mediation of noxious stimuli occurs by releasing substance P, mainly in lamina I of the dorsal horn. A-beta fibres are innervated deep in laminae III to V and are responsible for touch mediation (Woolf et al, 1992; Koerber et al, 1994; Bouhassira, 1999). Peripheral sensitization and sustained hyper-excited impulses at the dorsal horn cause an increase in responsiveness to noxious and non-noxious stimulation. This was believed to be due to the structural plasticity of sprouting of A-beta fibres, which leads to “rewiring” of the dorsal horn laminae in the central nervous system (CNS) (Bouhassira, 1999). As a result, the CNS pathway, which is responsible for transmitting only non-noxious stimuli (touch), was replaced by sprouting A-beta fibres that transmit non-noxious impulses and release substance P in the dorsal horn, thereby mediating allodynia (Harris, 1999). This hypothesis was mainly based on experiments that showed that the uptake of the cholera toxin B (CTB) subunit, which is a selective tracer for large myelinated A-fibres, terminated in lamina II (Lekan et al, 1996). The selectivity of this toxin after peripheral nerve injury is somewhat controversial. Experiments demonstrated that uptake of the CTB tracer was not selective and that CTB was found in axons of all types including, A-delta fibres and C fibres, and that the CTB tracer incorporated in C fibres that terminated in lamina II (Hughes et al, 2003). This contradicts the hypothesis of structural plasticity and A-beta fibres sprouting in lamina II. However, studies with immune-staining and

electrophysiological recordings have clearly established that peripheral nerve injury causes large myelinated fibres to begin to drive nociceptive neurons in superficial lamina (Bester et al, 2000; Woodbury et al 2008). The persistent incoming nerve impulses lead to activation of N-methyl-D-aspartate (NMDA) receptors on post-synaptic membranes in the dorsal horn of the spinal cord. This leads to the release and binding of glutamate (an excitatory neurotransmitter), which causes an influx of sodium and calcium and an efflux of potassium. This generates a larger post-synaptic action potential and augments the perception of normal stimuli, thereby resulting in allodynia (Chen and Huang, 1992).

#### ***1.2.2.8 Central inhibition & Central facilitation***

Impulses from the brainstem nuclei descend to the spinal cord and influence the transmission of pain signals at the dorsal horn. The periaqueductal grey matter (PAG), locus coeruleus, the nucleus raphe magnus and several bulbar nuclei of reticular formation give rise to descending modulatory pathways. These pathways dampen or enhance the pain signal. Increased descending facilitation has been demonstrated in chronic pain models. The injection of lidocaine in to the rostral ventromedial medulla of rats with peripheral nerve injury abolished the enhance abnormal pain (Pertovaara et al, 1996). The projections from the nucleus raphe magnus to the spinal cord are the major source of serotonin in the spinal cord. Exogenous opioids imitate the endogenous opioids and induce analgesia by acting upon the PAG, reticular formation and the spinal dorsal horn (Willis and Westlund, 1997). The antidepressant serotonin and norepinephrine reuptake inhibitors (SNRIs) (Goldstein et al, 2005) and opioids (Harati, et al, 1998) have been found to be beneficial in the treatment of neuropathic pain as these medications increase the availability of these neurotransmitters and, hence, increase inhibition at the spinal

cord. Psychological factors, such as fear and anxiety, can influence the inhibitory mechanism through the modulatory system. Cognitive behavioural therapies are thought to be beneficial in modulating the pain by reducing the fear and anxiety (Otis et al, 2013).

#### ***1.2.2.9 Thalamic abnormalities***

The nociceptive hyper-excited impulse generated within primary afferent nerves is not only modulated and amplified at the DRG-spinal cord level, but also at the thalamic ventral posterolateral (VPL) level, before being relayed to the cerebral cortex. This was experimentally proved in streptozotocin rat model with PDN. The experiment demonstrated hyper-excitability in thalamic VPL neurons, with increased responses to phasic brush, press, and pinch stimuli applied to peripheral receptive fields. VPL neurones from diabetic rats also displayed enhanced spontaneous activity, independent of ascending afferent impulses, and enlarged receptive fields (Fischer et al, 2009). Salverajah et al investigated this further in humans using a magnetic resonance (MR) perfusion scan in patients with PDN. This study demonstrated increased thalamic vascularity and sluggish blood flow (Salverajah et al, 2011). Similar vascular perfusion findings were also observed at the sural nerve in patients with PDN (Eaton et al, 2003). It was suggested that increased perfusion at thalamus VPL neurons in PDN patients causes an increase in neuronal activity and, hence, further modulates pain and central sensitization.

#### ***1.2.2.10 Chronic neuropathic pain and plasticity of brain***

Neuroplasticity or plasticity of the brain is the term used to describe the adaptive change in structure, chemical balance and function of the brain in response to changes within the

body or in the external environment. In response to chronic neuropathic pain, neuroplasticity is associated with somatosensory cortex remodelling, reorganization and hyperexcitability in the absence of external stimuli. A study of patients with chronic neuropathic and non-neuropathic pain using functional and anatomical magnetic resonance imaging found cortical reorganization and changes in somatosensory cortex activity only in the neuropathic pain group (Gustin et al, 2012). Provoked pain and spontaneous stimuli may reverse the remodelling and reorganization at the somatosensory cortex. Other studies have also shown a beneficial effect of pain relief with transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), which suggests a reversal of plasticity (Knotkova and Cruciani, 2010; Treister et al, 2013).

### **1.2.3 Diagnosis of painful diabetic neuropathy**

Diagnosis of painful diabetic neuropathy is mainly based on a clinical history of pain. The classical description of PDN pain is that it usually begins distally from the feet bilaterally, or in both feet and hands in the “gloves and stockings” distribution, with progressive or spontaneous burning sensations, shooting pains similar to electric shock, stabbing, pins and needles, tingling, and hot or cold feelings with or without contact hypersensitivity (allodynia). In rare cases, it can focally affect the dermatome region. (Fonseca A, 2006)

Sensory assessment using nerve conduction studies, vibration perception threshold tests, or the 10-gram monofilament test could be normal, as these tests assess only large A Beta fibres. As discussed earlier, pain is generated and mediated solely via small C fibres and large A delta fibres (Larsen and Kronenberg, 2002). Quantitative sensory testing (QST) is the means of testing to assess the thermal pain thresholds to hot

(C fibre) and cold (A delta fibre) (Sorensen et al., 2006; Kelly et al., 2005). However, these assessments are known to be highly subjective and also not widely available; therefore, they are not commonly used in clinical practice. Direct examination of nerve fibres by punch biopsy found a loss of intra-epidermal nerve fibres (IENF) in the small fibres of patients with painful neuropathy. However, loss of IENF cannot explain pain in all cases, suggesting that different pain mechanisms trigger pain in neuropathy (Sorensen et al., 2006). So far there is no consensus supporting the use punch biopsy in clinical practice, and it would be difficult to do this invasive procedure in all patients. There have, however, been advancements in the detection of pain using functional Magnetic Resonance Imaging (fMRI), which measures the changes in brain in the form of a pain matrix after painful stimulus. This method can help in quantifying the intensity and location of pain (Melzac, 1999). However, further studies are needed before this mode of imaging can be fully utilized in clinical practice.

#### ***1.2.3.1 Scales available to aid the diagnosis of neuropathic pain***

There are several validated neuropathic pain scales available to aid the diagnosis of neuropathic pain, such as the Neuropathic Symptom Score (NSS), the neuropathic pain scale (NPS), the Douleur Neruopathicque en 4 Questions (DN4), the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale, and the Self completed LANSS (S-LANSS). These scales have been used in clinical practice to diagnose painful diabetic neuropathy (Jambart et al., 2011; Abbott et al., 2011; Erbas et al., 2011, Liberman et al., 2014; Gu et al., 2012; Yunus and Rajbhandari, 2011). The visual analogue score is widely used in monitoring the pain (Athanasakis et al., 2013). The McGill pain questionnaire has been used to assess the severity of the symptoms of neuropathic pain (Melzack, 1975); however, it is not widely used in clinical practice.

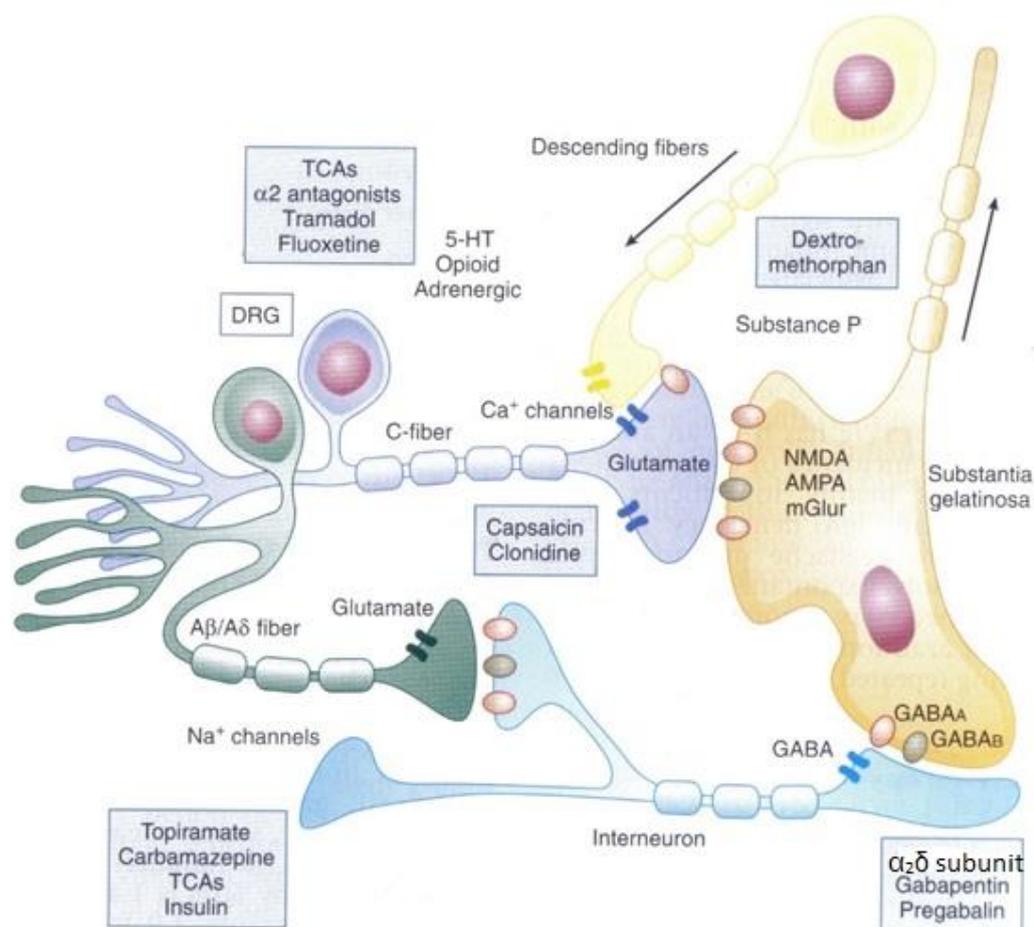
The brief pain inventory (BPI) has been used to assess the severity of pain, response to medications, and the physical and psychological impact of pain. The BPI has been shown to be effective in evaluating painful diabetic neuropathy (Zelman et al., 2005).

#### **1.2.4 Management of painful diabetic neuropathy**

There are several pharmacological and non-pharmacological therapies that have been proven to alleviate neuropathic pain, but not a single therapy restores nerve function. The main aim of treatment is symptomatic relief. Table 1.2 display the various pharmacological treatments and adverse reactions. Figure 1.3 displays the various pharmacological treatments with modes of action (see Figure 1.3 and Table 1.2)

**Table: 1.2:** Pharmacological therapies for the treatment of PDN

Drug Classes	Examples	Adverse reactions
Tricyclic antidepressants	Amitriptyline Nortriptyline	Agitation, anxiety, ataxia, confusion, dry mouth, arrhythmia
Serotonin norepinephrine reuptake inhibitor (SNRI) antidepressants	Duloxetine	Nausea Somnolence, headache, dizziness, insomnia, diarrhoea, constipation, decreased appetite
Anticonvulsants	Pregabalin Gabapentin  Carbamazepine	Oedema, somnolence, dizziness, ataxia, fatigue  Decrease appetite, weight loss, somnolence, dizziness, fatigue
Topical Anaesthetic	Lidocaine patch 5%	Burn
Opioids	Tramadol Morphine Oxycodone	Nausea, vomiting, drowsiness, somnolence, constipation



**Figure 1.3:** Schematic pathway of pain and sites of action of pain-relieving drugs.

AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; DRG, dorsal root ganglion; GABA,  $\gamma$ -amino butyric acid; 5-HT, serotonin; mGluR, metabotropic glutamate receptor; NMDA, N-methyl-D-aspartate; TCA, tricyclic antidepressant.

(Modified from Vinik & Mehrabyan, 2004)

## **1.2.4.1 Pharmacological Therapies**

### ***1.2.4.1.1 Antidepressants***

#### *Tricyclic Antidepressant (TCA)*

The TCA amitriptyline has been the drug of first choice for neuropathic pain since 1970 (Collins et al., 2000). Several studies have reported the significant relief of symptoms of neuropathic pain in diabetes patients using this drug (Nash, 1999; McQuay et al., 1996). TCAs relieve pain by inhibiting the reuptake of 5-HT and noradrenaline and blocking the sodium and calcium channels (Jensen et al., 2006). Side effects such as dry mouth, sweating, sedation and dizziness are mainly due to anti-cholinergic actions. The starting dose of Amitriptyline is 10 mg, and can gradually be titrated up to a maximum of 75 mg at night (NICE guidance on PDN, 2013)

#### *Serotonin noradrenaline reuptake inhibitors (SNRI)*

The efficacy of the SNRI duloxetine in PDN has been investigated in several studies and found to be effective pain in relief at the doses of 60 and 120 mg/day (Jensen et al., 2006; Goldstein et al., 2005). SNRIs relieve the pain by increasing the availability of serotonin and noradrenaline in the descending pathways, which are inhibitory to pain impulses. The most frequently reported side effects are nausea, somnolence, dizziness and constipation (Goldstein et al., 2005; Raskin et al., 2005). Duloxetine is licensed for the treatment of painful diabetic neuropathy in UK (NICE guidance on PDN, 2013)

Other studies have found that the SNRI venlafaxine is also effective for pain relief in painful diabetic neuropathy (Kadiroglu et al., 2008). Side effects of this drug included somnolence, nausea, hypertension and in some cases, ECG changes. Because arrhythmia

is a major concern, especially when diabetes patients have coexisting cardiovascular disease, venlafaxine is not licensed for PDN (Jensen et al., 2006).

#### ***1.2.4.1.2 Anticonvulsants***

There are several old-fashioned and newer generation anticonvulsants that have been found to have beneficial effects in painful diabetic neuropathy. These include carbamazepine, phenytoin, sodium valproate, pregabalin, gabapentin, lamotrigine and topiramate. Anti-convulsants inhibit pain by either blocking sodium channels or binding to calcium ion channels, reducing the flux of sodium or calcium and thus reducing the release of neurotransmitter in hyperexcited neurones (Tesfaye, 2009). The common side effects from the use of anticonvulsants are somnolence, dizziness and in rare cases, liver derangements (Wong et al., 2007).

##### *Carbamazepine*

Carbamazepine stabilizes membranes by inhibiting sodium channels. Several double-blind placebo-controlled studies have demonstrated carbamazepine's effectiveness in the management of painful diabetic neuropathy, finding that it is particularly useful for lightning-like or shooting pain (Vinik et al., 1992). Carbamazepine is known to be associated with bone marrow suppression and osteoporosis. Due to its toxic side effects, and the development of newer anticonvulsants, its use is limited in PDN (Chong and Hester, 2007).

##### *Phenytoin*

Phenytoin was one of the first sodium channel blockers and it has long been used in PDN. Two crossover studies with phenytoin conducted in 1970 showed some benefit at 5 weeks

of treatment compared to placebo, but no benefit at 20 weeks (Chadda and Mathur, 1978). The long-term use of phenytoin is also known to be associated with osteoporosis, peripheral neuropathy and cerebellar ataxia. It is known to be toxic to the liver and thus requires monitoring of liver function. For these reasons, phenytoin is not generally used in painful diabetic neuropathy (Chong and Hester, 2007).

### *Sodium Valproate*

Sodium valproate potentiates the inhibitory neurotransmitter  $\gamma$ -Aminobutyric acid (GABA) in the brain. Its mechanism of action in neuropathic pain is still not fully understood. Double blind studies have shown modest benefits from sodium valproate treatment compared to placebo in PDN (Kochar et al., 2002; Sindrup et al., 2003). However, the long-term use of sodium valproate is associated with hair loss, weight gain, and in rare cases, liver toxicity. Because of the adverse effects and modest evidence of efficacy, sodium valproate is not widely used for PDN (Tesfaye, 2009; Chong and Hester, 2007).

### *Lamotrigine*

Lamotrigine is a new anticonvulsant sodium channel and presynaptic glutamate therapy, which may possess beneficial properties for pain relief. Studies have shown the possible benefits of lamotrigine in the treatment of PDN. However, these studies were small in sample size (n=10) and (n=59) (Eisenburge et al., 2001a; Eisenburge et al., 2001b). Lamotrigine is also known to be associated with Steven Johnson syndrome and bradycardia; therefore, careful titration of dose is needed (Fonseca, 2006). Due to limited evidence at present, lamotrigine is not widely used in painful diabetic neuropathy.

## *Gabapentin*

Gabapentin has been used since 1994 as an effective anticonvulsant that also has an analgesic effect in neuropathic pain (Gorson et al., 1999). Gabapentin inhibits voltage-gated sodium and calcium channels and has an analgesic effect at spinal cord (Backonja, 1999). Several studies have reported significant pain relief in PDN along with positive effect on mood and quality of life (Backonja, 1999; Vinik et al., 1998). A dosage of 1800 mg to 3600 mg per day may be required (American Diabetes Association (ADA) guidance on PDN, 2013). Doses that high, however, may have untoward side effects, the most disconcerting being weight gain (Fonseca, 2006). Gabapentin is licensed in the US for the treatment of PDN (ADA guidance on PDN, 2013).

## *Pregabalin*

Pregabalin is structurally related to gabapentin and has the same mode of action. Several studies have shown significant alleviation of pain in painful diabetic neuropathy (Rosenstock et al., 2004; Lesser et al., 2004; Richter et al., 2005; Freyhagen et al., 2005). While the doses used in these studies range from 150 mg/day to 600 mg/day, the drug was found to be significantly more effective at 300 mg/day to 600 mg/day. Rapid dose titration increases the risk of sedation and dizziness. High doses of pregabalin were reported to cause ankle edema and weight gain, and abrupt discontinuation could lead to cerebral edema (Oaklander and Buchbinder, 2005). In US and UK, pregabalin is licensed to treat PDN (NICE guidance on PDN, 2013; ADA guidance on PDN, 2013).

#### ***1.2.4.1.3 Opioids agonists***

Opioid agonists modulate pain by acting on peripheral nociceptors, presynaptic receptors, postsynaptic receptors, and on the descending system (Tesfaye, 2009). Tramadol has been found to show significant pain relief in PDN. In a randomised controlled study of 130 patients, tramadol at an average dose of 200 mg/day for 6 weeks showed statistically significant pain relief compared to placebo (Harati et al., 1998). However, higher doses (300 to 400 mg/day) are associated with high incidence of adverse effects, such as drowsiness, headache, nausea and constipation. The other opioid reported to be beneficial in PDN is oxycodone. Studies on oxycodone have shown alleviation of pain compared with placebo (Gimbel et al., 2003; Watson et al., 2003). Physicians are generally reluctant to use opioids for the long term in PDN due to serious adverse effects, including opioid dependency, constipation and impaired cognitive function.

#### ***1.2.4.1.4 Topical agents***

##### ***Capsaicin 0.075 % cream***

Capsaicin, a natural colloid extracted from red chilli peppers, works by depleting substance P from nerve terminals and has been found to be effective in neuropathic pain (Donofrio and Walker, 1991). Several studies have reported significant pain relief with topical application of capsaicin 0.075% in patients with PDN (Scheffler et al., 1991; Chad et al., 1990; Low et al., 1995). Sometimes, within the first 2 to 4 weeks of application, the treatment may actually cause worsening of neuropathic pain symptoms, including burning, tingling, stinging and erythema at application site. However, in general, when used sparingly 3 to 4 times a day on affected areas, it can provide effective relief of pain.

### *Lidocaine 5% Patch*

The lidocaine 5% patch acts as a local anaesthetic by blocking sodium channels and studies have reported significant improvements in the treatment of PDN (Devers and Galer, 2000; Barbano et al., 2004). One systematic review in 2010 compared lidocaine 5% plaster with various other medications in PDN and that found it to be comparable to amitriptyline, capsaicin, gabapentin and pregabalin, with no significant adverse effects reported with topical application (Wolff et al., 2010).

### *Topical nitrate*

The impairment of nitric oxide synthesis contributes to the pathogenesis of diabetic neuropathy. Topical nitrate acts by producing nitric oxide and working locally at the nerve site. Several studies on patients with PDN have demonstrated significant improvement in pain relief upon topical application of isosorbide dinitrate spray or glyceryl trinitrate patches (Yuen et al., 2002; Rayman et al., 2003).

### ***1.2.4.1.5 Other Pharmacological Treatments***

#### *Dextromethorphan*

Dextromethorphan is an NMDA receptor antagonist found to be effective in painful diabetic neuropathy. A randomized control trial comparing the drug to placebo reported significant pain relief in diabetic painful neuropathy using dextromethorphan (Nelson et al., 1970). However, the sample size was too small (n=13) to provide convincing evidence of efficacy. Further large studies are needed.

### *Lignocaine infusion*

Lignocaine is a sodium channel blocker first synthesized by Swedish chemist Nils Lofgren in 1943 (Lofgren et al., 1946). Lignocaine is widely used as a local anaesthetic and peripheral nerve blocker. It has been used intravenously for the treatment of arrhythmias and has also been found effective in chronic neuropathic pain (Tremont-Lukats et al., 2006) and chronic pain disorders (Cahana et al., 1998; Wallace et al., 2000). Furthermore, it is not associated with any significant side effects (Challapalli et al., 2005). The potential use of lignocaine infusion as a treatment for PDN was first evaluated by Kastrup in 1986 (Kastrup et al., 1987). Since then, several studies have reported pain relief in PDN. The duration of pain relief post lignocaine transfusion was variable among studies, from 3 days to 28 days (Bach et al., 1990; Kastrup et al., 1987; Viola et al., 2006). Lignocaine infusion is often reserved only for patients with persistent excruciating pain and for whom other medications are not beneficial. Due to practicalities of lignocaine infusion, including intravenous mode of administration the need for cardiac monitoring, its use is very limited.

### *Mexiletine*

Mexiletine, the structurally-similar, oral analogue of lidocaine, has the same mechanism of action, the blockade of sodium channels. The evidence thus far has shown variable pain relief in PDN (Jarvis and Couked, 1998). Two studies have reported significant pain reduction compared to placebo (Dejgard et al., 1988; Oskarsson et al., 1997), while two others reported no pain reduction compared to placebo (Stracke et al., 1992; Wright et al., 1997). Since it is an analogue of lidocaine, it could therefore be a drug of choice for those

people who respond well to IV lignocaine. However, further studies are needed to assess the efficacy of mexiletine.

## **1.2.4.2 Non- Pharmacological Therapies**

### *1.2.4.2.1 Transcutaneous electrical nerve stimulation (TENS)*

TENS has been used in variety of pain syndromes and has been found to be beneficial in PDN (Meyler et al., 1994). Its mode of action is thought to be the stimulation of nerves causing release of endogenous opioids and induction of the gate principle to prevent pain mediation (Shafter and Kitay, 1988). Several studies on TENS treatment have reported amelioration of pain perception in painful diabetic neuropathy (Alvero et al., 1999; Kumar and Marshall, 1997; Kumar et al., 1998; Julka et al., 1998). The advantage of TENS treatment is that it is portable and can be done by the patient, the current is low frequency, and it is safe to use (apart from someone who has pacemaker, in which case it is contraindicated).

### *1.2.4.2.2 Acupuncture*

Acupuncture works on the same principle of TENS. It is a well-known non-pharmacological method of treatment for a variety of pain syndromes. Several studies have shown that acupuncture significantly reduces pain perception in patients with PDN (Ahn et al., 2007; Kasuya, 2012; Abuaisha et al., 1998; Ewins et al., 1995). There are, however, limitations to the use of acupuncture, as it requires specialized skills and there is a lack of trained specialists in this field. Further research is needed to determine whether it is cost effective to provide acupuncture as a treatment under NHS.

#### *1.2.4.2.3 Electrical spinal cord stimulation*

Electrical spinal cord stimulation is an invasive treatment for PDN. An electrode is fitted into the spinal cord epidural space in the thoracic or lumbar region, and on stimulation it causes the release of endogenous opioids. Thus, it works on the same principle as TENS or acupuncture. Tesfaye et al. (1996) used electrical spinal cord stimulation for the first time in 1996 on patients with PDN and found promising results: 8 out of 10 patients showed significant pain reduction. In another study performed on 9 patients with whom conventional treatment was ineffective, 8 out of 9 patients reported to have significant pain relief for up to 6 months. For 6 of these patients, it was their only pain treatment (de Vos et al., 2008). There was another large multicentre prospective study on 36 patients with PDN resistant to conventional treatment used spinal cord stimulator and found 59% had adequate response till 6 months (Slangen et al, 2014). Electrical spinal cord stimulation has also been found to be safe overall, with the only side effects being peeling of the skin at the site of stimulator, and accidental damage of electrodes causing the need for replacement (Daousi et al., 2005).

#### *1.2.4.2.4 Psychological therapy*

Painful diabetic neuropathy has a huge psychological impact on patients, causing both physical and mental distress. The unremitting pain with contact hypersensitivity (allodynia) causes disturbances in sleep and withdrawal from social activity. Some patients may enter into a depressive phase. Psychological treatment mainly involves learning how to tackle the thoughts, emotions and distress that come with chronic pain. The aim is to train the patients cognitively in order to influence their thoughts and perceptions of the pain response, thus leading to diminution of distress and improvement

in activity and performance (Pither and Nicholas, 1991). A randomized controlled study of patients with PDN compared cognitive behavioural therapy (CBT) to treatment as usual (TAU). Out of the 20 patients who participated, 12 received CBT and 8 received TAU. Participants receiving CBT showed a significant decrease in pain severity and interference compared to the TAU group (Otis et al., 2013). There exist several challenges to the success of psychological therapy, including patient commitment, compliance with therapy, and availability of resources, such as the ability to provide such a service within the diabetes neuropathy clinic.

### **1.2.4.3 Combination treatment and National Guidance**

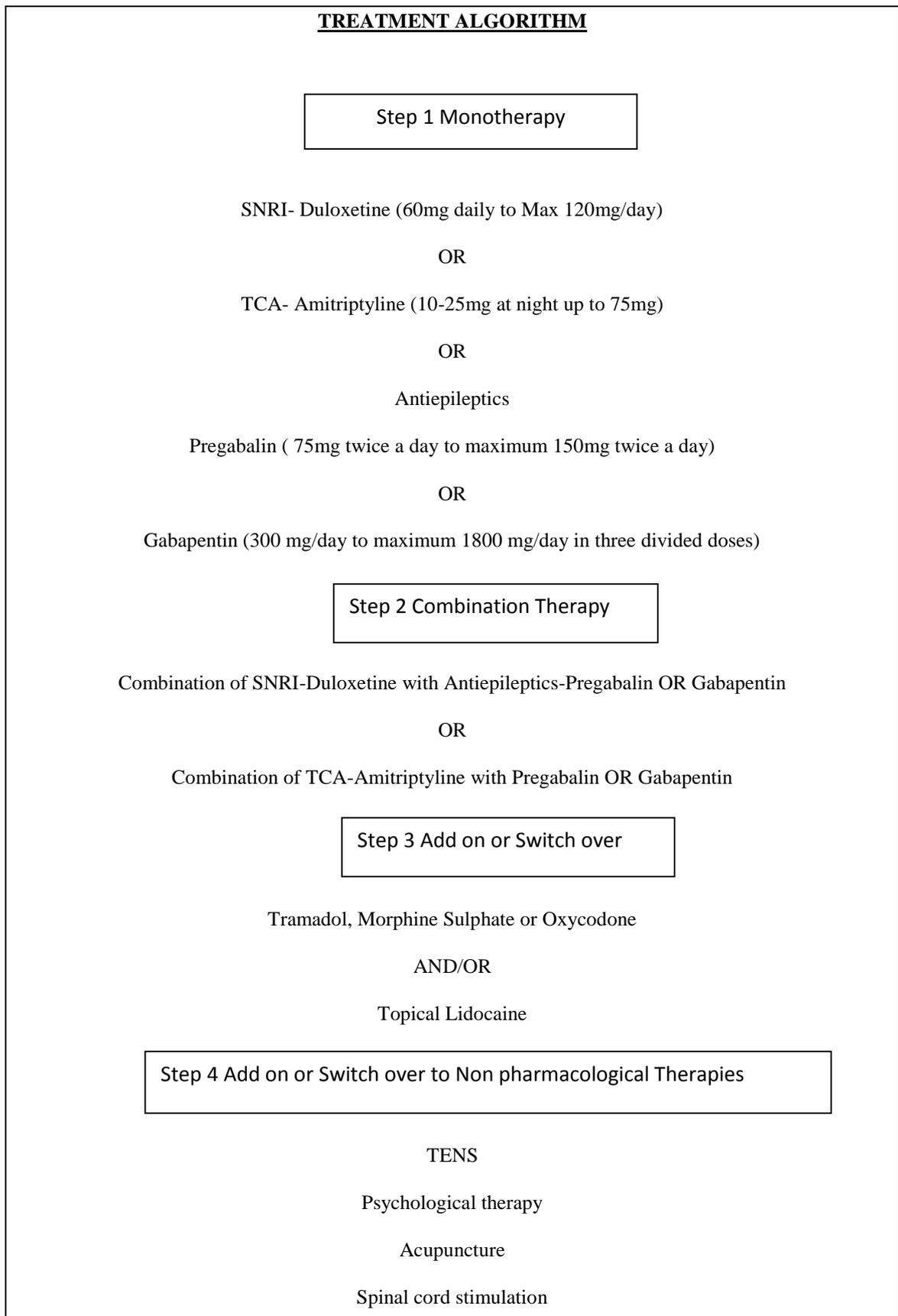
In March 2013, NICE (UK) issued their guidance regarding pharmacological treatment of neuropathic pain including PDN (NICE guidance on PDN, 2013). The first line treatment recommended by NICE is either duloxetine, amitriptyline, pregabalin or gabapentin. The choice of drug should be patient centred and consider tolerance of side effects and comorbidities. If one drug is not effective or not tolerated then switch over to one of the remaining 4 drugs. Tramadol to considered as a rescue drug for pain relief. The recommended starting duloxetine dose is 30 mg/day, with upward titration to a maximum of 120 mg/day. Amitriptyline starting dose at 10 mg/day with upward titration to a maximum of 75 mg/day. Pregabalin starting dose is 150 mg/day in divided dose to a maximum of 600 mg/day in divided dose and gabapentin starting dose is 300mg/day in divided dose to maximum 1800mg/day with upward titration. If first line treatment is unable to achieve satisfactory pain relief at the maximum tolerated dose, then NICE recommended, as a second line, to switch over to, or employ combinations of, other first-line medications. For example, if the first-line medication was with duloxetine, then the patient would switch to amitriptyline or pregabalin or combine duloxetine with

pregabalin. If first-line treatment was amitriptyline, then the patient would switch to pregabalin or combine amitriptyline with pregabalin. The third-line treatment recommended is to switch over to or add tramadol from 50 to 100 mg, 4 hourly, to a maximum of 400 mg/day. If pain control is still not satisfactory, this will require referral to a specialist in painful neuropathy.

For the US, the American Diabetes Association's (ADA) 2013 clinical practice recommendation for the treatment of PDN (ADA guidance on PDN, 2013) recommends first-line treatment with Amitriptyline, at a dose of 25 mg to 150 mg at bed time. The second line of treatment is to add on gabapentin gradually titrated up to 1.8 gram /day in three divided doses. The third line is to add on tramadol or oxycodone, and if pain control is not achieved, then consider referral to the pain clinic.

A large multinational double-blind study on 804 PDN patients evaluated duloxetine or pregabalin as a monotherapy at higher doses (duloxetine 120 mg/day and pregabalin 600mg/day) vs. combination therapy with standard doses of duloxetine (60 mg/day) and pregabalin (300mg/day). The study found no difference between the higher-dose monotherapy and the standard-dose combination therapy. However, at standard doses duloxetine was found to be superior in monotherapy compared to pregabalin (Tesfaye et al., 2013). The treatment algorithm flow chart, expressed as per National guidance NICE/ADA, is presented in Table 1.3 below.

**Table 1.3:** Treatment Algorithm of Painful diabetic neuropathy



### **1.2.5 Prognosis**

Patients with PDN usually suffer from constant and unremitting neuropathic pain, causing disturbances to sleep and having a huge impact on daily life. Social withdrawal and constant pain causes lowered mood and depression (Archer et al., 1983).

Acute painful neuropathy is usually observed in newly diagnosed diabetes or in patients with poor control of diabetes after starting insulin or other hypoglycaemic agents, termed in the literature as insulin neuritis (Larsen and Kronenberg, 2002; Caravati, 1933). Several case studies have reported the acute symptoms of painful neuropathy, including weight loss termed diabetic cachexia (Ellenberg, 1974; Larsen and Kronenberg, 2002; Archer et al., 1983; Caravati, 1933; Dabbya et al., 2009; Wilson et al., 2003). In all the cases studied, symptoms completely resolved and patients regained weight under neuropathic treatment within 6 months.

Despite advances in treatment, the chronic symptoms of PDN are challenging for clinicians and distressing to patients. Boulton et al. (1983) followed 39 patients with PDN over a period of 4 years after treatment and found no significant difference in the intensity of pain. Another 5-year follow-up study on PDN with conventional treatment reported that symptoms were resolved in only 23% of patients (Daousi et al., 2006). There have been limited studies on the natural course and prognosis of painful neuropathy; thus, further studies are needed. However, clinicians should be aware of the negative symptoms. If pain has resolved, the feet need to be examined. Sensory neuropathy may have gotten worse, which would cause disappearance of pain.

**(a) Working Hypothesis:**

Different aetiological factors are associated with painful diabetic neuropathy, including longer duration of diabetes, poor glycaemic control, increasing age, smoking, renal impairment and increased prevalence in Northwest England—all of which have significant impact on the quality of life for patients. In most cases, patients can be symptomatically treated with medications such as duloxetine, amitriptyline, and/or pregabalin, with lignocaine infusion used in challenging cases.

**(b) Main aim:**

The main aim of the project was to investigate the prevalence of PDN in the Chorley & Whiston towns of England, to identify the risk factors associated with the disorder, and to investigate the treatment and psychological impact of PDN.

**(c) Specific Aims of the Research:**

1. To identify prevalence of PDN in the Chorley and Whiston towns of England and identify the association of gender, age, duration of diabetes, smoking, alcohol, HbA1c, lipid profile and eGFR as risk factors for painful diabetic neuropathy as compared to diabetic neuropathy without pain.
2. To evaluate the psychological and physical impact of PDN on patients' lives.
3. To evaluate the effectiveness of lignocaine infusion treatment for PDN in challenging cases.

## **Format of the thesis**

This MSc by Research thesis contains one review article (part of the Introduction in Chapter 1) and three original research papers (each including an abstract, introduction, materials and methods, results and discussion) that are presented in Chapters 2, 3 and 4. All references are provided at the end of the paper. In addition, a general discussion is presented in Chapter 5, with concluding remarks and suggestions for future study.

## *Chapter 2*

*Prevalence and characteristics of painful diabetic neuropathy in  
the diabetic population of Northwest England.*

**Submitted to the Canadian Journal of Diabetes (under review)**

## **2.1 Abstract**

**Objective:** This study was conducted to assess the prevalence of painful diabetic neuropathy (PDN) and its relationship to various cardiovascular characteristics in diabetes subjects.

**Methods:** This was an observational study conducted in Chorley & Whiston towns of England, UK (n =204). The Self-completed Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) questionnaire was used by post to diagnose PDN. Consent for participation and access to blood results were provided by the diabetes subjects and ethical approval was granted National Research Ethics Committee UK.

**Results:** In this study, the crude prevalence of PDN was 30.3%. The prevalence of type 2 DM in the subjects was higher (33.1%) than type 1 (14.1%). We found a significant association of obesity, smoking and height in males to PDN, compared with the non-PDN group ( $P < 0.05$ ). We also saw a significant trend of increasing prevalence of PDN with duration of diabetes, increased HbA1c and increased BMI ( $P < 0.05$ ). A trend of increasing prevalence with age was also found ( $P > 0.05$ ); however, due to the small sample, the data was not statistically significant. There was no relationship between PDN and systolic or diastolic blood pressure, nephropathy, alcohol intake or blood cholesterol ( $P > 0.05$ ).

**Conclusion:** In this study, about 1/3 of all diabetic subjects suffered from PDN diabetic neuropathy. PDN was twice as prevalent in type 2 DM than in type 1, and a significant correlation with smoking, weight and height were seen. Prevalence of PDN increased with age, duration of diabetes, poor glycaemic control and obesity. These results highlight the importance of achieving better control of modifiable factors such as smoking, glycaemic control (HbA1c) and obesity.

## 2.2 INTRODUCTION

Diabetes mellitus (DM) affects about 382 million people worldwide and its prevalence is expected to increase to 592 million by the year 2035 (International Diabetes Federation (IDF), 2013). Diabetic neuropathy (DN), a well-known, long-term complication of DM, may affect almost half of the diabetic population (Tapp and Shaw, 2009) and is associated with higher morbidity and mortality (Vinik et al., 1994). DN encompasses a variety of clinical and sub-clinical presentations. Painful diabetic neuropathy (PDN) is a common type of diabetic neuropathy and the most common cause of neuropathic pain (Chong and Hester, 2007). The reported prevalence of PDN has varied from 11% in Rochester, Minnesota, USA, (Dyck et al., 1993) to 53.7 % in the Middle East (Jambart et al., 2011). One UK study published in 2011 reported the prevalence of PDN to be 21.5% in type 2 (T2) DM patients and 13.4% in type 1 (T1) DM patients, resulting in an overall prevalence of 21% (Abbott et al., 2011). Several studies have observed that that duration of DM and increased age are directly related to PDN (Jambart et al., 2011; Abbott et al., 2011; Tesfaye et al., 1996, Partanen et al., 1995). In a large, prospective EURODIAB study conducted in 16 European countries, almost one-quarter of type 1 DM patients developed new-onset PDN over a seven-year period (Teskaye et al., 1996). A prospective study in Finland followed newly diagnosed diabetes patients between the ages of 45 and 64 years for 10 years and found a 6% prevalence of PDN at the time of DM diagnosis and a 26.4% prevalence at the 10-year follow-up (Partanen et al., 1995). Most studies found no significant difference in genders; However. Abbot et al. (2001), reported a slightly higher prevalence of painful symptoms of neuropathy in females (38%) than in males (31%). The same study also found a higher prevalence of painful symptoms in South Asians (38%) compared to Europeans (32%).

Several validated diagnostic questionnaires are available to aid in the diagnoses of neuropathic pain, including the Neuropathic Symptom Score (NSS), the Douleur Neuropathique en 4 Questions (DN4), the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale and the Self completed LANSS (S-LANSS). These questionnaires have all been used in various prevalence studies of PDN. Jambart et al. (2011) used the DN4 questionnaire in the Middle East and reported highest prevalence of PDN found to date, at 53.7%. Erbas et al. (2011) used the LANSS questionnaire and reported a PDN prevalence of 16% in the Turkish diabetic population. Abbot et al. (2011) used the NSS questionnaire and observed a 21% prevalence in United Kingdom diabetic population. S-LANSS is a self-completed version of LANSS. Bennett et al. (2005) compared the S-LANSS postal survey with the interview format and found that the S-LANSS scale correctly identified 75% of pain types when self-completed and 80% when used in interview format. These findings support the use of the S-LANSS scale as a valid and reliable self-report instrument for identifying neuropathic pain that is also acceptable for use in postal survey research. As such, several studies have used the S-LANSS questionnaire to diagnose neuropathic pain including PDN (Yunus and Rajbhandari, 2011; Cho et al., 2014, Torrance et al., 2013). Liberman et al. (2014), for example, used the S-LANSS questionnaire and observed a 46.5% prevalence of PDN in the Israel diabetic population, while Younis and Rajbhandari (2011) used the S-LANSS to confirm the presence of neuropathic discomfort in diabetic foot ulcers.

The S-LANSS questionnaire is based on self-assessment performed by the patient and thus does not require healthcare professional input or examination to complete. It is a validated tool, is easy to use, and data can be collected easily from the targeted population via postal service. It is also routinely used in some diabetes neuropathy clinics. In contrast, the NSS questionnaire used by Abbot et al. (2011) in a PDN prevalence study

on 10,000 diabetic patients required assessment and examination by the healthcare professionals in order to complete the questionnaire. Although the S-LANSS questionnaire is comparatively easier to use, its completion depends on patient understanding of the questions. We chose the S-LANSS questionnaire for this study due to its ease of use and the fact that it is a validated tool that can be administered via postal survey (Bennett et al., 2005).

The main aim of this study was to assess the prevalence of PDN using the postal self-administered S-LANSS questionnaire and to identify the associations of gender, age, duration of diabetes, smoking, alcohol, HbA1c, lipid profile and eGFR as risk factors for PDN in comparison to diabetic neuropathy without pain.

### **2.3 SUBJECTS & METHODS**

Primary care subjects were identified from patients with the diagnosis of DM in the General Practice database of Aston Healthcare, Whiston, Merseyside. Secondary care subjects were identified from the Diabetes Alliance for Research in England (DARE) database at Lancashire Teaching Hospitals NHS Trust. Patients under 16 and over 80 years of age were excluded. All patients were mailed a Modified S-LANSS questionnaire through the postal service. An information leaflet, consent form for participation and access to blood results, and a self-addressed return envelope were included in the mailing. In the modified S-LANSS questionnaire, a score of 12 or more and a bilateral stockings, or stockings and gloves distribution of pain were the criteria for the diagnosis of PDN in this study. The laboratory data and medical records held at Lancashire hospitals NHS Trust and Aston Health Care, Whiston were used for this study. Ethical approval was granted by the National Research Ethics Service, UK, and institutional approvals were

obtained from Lancashire Hospitals NHS Trust, Aston Health Care, Whiston, and the University of Central Lancashire.

### ***2.3.1 Statistical Analysis***

Data were analysed using Graph Pad software (Graphpad Inc USA, 2013). The continuous variable were normally distributed and expressed as means, +/- standard deviation (SD), median, 95% confidence interval and *P* value. The means were analysed by unpaired Student's *t*-test. Categorical data were expressed as frequency distribution and percentage of subjects groups along with *p* value. The categorical data were also analysed by 2x2 table using Fischer's exact test. The continuous variable descriptive statistics and trend in groups were calculated with the chi-square test using Minitab statistical software (Minitab statistical software, 2013).

## ***2.4 RESULTS***

A total of 205 patients with diabetes were identified from primary care and 266 from secondary care and sent the pre-paid postal questionnaire. The total of 204 (43.3%) returned the postal modified S-LANSS questionnaire with the signed consent form. The number of secondary care subjects that responded was 48.7% (n=130) compared to 36% (n=74) from the primary care group. The mean age (+/-SD) of subject was 64.1 +/- 12.11 years. There was a total of 125 males (61.2%) with mean age (+/-SD) of 64.5 +/- 11.5 years, and 79 females (38.7%) with mean age (+/-SD) of 63.7 +/- 13.2 years. The ages in both genders were similarly distributed (*P* > 0.05). A total of 123 (60.2%) subjects with diabetes reported pain in the questionnaire. Further S-LANSS questionnaire assessment was done on all 123 of the subjects who reported pain. A total of 62 (50.4%) of the subjects who had complained of pain fulfilled the criteria of PDN with the mean (+/-SD)

S-LANSS score of 18.1 (+/- 4.0). The overall prevalence of PDN in the population studied was 30.3% (n = 62, confidence interval (CI) = 24.4 – 37.0), and fairly comparable for males (30.4%, n=38, CI 23.0 – 38.9) and females (30.3 %, n= 24, CI 21.3 – 41.2) ( $P = 1.0$ ). The prevalence of PDN among T2DM patients was 33.1% (n= 57, CI 26.5 – 40.4), which was significantly ( $P < 0.05$ ) higher than in T1DM (14.2% (n= 4, CI 5.0 – 32.1) ( $P = 0.048$ ) (see Table 2.1).

**Table 2.1:** Prevalence of PDN in the study population. Data expressed as percentages.

Groups (n)	Subjects with PDN			Prevalence of PDN	
	(n)	(Age) Yrs +/- SD	(Duration of DM) Yrs +/-SD	(%)	(95% CI)
Total study group (n=204)	62	62+/- 10	12.9+/-8.8	30.3	24.4 – 37.0
Males (n=125)	38	63.7+/- 13.2		30.4	23.0 – 38.9
Females (n=79)	24	60+/- 12.1		30.3	21.3 – 41.2
T1DM (n=28)	4	55.5+/- 9.11	31.75+/-13.2	14.2	5.0 – 32.1
T2DM (n=172)	57	62.93+/- 10.94	11.79+/-6.82	33.1	26.5 – 40.4
Unknown type (n=4)	1			25	3.4 – 71

The overall prevalence of PDN in the secondary care group was 33% (n=43). This was statistically no different from the primary care group (25.6%; n=19) ( $P= 0.34$ ). Details are provided in Table 2.2.

**Table 2.2:** Prevalence of PDN in Hospital and GP groups. Data expressed as percentages.

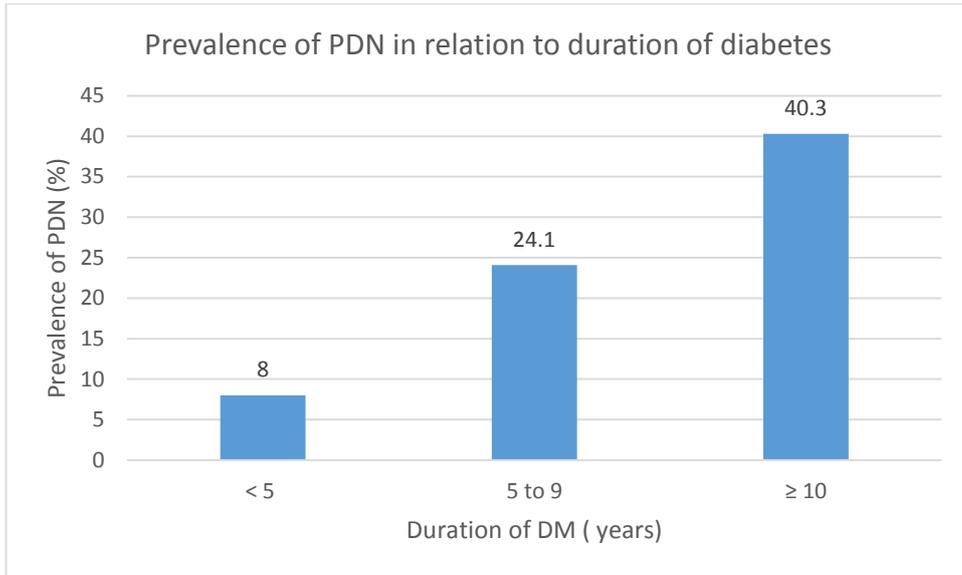
Prevalence of PDN			
Group (n)	Hospital Group (n)	GP Group (n)	P value
(n = Total )	(n = subjects with PDN)		
Male (125)	34.5% (28)	22.7% (10)	0.222
Female (79)	30.6% (15)	30.0% (9)	1.000
Type 1 Diabetes (28)	11.5% (3)	50% (1)	0.269
Type 2 Diabetes (172)	39.0% (39)	25.0% (18)	0.070

The clinical and biochemical characteristics of the study groups, either with or without PDN, are shown in Table 2.3. Taller height in males, increasing body weight and BMI, and smoking history, were associated with the presence of PDN ( $p<0.05$ ).

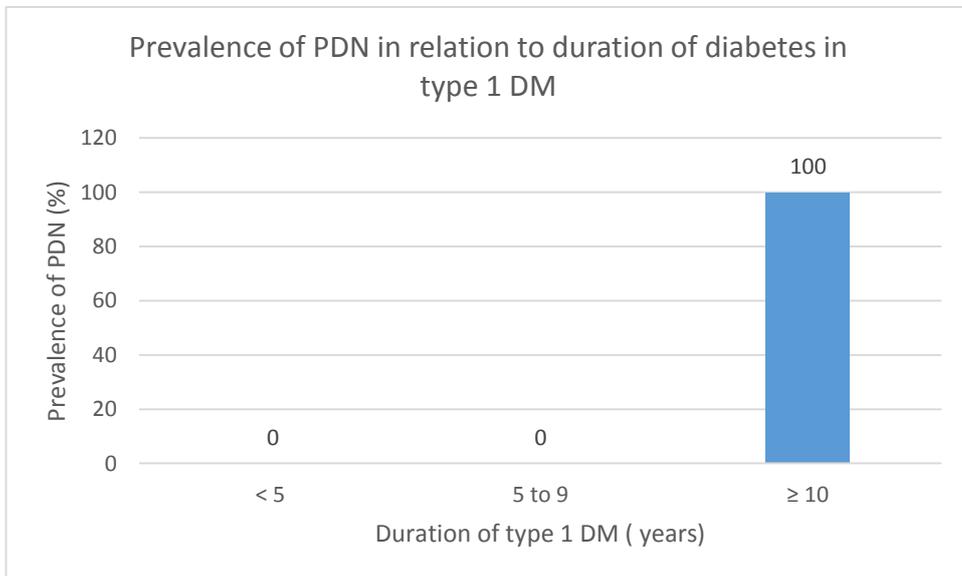
**Table 2.3:** Demographic and clinical variables and characteristics comparing subjects between PDN and non- PDN groups. Data are mean +\_SD; \*  $p < 0.05$  statistical significant

	(Non PDN group)	(PDN group)	
Variables	(n = 142)	(n = 62)	P value
	Mean +/- SD	Mean +/- SD	
Age (years)	64 +/- 12	62 +/- 10	0.179
Males (n=125)	64.5 +/- 11.5	63.7 +/- 13.2	0.634
Females (n=79)	65.0 +/- 13.5	60 +/- 12.1	0.177
Height (cm)	168.96 +/- 8.94	170.36 +/- 11.07	0.423
Male	173.3 +/- 6.4	176 +/- 6.7	0.023*
Female	160.2 +/- 6.3	159.1 +/- 7.61	0.591
Weight (Kg)	90.1 +/- 23	106.6 +/- 27	0.0001*
> 80 Kg	99.9 +/- 20.8	110.4 +/- 26.3	0.015*
< 80 Kg	67.4 +/- 8.3	68.0 +/- 4.24	0.894
Body mass index (Kg/m <sup>2</sup> )	31.8 +/- 8.1	37.1 +/- 9.0	0.0005*
Systolic BP (mm Hg)	135.8 +/- 19.1	138 +/- 16.8	0.473
Diastolic BP (mm Hg)	75.5 +/- 12.0	76.8 +/- 9.1	0.453
Duration of diabetes (years)	13.5 +/- 9.8	12.9 +/- 8.8	0.725
HbA1c (mmol/mol)	59.2 +/- 15.4	60.5 +/- 14.8	0.588
Urine ACR (mg/mmol)	4.8 +/- 21.6	9.6 +/- 32.6	0.233
eGFR (mls/min/1.73 <sup>2</sup> )	70.8 +/- 19.3	71.2 +/- 18.3	0.889
Creatinine (umol/L)	92.4 +/- 69.5	90.3 +/- 39	0.826
Total Cholesterol (mmol/L)	4.0 +/- 0.9	4.1 +/- 1.2	0.672
Smoking % (n)	47.1 (67)	74.1 (46)	0.0004*
Alcohol n (%)	85 (59.8)	36 (58.0)	0.877
Management n (%)			
Diet only	11 (7.7)	5 (8.0)	1.000
OGLA	68 (47.8)	33 (53.2)	0.540
Insulin	31 (21.8)	9 (14.5)	0.25
OGLA + Insulin	32 (22.5)	15 (24.1)	0.857

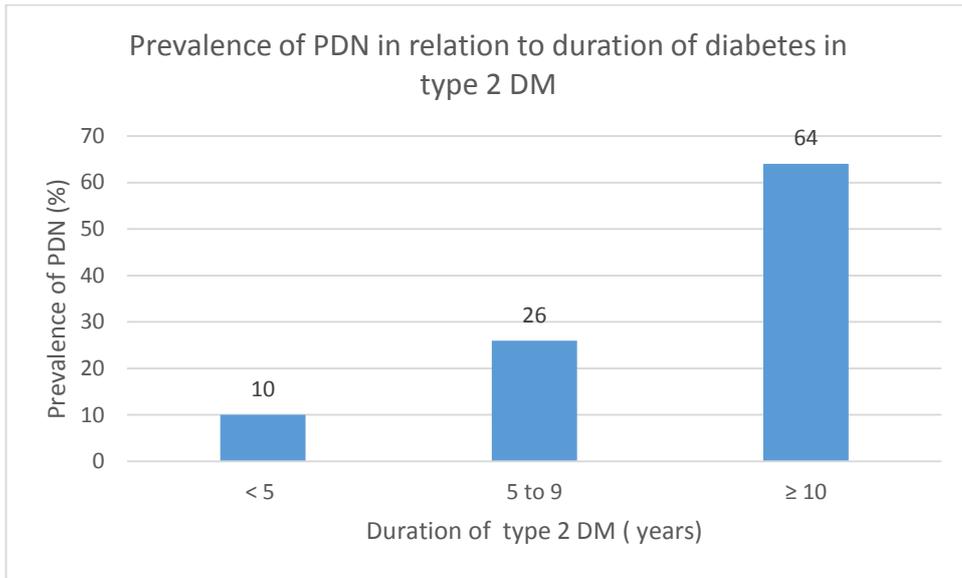
The results also show a significant ( $P < 0.0001$ ) linear trend in the prevalence of PDN with the duration of DM in years overall (<5years: 8%; 5-9: 24.1%;  $\geq 10$ : 40.3%, trend  $X^2$ : 99.38,  $P < 0.0001$ ) (Figure 2.1), in type 1 DM (<5years:<1%; 5-9: <1%;  $\geq 10$ : 100%, trend  $X^2$ : 23.58,  $P < 0.0001$ ) (Figure 2.2), in type 2 DM (<5years:10%; 5-9: 26%;  $\geq 10$ : 64%, trend  $X^2$ : 60.49,  $P < 0.0001$ ) (Figure 2.3), increasing HbA1c (HbA1c < 6.5% (48 mmol/mol): 20%; 6.6% – 7.4% (49-57 mmol/mol): 34%;  $\geq 7.5\%$  (58 mmol/mol): 53.1%; trend  $X^2$ : 107.83,  $P < 0.0001$ ) (Figure 2.4) and increasing BMI (BMI <28: 12.7%; 28-34: 34%;  $\geq 35$ : 53.1%; trend  $X^2$ : 16.27,  $P < 0.023$ ) (Figure 2.5). There was also a linear trend in the prevalence of PDN observed with increasing age (age < 40: 3.2%; 40-49: 6.4%; 50-59: 17.7%; 60-69: 32.3%; > 65: 40.3%; trend  $X^2$ : 14.38,  $P = 0.109$ ) (Figure 2.6). However, these data were not statistically significant.



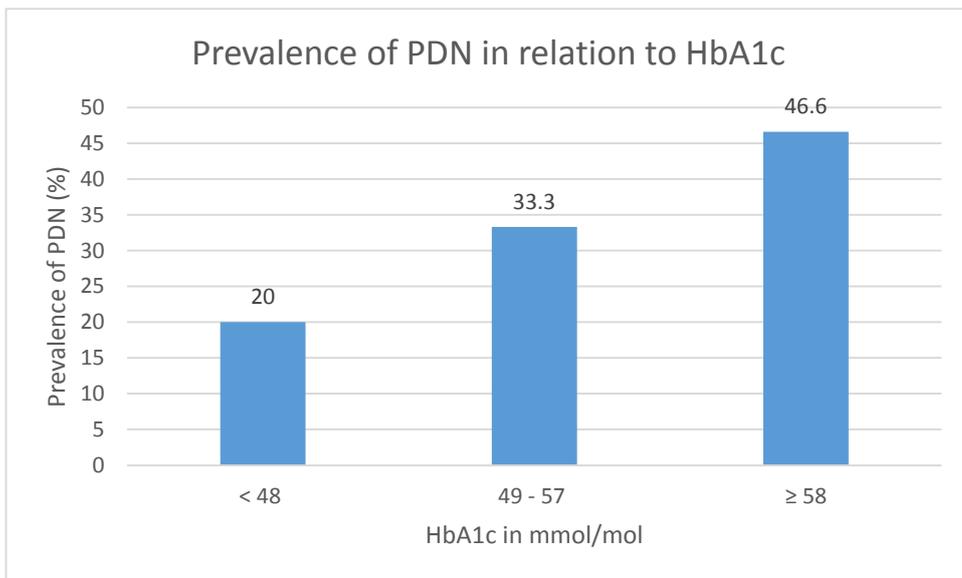
**Figure 2.1:** Prevalence of PDN in relation to duration of DM in years. Trend  $X^2$ : 99.38;  $*P < 0.0001$ .



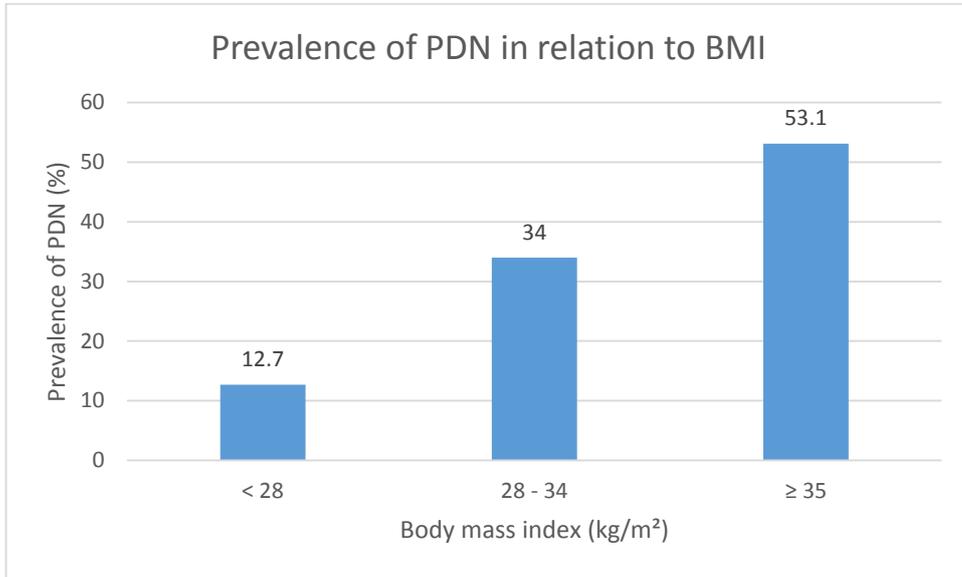
**Figure 2.2:** prevalence of PDN in relation to duration of diabetes in type 1 DM in years. Trend  $X^2$ : 23.58;  $*P < 0.0001$



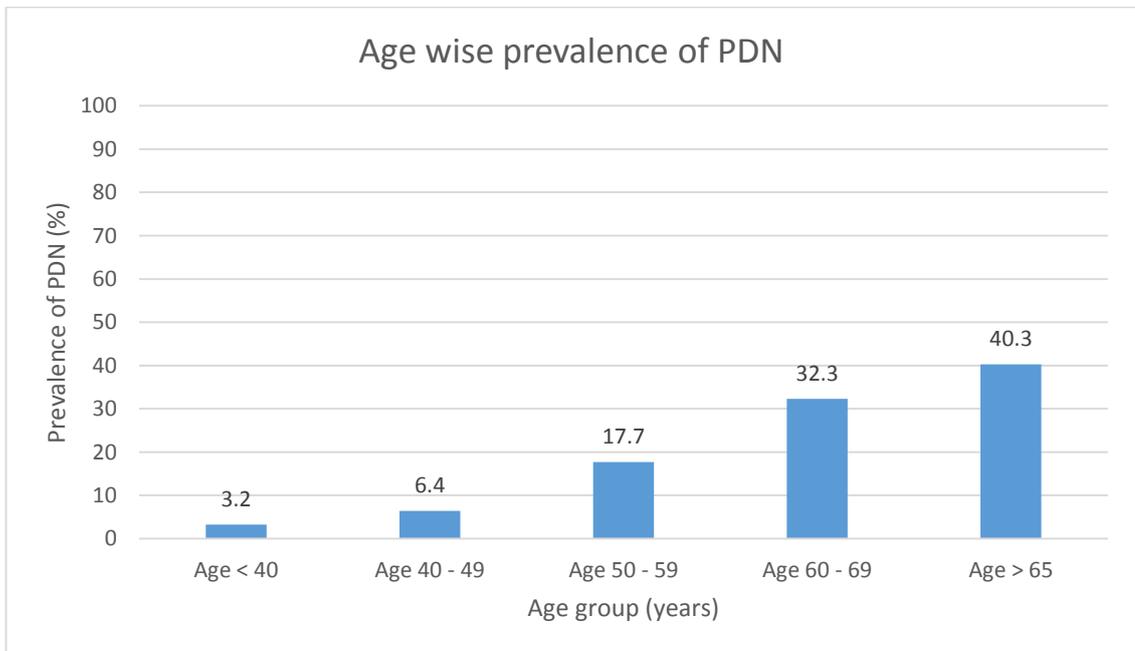
**Figure 2.3:** prevalence of PDN in relation to duration of diabetes in type 2 DM in years. Trend  $X^2$ : 60.49;  $*P < 0.0001$



**Figure 2.4:** Prevalence of PDN in relation to HbA1c in mmol/mol. Trend  $X^2$ : 107.83;  $*P < 0.0001$ .



**Figure 2.5:** Prevalence of PDN in relation to body mass index (BMI) kg/m<sup>2</sup>. Trend  $X^2$ : 16.27; \*  $P = 0.023$



**Figure 2.6:** Prevalence of PDN in relation to age in years. Trend  $X^2$ : 14.38,  $P > 0.109$

## **2.5 Discussion:**

Painful diabetic neuropathy (PDN) is a common type of diabetic neuropathy and the most common cause of neuropathic pain (Chong and Hester, 2007). It has a huge impact on people's quality of life, both physically and mentally. In this investigation, the crude prevalence of PDN in the study population in Chorley & Whiston towns of England, UK was 30.3%. The prevalence of T2DM among subjects was higher (33.1 %) compared to T1DM subjects (14.1%). There was a significant association of obesity (increasing weight and BMI), smoking and height in males to PDN, compared with the non-PDN group. There was also a significant trend of increasing prevalence of PDN with duration of DM, increasing HbA1c and increasing BMI. There was also a trend of increasing prevalence with age; however, due to the small sample size, the data were not statically significant.

### ***2.5.1 Comparison with existing data***

Numerous studies have reported the prevalence of PDN in diabetes with varied results, reporting levels from 11% in Rochester, USA (Dyck et al., 1993) to 53% in the Middle East (Jambart et al., 2011). The variation in PDN prevalence numbers is likely due to the different diagnostic criteria used in the studies. Likewise, there are some actual geographical and population contributions to these findings. Jambart et al. (2011) reported the highest prevalence of PDN seen to date, in the Middle East (53%) using the DN4 score. Similarly, using the S-LANSS questionnaire, Liberman et al. (2014) observed 46.5% prevalence of PDN in the Israel diabetic population. Erbas et al. (2011) used the LANSS questionnaire in Turkey and reported 16%. The present study used the S-LANSS questionnaire in Northwest England and found a crude prevalence of 30.3%, which is comparable to a study by Abbot et al. (2011) in the Northwest England that used the NSS questionnaire and reported a prevalence of painful symptoms of 34%. Similarly, a study

by Davies et al. (2006) in the Wales population in the UK used neurological history and examination with the Toronto clinical scoring system and reported a 26.4% prevalence of PDN in diabetes sufferers.

### *Type 1 vs. type 2 diabetes*

In the present study, the prevalence of PDN in T1DM was 14.1% and 33.1% in T2DM. These results are more or less similar to the study of Abbot et al. (2011), who reported a prevalence of 22.7% and 35% for painful symptoms in T1DM and T2DM, respectively.

### *Gender*

In present study, there was no difference in prevalence by gender (males: 30.4% and females 30.3%). This is similar to other studies, but differs from Abbot et al. (2011) who reported higher prevalence of in females (38%) compared to males (31%).

### *Height*

The present study also found that increasing height among males was significantly associated with PDN. This is similar to the results of a EURODIAB study (Tesfaye et al, 1996) in which the authors found an association between increasing height and PDN.

### *Obesity*

Jambart et al. (2011) reported that obesity with BMI greater than 30 was significantly associated with PDN. Similarly, the present study found a strong association of obesity, with weight above 80 Kg ( $P < 0.0001$ ) and increasing BMI ( $P < 0.0005$ ) showing a linear trend of increasing prevalence of PDN (BMI <28: 12.7%; 28-34: 34%; and  $\geq 35$ : 53.1%; trend  $X^2$ : 16.27,  $P < 0.05$ ) (Figure 3).

### *Smoking*

In the EURODIAB study, Tesfaye et al. (1996) reported smoking to be significantly associated with PDN, similar to the results from this study where PDN was significantly associated with smoking ( $P < 0.0004$ ). In contrast, Abbott et al. (2011) found no correlation between PDN and smoking.

### *Alcohol*

The present study shows no significant association between PDN and alcohol consumption. These findings are similar to the studies by Abbot et al. (2011) and Tesfaye et al. (1996), who reported no significant correlation between PDN and alcohol consumption.

### *Cholesterol*

The present study demonstrated no correlation between PDN and increasing levels of cholesterol. This is similar to Tsuji et al.'s (2013) study, in which the authors found no correlation between PDN and cholesterol. In contrast, the EURODIAB study by Tesfaye et al. (1996) found a significant correlation between PDN and increasing levels of cholesterol.

### *Blood pressure*

The present study found no correlation between systolic or diastolic blood pressure and PDN. These data are similar to those obtained by Tsuji et al. (2013). In contrast, Tesfaye et al. (1996) found significant correlation between diastolic blood pressure and PDN in their EURODIAB study.

### *Nephropathy*

The present study demonstrated no correlation between renal function and PDN. These data are similar to those obtained by Tsuji et al. (2013) but in contrast to the findings of Jambart et al. (2011) of significant correlation between nephropathy with PDN. In the present study, urine ACR was higher in the PDN group (mean 9.6 +/- 32.6) compared to the non-PDN group (mean 4.8 +/- 21.6). However, due to the small sample size, the data were not statistically significant.

### *Duration of diabetes*

The present study also found a statistically significant linear trend of increasing prevalence with duration of DM—8% in those with DM for less than 5 years, 24.1% with up to 9 years and almost double, and 40.3% with 10 years. The present data are in close agreement with those obtained by Jambart et al. (2011) and Tesfaye et al. (1996).

### *Poor Glycaemic control*

Similarly, the present study found a linear trend of increasing prevalence with poor glycaemic control (HbA1c < 6.5% (48 mmol/mol): 20%; 6.6% - 7.4% (49-57 mmol/mol): 33.3%; and HbA1c ≥ 7.5% (58 mmol/mol): 46.6%; trend  $X^2$ : 107.83,  $P < 0.0001$ ). In their study, Tesfaye et al. (1996) found significant correlation between PDN and poor metabolic control.

### *Age*

The present study also found a linear trend of increasing prevalence of PDN with increasing age (age < 40: 3.2%; 40-49: 6.4%; 50-59: 17.7%; 60-69: 32.3%; > 65: 40.3%;

trend  $X^2$ : 14.38,  $P=0.109$ . This was similar to the findings of Abbot et al. (2011), who demonstrated a significant increase in PDN prevalence with increasing age. The age-wise prevalence data in this study, however, were not statistically significant due to a small sample.

### ***2.5.2 Strengths and limitations of the study***

The study population was well defined for both the Hospital and General Practice groups. All subjects with diabetes between the ages of 16 to 80 registered at GP practice and all subjects with diabetes in the DARE database had previously agreed to participate in future research at Lancashire Hospitals NHS Trust, and were invited to participate in our study by post. Because we aimed to minimize the Berkson selection bias, participants were recruited from both hospital/secondary care and general practice/primary care. Regarding responses, both groups of participants responded to the study, but with less than 50% of the total invited. Of this percentage, 48.7% came from hospital group and 36% from GP practice group. Both groups completed the S-LANSS questionnaire and provided demographic data. Both groups were also similar in age and had a similar ratio of males to females.

A major limitation of the study was related to the selection bias of both Hospital group and GP group patients. Hospital group patients were selected from the DARE database where patients were already volunteered for future diabetes research. Secondary care enrolment suggests severity of the disease with multiple comorbidities. Furthermore primary care group lies in the low socioeconomic community status area. Poor socioeconomic areas are known to have higher cardiovascular risks and comorbidities. Cardiovascular risks and comorbidities are known to have direct association with PDN. These discrepancies and lack of randomisation in the study, could have led to selection

bias, which could have an impact on outcome. Recall bias could exist during completion of the questionnaire. Questions on the S-LANSS questionnaire were based on current or recent characteristics of pain; hence, recall bias in the best scenario is expected to be minimal. However it requires ability to read, understanding of the questions and physically able to write the response and post it to the researcher. The outcome was based only on those patients who responded with their understanding of the questions hence recall bias could not be ruled out.

## **2.6 Conclusion**

The study found that about 1/3 of all diabetic subjects in the study suffered from painful diabetic neuropathy. It was twice as prevalent in type 2 diabetes than in type 1. There was a significant correlation of PDN with smoking & height. Prevalence of PDN also increased with age, duration of diabetes, poor glycaemic control and obesity. As painful diabetic neuropathy has a huge impact on quality of life (Quattrini and Tesfaye, 1996), this study highlights the importance of better control of modifiable factors such as smoking, glycaemic control (HbA1c) and obesity. Controlling these factors may not only prevent cardiovascular disease but also prevent the occurrence of painful diabetic neuropathy.

## ***Chapter 3***

***The impact of painful diabetic neuropathy on quality of life***

**Currently in press in the journal Diabetes and Primary Care**

### **3.1 Abstract**

Diabetes is a common disorder affecting over 380 million people worldwide. It is associated with several long-term complications, one of which is painful diabetic neuropathy (PDN). About a third of diabetes subjects experience PDN, a distressing condition that affects patients both physically and emotionally. This aim of this study was to assess the quality of life (QoL), mood and anxiety in diabetic patients with PDN using the Short form (SF36) and Hospital Anxiety and Depression Scale (HADS Scale) questionnaires. When PDN patients were compared with diabetic patients without PDN (Control group), the results revealed that PDN was significantly associated with impaired QoL, both physically ( $p < 0.0001$ ) and mentally ( $p < 0.026$ ). Anxiety also was significantly associated with the PDN group compared to control ( $p < 0.018$ ), and depression was 16% more prevalent in the PDN group than in control.

### **3.2 Introduction**

There are currently about 382 million people worldwide living with diabetes mellitus (DM) and it is estimated that this figure will rise to 592 million by the year 2035 (International Diabetes Federation, 2013). The prevalence of DM-related complications are also rising. PDN is a common complication of DM, affecting about 1/3<sup>rd</sup> of all patients with diabetes (Tesfaye and Boulton, 2009). PDN is characterized by bilateral symmetrical distal neuropathic pain in the lower extremities with varied symptoms from mild pins and needles, tingling sensations, shooting pain similar to electric shock, constant burning sensation with nocturnal exacerbation, and contact hyper-sensitivity-allodynia (Larsen and Kronenberg, 2002). Relentless pain and allodynia affect patients both physically and mentally, causing disturbances in sleep, lowered mood, sexual impotence and social withdrawal. In extreme cases, the patient is unable to walk (Galer et al., 2000; Quattrini and Tesfaye, 1996; Gardner and Shoback, 2007). PDN can thus significantly alter a patient's quality of life. Currently, there are only few studies that have specifically measured the physical and mental impacts of PDN on patients' quality of life. This study was designed to assess the quality of life (QoL), mood and anxiety in patients with PDN (PDN group) compared to patients with diabetes not known to have PDN (Control group).

There are several health related questionnaires available to assess QoL, and physical and mental wellbeing (Healthmeasurement.org, 2014). Most researchers typically use the short form health survey (SF36) for the assessment of QoL and hospital anxiety and depression scale (HADS) for the assessment of mood and anxiety. Ware and Sherbourne (1992) introduced the 36-item short form health survey (SF36) in 1992. It was designed for use in clinical practice and research, health policy evaluations, and general population surveys.

The SF36 includes 36 subjective questions that assess eight health concepts of QoL from the patient's point of view. These include:

- 1) Limitations on physical activities due to health problems.
- 2) Limitations on social activities due to physical or emotional problems
- 3) Limitations on usual roles and associated activities due to physical health problems
- 4) Bodily pain
- 5) General mental health (psychological distress or well-being)
- 6) Limitations on usual roles and associated activities due to emotional problems
- 7) Vitality (energy or fatigue)
- 8) General health perceptions

SF36 is practical, reliable and valid measure of physical and mental health and has been used in a variety of chronic health conditions, including diabetic neuropathic pain (Ware et al., 1994; Garratt, 1993; Vinik et al. 2013; Rosenstock, 2004) and published in more than 4,000 documents (Turner-Bowker et al., 2002).

The HADS questionnaire was originally developed by Zigmond and Snaith (1983) for use in psychometric evaluation. Since then, it has been widely used worldwide by health professionals, both in the community and hospital settings and has been found to be both a reliable and a valid measure of anxiety and depression (El-Rufaie and Absood, 1987; Nortvedt and Riise, 2006). The HADS questionnaire contains 14 questions, seven for the assessment of anxiety assessment and seven for depression. HADS provides clear cut-off scores for the severity of anxiety and depression. Since HADS is believed to be

an ideal tool for screening and an index measuring clinical change, it was decided to employ this questionnaire to measure the QoL in diabetic patients along with the SF-36.

### **3.3 Methods**

#### ***3.3.1 Participants***

This was an observational study conducted to assess quality of life, mood and anxiety in patients with PDN attending the Diabetic Neuropathic Pain Clinic at Chorley District General Hospital (CDGH). The PDN group was compared to diabetic patients not known to have neuropathic pain (Control group), who attended the Aston Healthcare General Practice (GP) Surgery for diabetes review at Whiston in Merseyside, UK. Institutional approvals were obtained at both centres for the study. A total of 25 consecutive patients with PDN were selected at Chorley DGH during their follow-up visit at the diabetic neuropathy pain clinic. The mean age ( $\pm$  SD) of subject was 56.4  $\pm$  11.4 years. There was a total of 15 males (60%) with mean age ( $\pm$  SD) of 55  $\pm$  10.2 years, and 10 females (40%) with mean age ( $\pm$  SD) of 58.6  $\pm$  13.4 years. The ages in both genders were similarly distributed ( $P > 0.05$ ). Another 25 consecutive patients with diabetes but without PDN were selected on their routine visits at GP surgery. There was a total of 14 males (56%) with mean age ( $\pm$  SD) of 57.7  $\pm$  14.5 years, and 9 females (44%) with mean age ( $\pm$  SD) of 55  $\pm$  15.8 years. The ages in both genders were similarly distributed ( $P > 0.05$ ). Patients under 16 and over 80 years of age were excluded from participation. All patients gave consent for participation.

#### ***3.3.2 Study Design***

The SF36 and HADS (Hospital Anxiety and Depression Score) questionnaires were used for data collection, based on the rationale described above. The SF36 requires about 15

minutes to complete, and HADS 5 minutes, which meant that participants were able to complete the questionnaires while waiting for their appointments. Alternatively, they were given the choice to send it through post after completing it at home.

### ***3.3.3 Assessment of quality of life, anxiety and mood.***

#### *SF36 used for QoL assessment*

The SF36 questionnaire consisted of 36 questions that were scored from 0 (worse possible functioning) to 100 (highest level of function). Aggregate scores were compiled as a percentage of the total points possible using the RAND scoring system (Rand.org, 2013). The average scores from those questions that addressed a specific functional health domain were the final score of the domain. There were eight domains: four for physical health (physical function, role limitation due to physical health, pain and general health) and four for mental health (role limitations due to emotional problems, low energy/fatigue, emotional well-being and social functioning). The scores for each individual domain and the average aggregate scores for the physical and mental health domains were expressed as a percentage, with 0 representing the worse possible health state and 100 representing highest level of functioning and health.

#### *HADS questionnaire used for the assessment of anxiety and mood*

The HADS questionnaire contained a total of fourteen questions, seven questions for anxiety and seven for depression. Each question was scored from 0 (excellent mental health) to 3 (poor mental health). The sum of all seven questions score was the final score for either anxiety or depression, which ranged from 0 to a maximum of 21 (worst possible mental health). Scores between 0 to 7 were normal HADS scores for both anxiety and

depression assessment. Scores 8 and above were considered to be significant for the diagnosis of both anxiety and depression (El-Rufaie and Absood, 1987; Nortvedt and Riise, 2006).

### **3.3.4 Statistical Analysis**

Data were analysed using Graph Pad software (Graph pad software Inc. USA, 2013). The continuous variable of SF36 and HADS were normally distributed and expressed as means, +/- standard deviation (SD), median, 95% confidence interval and *P* value. The means were analysed using an unpaired Student's *t*-test. Categorical data were expressed as frequency distribution and percentage of subjects groups and *p* value. The categorical data from the HADS were also analysed by 2x2 table using Fischer's exact test. Boxplots were created with descriptive statistics using Minitab statistical software (2013). The plots display the median (horizontal band) along with minimum and maximum, and the boxes represent the lower (Q1=25%) and upper (Q3=75%) quartile range.

## **3.4 Results**

Both groups were similarly distributed ( $P > 0.05$ ) in age and gender. Subjects in the PDN group had significantly ( $p < 0.05$ ) lower scores in seven out of eight domains of SF36 compared to the control group (Table 3.1). These included physical functioning ( $p < 0.0001$ ), physical health limitations ( $p < 0.0002$ ), pain ( $p < 0.0005$ ), general health ( $p < 0.0034$ ), emotional problem limitations ( $p < 0.0188$ ), fatigue ( $p < 0.0073$ ) and social functioning ( $p < 0.0292$ ). The only exception was emotional well-being, in which the PDN group was not significantly different from control ( $p > 0.05$ ). Both physical health ( $p < 0.0001$ ) and mental health ( $p < 0.026$ ) summary scores were significantly lower in the

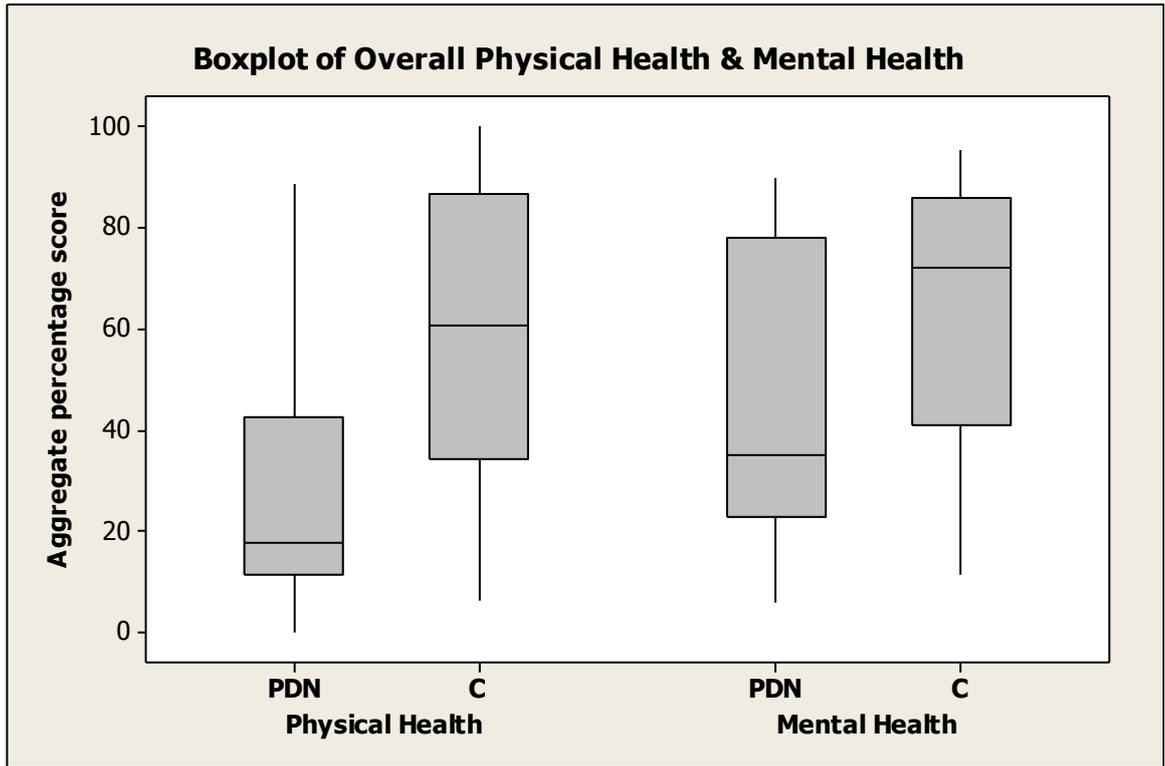
PDN group compared to the control group. The summary of physical health and mental health aggregate scores from the SF36 is given in Figure 3.1.

**Table 3.1:** SF36 eight domains data in PDN and control group.

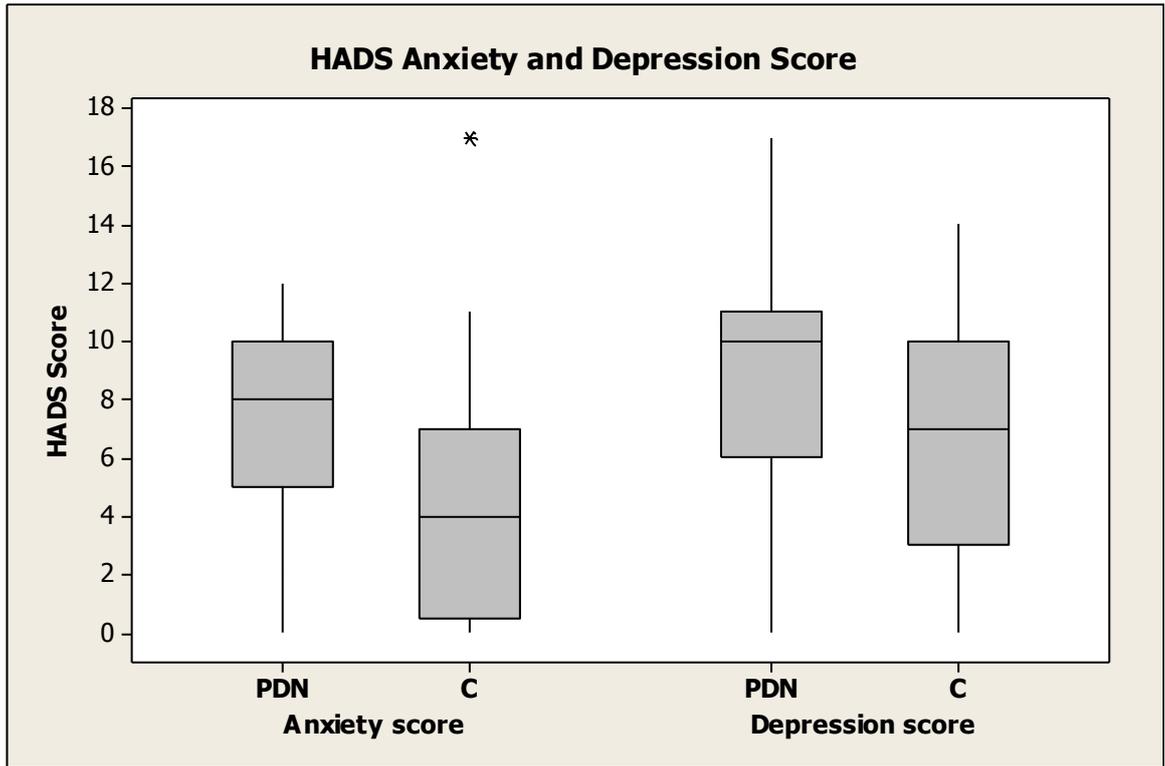
<b>SF36 Domains</b>	<b>PDN Mean</b>	<b>Control Mean</b>	<b>95% Confidence interval</b>	<b>P value</b>
Physical Functioning	28.38	65.2	18.91 to 54.71	<0.0001*
Physical Health Limitation	17.0	61.0	21.94 to 66.06	<0.0002*
Pain	29.3	59.9	14.21 to 46.98	<0.0005*
General Health	31.06	52.0	7.27 to 34.59	<0.0034*
Social Functioning	48.8	68.0	2.03 to 36.36	< 0.0292*
Emotional well-being	61.44	69.28	-6.96 to 22.64	0.292
Fatigue	25.36	42.4	4.8 to 29.26	<0.0073*
Emotional Limitation	41.33	71.99	5.30 to 56.02	<0.0188*

Table 3.1 gives the SF36 eight domain score means, 95% confidence interval and P values for the PDN and control groups. The subjects in PDN group had significantly lower scores compared to control group in physical functioning domain ( $p < 0.0001$ ), physical health limitation domain ( $p < 0.0002$ ), pain domain ( $p < 0.0005$ ), general health domain ( $p < 0.0034$ ), social functioning domain ( $P = 0.0292$ ), fatigue domain ( $p < 0.0073$ ) and emotional problem limitation domain ( $p < 0.0188$ ). The data for emotional wellbeing domain was not statistically significant ( $P < 0.292$ ; not significant).

Subjects in PDN group had significantly ( $p < 0.001$ ) higher HADS anxiety scores in comparison to the C group. However, HADS depression scores were not statistically significant (Figure 3.2).



**Figure 3.1:** The box plot analysis shows the overall physical and mental health domain aggregate scores from the SF36 in the PDN and C groups. Data are mean  $\pm$  SD;  $n=25$ . In the physical health aggregate domain, the PDN group's mean score was 27.26 (SD 23.15, median 17.5) and the C group's mean score was 59.52 (SD 29.71, median 60.62) ( $P<0.0001$ ). In the mental health aggregate domain, the PDN group's mean score was 44.43 (SD 27.52, median 35.16) and the C group's mean score was 62.31 (SD 27.59, median 72.25) ( $P<0.0262$ ). The plot shows the median score (horizontal band) along with the minimum and maximum score. The box represents the lower (Q1=25%) and upper (Q3=75%) quartile range of the score.



**Figure 3.2:** The box plot analysis shows the HADS anxiety and depression scores for the PDN and C groups. Data are mean  $\pm$  SD; n=25. For the HADS anxiety score, the PDN group's mean score was 7.32 (SD  $\pm$  3.42, median 8) and the C group's mean score was 4.72 (SD  $\pm$  4.34, median 4) ( $P= 0.023$ ). For the HADS depression score, the PDN group's mean score was 8.36 (SD  $\pm$  4.05, median 10) and the C group's mean score was 6.6 (SD  $\pm$  4.16, median 7) ( $p= 0.136$ ). The plot shows the median score (horizontal band) along with the minimum and maximum score. The box represents the lower (Q1=25%) and upper (Q3=75%) quartile range of the score.

Fourteen (56%) subjects out of 25 had anxiety in the PDN group, mean score was 7.32 +/- 3.42 SD. In the C group, 5 (20%) had anxiety, mean score 4.72 +/- 4.34 SD. *P* value calculated by both continuous data of means by unpaired *t* test ( $p < 0.023$ ) and categorical 2x2 table analysis with frequency of anxiety diagnoses ( $P=0.018$ ). Fifteen (60%) out of 25 were diagnosed with depression in the PDN group, mean score 8.36 +/- 4.05 SD. In the C group, 11 (44%) were diagnosed with depression, mean score 6.6 +/- 4.16 SD. *P* value calculated by both continuous data of comparison of means by unpaired *t* test ( $p = 0.136$ ) and categorical 2x2 table analysis with frequency of depression diagnoses ( $P = 0.396$ ).

### **3.5 Discussion**

Painful diabetic neuropathy (PDN) is one of the most common complications of diabetes mellitus, with about 1/3 of all DM patients suffering from diabetic neuropathic pain (Tesfaye and Boulton, 2009). Although it has a huge impact on quality of life (QoL) (Galer et al., 2000; Quattrini and Tesfaye, 1996; Gardner and Shoback, 2007), few studies have specifically reported the impact of DPN on QoL and or looked specifically at the psychological well-being of diabetes patients (Galer et al., 2000; Quattrini and Tesfaye, 1996; Van Acker, 2009; Benbow et al., 1998; Gore et al., 2005; Argoff et al. 2006). Our data shows a significant association of PDN with poor QoL and anxiety symptoms, but not with depression. This could be because a number of patients with PDN are treated with antidepressants for their neuropathic pain. Hence, the underlying symptoms of depression could have been minimized to some extent. Also, the control group data, which were collected from the GP surgery, belong to a low socioeconomic area of Northwest England. It is known that low socioeconomic community status is associated

with higher prevalence of depression (Murali and Oyebode, 2004). These are possible reasons for the lack of statistical significance in the depression data.

### ***3.5.1 Comparison with existing data***

The data from this study showed significant impairment of QoL with lower SF36 scores for both physical and mental health in the PDN group compared to control. The results are consistent with a similar study that used the short version 12-item (SF12) questionnaire. In that study, Van Acker (2009) found significant impairment in both physical and mental health components of QoL. Another study by Benbow et al. (2000), used the Nottingham health profile questionnaire and found significant impairment in QoL for PDN patients in 5 out of 6 domains, including emotional reaction, energy, pain, physical mobility, and sleep. The only exception was the social isolation domain. Similarly, in the present study, the data showed significant impairment in 7 out of 8 domains, including physical functioning, physical health limitation, pain, general health, emotional problem limitation, fatigue and social functioning. The only exception was emotional well-being. In cases of severe PDN, patients have reported experiencing constant unrelenting neuropathic pain, disturbance of sleep, and even inability to walk due to the severity of the pain (Galer et al., 2000; Quattrini and Tesfaye, 1996; Gardner and Shoback, 2007). Such an experience, in turn, causes withdrawal from routine activities of life, including employment, and also affects the emotional well-being of a patient and causes social isolation. The data for the emotional well-being domain in this study and social isolation domain of Benbow et al. (2000) study were not significant, perhaps due to a lower number of severe PDN cases with extreme symptoms in the study groups. However, both studies showed a significant overall impairment of QoL in both physical and mental components.

The HADS score data in the present study showed that more than half of the patients (56%) in the PDN had anxiety symptoms (HADS A score > 7), significantly higher than the control group. The data were consistent with those reported by Gore et al. (2005), who used the HADS questionnaire and found that 35% of their PDN patients showed anxiety symptoms. However, they used a threshold HADS score of 11 or above (moderate to severe symptoms). The data for depression symptoms in this study showed that more than half of the PDN patients (60%) had symptoms of depression (HADS-D score > 7). However, the results were not statically significant compared to the control group, which had 44% with depression classification. In contrast, Gore et al. (2005) showed a significant association between depression and PDN. In their study, the prevalence of depression was 28% in painful diabetic neuropathy (HADS score 11 or above). A large of systematic review and meta analysis reported that the prevalence of depression in the diabetic population is around 17.5% (Ali et al., 2006). In the current study, the random control group of non-PDN diabetes patients were found to have unusually high prevalence of depression (44%), which is inconsistent with baseline prevalence previously reported. Since the control cohort of patients belongs to a poor socioeconomic area, the higher prevalence of depression in control group could be a confounding factor. The data, therefore, were not statically significant.

### ***3.5.2 Strengths and limitations of the study***

The study population was well-defined for both groups and was assembled with minimal selection bias since all participants were selected randomly using snowball sampling. Moreover, both groups of participants completed 100% of both questionnaires (SF36 and HADS). Both groups were similar in age had a similar ratio of males to females (PDN group: male 60%, female 40%; C group; male 56%, female 44%). Hence, selection bias

was minimal. Recall bias could exist during completion of the questionnaire. However, most questions from both the HADS and SF36 questionnaires were based on the current or recent physical and mental well-being of person; hence, recall bias is expected to be minimal.

A major limitation of the study relates to the selection of the control group. As mentioned above, the GP surgery from which the control group data were taken lies in an area of Northwest England with low socioeconomic status. It is known that low socioeconomic community status is positively associated with prevalence of depression (Murali and Oyebode, 2004). Furthermore, the two groups were selected from healthcare settings of different nature. These discrepancies, and the lack of randomisation in the study, could have led to selection bias, which in turn could have had an impact on outcomes. Data other than age and sex were not collected for comparison (duration of diabetes, presence of other complications, and treatment with antidepressants are among the other potential confounding factors). As with any non-randomised study, it is not possible to infer a causal relationship and thus our conclusions are tentative at best.

### **3.5.3 Conclusion**

Overall, this study supports past findings that painful diabetic neuropathy has a huge impact on quality of life and moreover, has a strong association with symptoms of anxiety and depression. When encountering patients with PDN, clinicians must thus consider exploring more about the psychosocial and mental well-being of patients and the overall impact of the condition on patients' quality of life.

## *Chapter 4*

*Treatment of painful diabetic neuropathy vs. chronic pain with intravenous lignocaine infusion.*

**Submitted to the journal, Pain Medicine (under review)**

#### **4.1 ABSTRACT**

##### **Objective:**

This study assessed the efficacy of lignocaine infusion as a treatment for chronic refractory pain where conventional treatment has proven unsatisfactory. We also assessed the difference in responses between painful diabetic neuropathy (PDN) and chronic pain (non-PDN).

##### **Methods:**

A total of 11 patients participated in the study, with 7 patients referred from pain clinic (non-PDN group) and 4 patients referred from the diabetes foot clinic (PDN group) for lignocaine infusion as a treatment for chronic refractory pain. Both groups of participants were on a combination of pain medications with inadequate response. All the subjects filled out a McGill short form (SF) questionnaire prior to and after lignocaine infusion to evaluate the response.

##### **Results:**

The mean duration of chronic pain (+/- SD) was 7.1 +/- 4.4 years. The mean somatic pain score on the McGill SF questionnaire dropped from 20.1 +/- 7.2 to 16.5 +/- 9.5 after lignocaine infusion ( $P < 0.05$ ). Similarly, the mean affective score dropped from 5.5 +/- 3.1 to 4.0 +/- 3.1 ( $P < 0.05$ ). The results showed a 33% reduction in visual analogue pain score after lignocaine infusion in the PDN group compared to an 11% reduction in the non-PDN group. These data were statistically significant ( $P < 0.05$ ). Similarly, there was a significant ( $p < 0.05$ ) reduction in affective pain score of 41% after lignocaine infusion

in the PDN group compared to 21% in the non-PDN group. In contrast, the somatic pain score reduction after lignocaine infusion was 23% in the PDN group compared to 17% in non-PDN group. These data were statistically not significant ( $P>0.05$ ). All 11 patients reported no adverse effects and their observations were within the normal limits throughout the lignocaine infusion.

**Conclusion:**

Overall, the study showed that lignocaine infusion is both effective and safe in reducing chronic intractable pain when conventional treatments are intolerable or unhelpful. The treatment was more effective in PDN patients compared to other causes of chronic pain.

## 4.2 INTRODUCTION

The International Association for the Study of Pain (IASP) defines neuropathic pain as “pain caused by a lesion or disease of the somatosensory nervous system.” Neuropathic pain is caused by direct injury or damage to, or pathological changes in, the peripheral or central nervous system. In contrast, nociceptive pain is caused by direct injury or disease (Treede et al., 2008). Chronic pain is generally defined as pain that lasts for more than 3 to 6 months (Debono et al., 2013). Chronic neuropathic pain is very common around the world, with almost 6% to 8% of world’s population estimated to suffer from chronic neuropathic pain (Torrance et al., 2006; Bouhassira et al., 2008). Diabetic neuropathic pain (aka painful diabetic neuropathy, PDN) is the most common type of chronic neuropathic pain. Despite advances in treatment options, chronic symptoms of PDN are challenging for clinicians and distressing for patients. Boulton et al. (1983) followed 39 patients with PDN over the period of 4 years and found no significant decreases in intensity of pain over time. Another 5-year follow-up study on PDN with conventional treatment reported that symptoms resolved in only 23% patients (Daousi et al., 2006).

Despite advanced treatments and multiple drug regimes, up to 50% of chronic neuropathic pain patients are resistant to conventional treatment. One study of chronic neuropathic pain patients taking combination conventional neuropathic medications showed poor response (Tesfaye et al., 2013). Furthermore, some treatment-resistant patients are in intractable pain. These patients have always been a challenge for physicians. Lignocaine infusion has been reported to show satisfactory response in some of these challenging, conventional-treatment-resistant patients (Kastrup et al., 1987; Viola et al., 2006; Bach et al., 1990).

Lignocaine is a sodium channel blocker first synthesized by the Swedish chemist Nils Lofgren in 1943 (Löfgren and Lundqvist, 1946). Lignocaine is widely used as a local anaesthetic and peripheral nerve blocker. It has been used intravenously for the treatment of arrhythmias and is not associated with any significant side effects (Challapalli et al., 2005). It has also been found to be effective in chronic neuropathic pain (Tremont et al., 2006) and chronic pain disorders (Cahana et al., 1998; Wallace et al., 2000). Lignocaine is metabolized in the liver and its elimination half-life following intravenous bolus injection is typically 1.5 to 2 hours. However, when chronic liver disease and congestive heart failure is present, its half-life may be prolonged.

The potential use of lignocaine infusion as a treatment for PDN was first evaluated by Kastrup in 1986 (Kastrup et al., 1987). Since then, several studies have reported pain relief in PDN with lignocaine infusion (Kastrup et al., 1987; Viola et al., 2006; Bach et al., 1990). Despite its rapid half-life, the duration of pain relief reported post lignocaine transfusion was up to 28 days (Kastrup et al., 1987; Viola et al., 2006). This could be due to the central de-sensitization effect of the lignocaine along with its peripheral action. The side effects in high doses of intravenous (IV) lignocaine can be sedation, hypotension and arrhythmia. Severe toxicity is rare, but when it does occur, requires cardio-pulmonary resuscitation using the standard protocol along with Intralipid infusion via peripheral vein. It expands the intravascular lipid phase that acts to absorb the unbound circulatory lipophilic lignocaine (Weinberg, 2012). Overall, studies have found that IV lignocaine infusion is very well-tolerated and safe (Kastrup et al., 1987; Viola et al., 2006; Wallace et al., 2000). However, because of its practical limitations, it is often reserved only for patients who have persistent excruciating pain and where other medications are not beneficial.

There are several pain assessment questionnaires available for the assessment of pain. This study used the McGill short form (SF) questionnaire, which was developed by Melzack in 1987 (Melzack, 1987). The McGill SF questionnaire is an easy, quick, and reliable tool to measure the quality of pain in three different aspects, including somatic, affective and visual analogue scores. It has been used as a measure of pain in a variety of pain conditions, including PDN (Viola et al., 2006).

The aim of this study was to assess the efficacy of lignocaine infusion in patients with chronic refractory pain and compare the responses between painful diabetic neuropathy patients (PDN group) and chronic pain patients (non-PDN group).

#### **4.3 SUBJECTS AND METHODS**

A total of 11 subjects participated and completed the McGill SF questionnaire before and after lignocaine infusion. The mean age ( $\pm$  SD) of subjects was 52  $\pm$  13.96 years. There were total of 4 males (36%) in PDN group with mean age ( $\pm$  SD) 58.7  $\pm$  15 years and 7 females (64%) in chronic pain group (non-PDN) with mean age ( $\pm$  SD) of 49  $\pm$  13 years. All 4 patients in PDN group had type 2 DM with mean duration of diabetes ( $\pm$  SD) 6.0  $\pm$  2.4 years. PDN subjects with chronic refractory pain for ( $\pm$  SD) 6.5  $\pm$  3.42 years, who had not responded to standard oral and topical treatments, were identified from the Foot Clinic at Chorley District General Hospital (CDGH). Chronic pain subjects (non-PDN) with chronic refractory pain for ( $\pm$  SD) 7.75  $\pm$  4.77 years, who had not responded to standard oral and topical treatment, were referred for lignocaine infusion from the Pain Clinic, Lancashire Hospitals NHS Trust. Both groups of patients had already tried and were currently taking a combination of pain medications without relief. All subjects attended the study treatment individually and were admitted to the CDGH

coronary care unit (CCU) as day cases for 3 hours and given lignocaine infusion 0.2% (2 mg/ml) at 5 mg/kg body weight over 2 hours with throughout monitoring of electrocardiogram, blood pressure, pulse and oxygen saturations. Nurses administered the McGill pain short form (SF) questionnaire before and after the infusion for each subject. All patients returned to the “pain clinic” after 6 weeks for follow-up.

The McGill SF consisted of 15 representative words from the somatic (n=11) and affective (n=4) pain, as well as visual analogue score (VAS). Each word descriptor was ranked by the patient on an intensity scale of 0 – none; 1 – mild; 2 – moderate; and 3 – severe. Somatic pain score ranged from 0 to 33, affective pain score ranged from 0 to 12, and VAS range from 0 to maximum 10 (Melzack, 1987).

#### ***4.3.1 Statistical Analysis***

Data were analysed using Graph Pad software (Graphpad Inc USA, 2013). The continuous variables were normally distributed and expressed as means, +/- standard deviation (SD), median and P value. The means of the McGill pain scores were analysed by paired Student’s *t*-test comparing the before- and after-lignocaine infusion results. Categorical data were expressed as frequency distribution, percentage of subjects groups, and *p* value. The categorical data were analysed by a 2x2 table using Fischer’s exact test. The boxplots were created with descriptive statistics using Minitab statistical software (2013). The plots show the median (horizontal band) along with minimum and maximum. The box represents the lower (Q1=25%) and upper (Q3=75%) quartile range.

## **4.4 RESULTS**

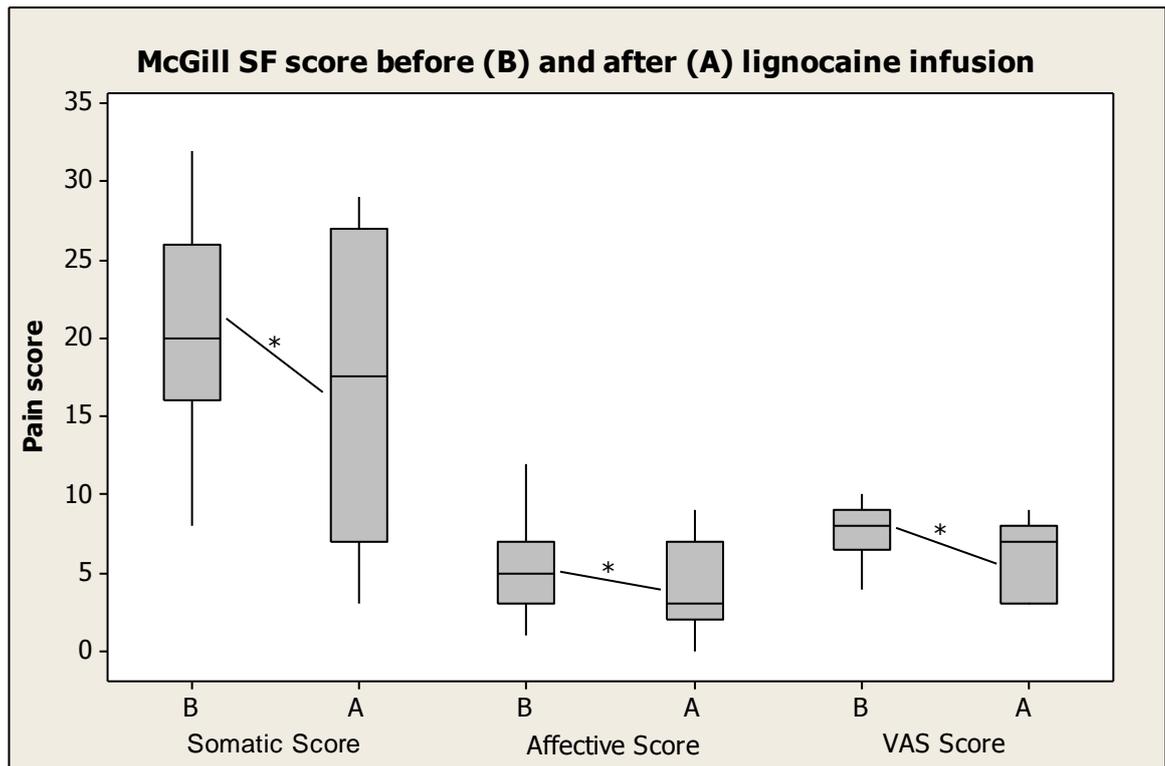
Table 4.1 shows the demographics and baseline characteristics of patients who participated in the study. The mean duration of chronic pain (+/- SD) was 7.09 +/- 4.37

years. The mean somatic score before lignocaine infusion was (+/-SD) 20.14 +/- 7.16 compared to a mean somatic score after lignocaine infusion of (+/-SD) 16.5 +/- 9.52. There was significant reduction in somatic pain score after lignocaine infusion ( $P<0.05$ ). The mean affective score before lignocaine infusion was (+/-SD) 5.5 +/- 3.09 compared to a mean affective score after lignocaine infusion of (+/- SD) 4.0 +/- 3.13. This represents a significant reduction in affective pain score after lignocaine infusion ( $P<0.05$ ). The mean visual analogue score (VAS) before lignocaine infusion was (+/- SD) 7.72 +/- 1.75 compared to mean a VAS score after lignocaine infusion of (+/- SD) 6.13 +/- 2.53. This showed a trend for reduction of VAS pain score after lignocaine infusion ( $P= 0.053$ ). (See Figure 4.1)

**Table 4.1:** Demographics and baseline characteristics of patients who participated in the study

Patient No	Age Yrs	Gender	Diagnosis of pain	Duration of pain Yrs	Medication tried not helped	Current pain medications	Before Lignocaine infusion			After Lignocaine infusion		
							VAS	Somatic	Affective	VAS	Somatic	Affective
1	79	Male	PDN	11	Amitriptyline , Imipramine, Carbamazepine, Capsaicin cream, Tramadol, Pregabalin , Mexiletine, GTN patch, Duloxetine, MST, Acupuncture, Alphalipoic acid, Lignocaine patch	Gabapentin, Oxycontin	7.5	8	1	3.5	3	3.5
2	60	Male	PDN	3	Pregabalin, Amitriptyline Duloxetine, Clonazepam, Durogesic patch, Oramorph PRN.	Pregabalin, Amitriptyline Duloxetine, Clonazepam, Durogesic patch, Oramorph PRN.	9	32	7	9	29	9
3	44	Male	PDN	5	Gabapentin, Butrans patch, capsaicin cream, colnazepam	Pregabalin, Amitriptyline, Topiramate	9	12	6	3	4	3
4	52	Male	PDN	7	Pregabalin, Gabapentin, topical Capsaicin, Duloxetine, BuTrans patch, Tramadol, Oxycontin,	Morphine Sulphate, Amitriptyline, Sodium Valproate	10	22	3	8	21	8
5	41	Female	Back pain	5	Carbamazepine, Duloxetine, Amitriptyline, Pregabalin, Ropinerole. SI joint injections, Facet joint injections, Butrans patch, TENS machine	Carbamazepine, Duloxetine, Amitriptyline, Pregabalin, Ropinerole.	8	30	9	8	29	8
6	66	Female	Fibromyalgia	3	TENS, acupuncture, physiotherapy, Gabapentin, amitriptyline, Naproxen, Codeine, Butrans patch	Ibuprofen 400mg prn	4	20	5	3	11	3
7	53	Female	Back pain	9	Epidural steroid injection, Gabapentin	Oxycontin, Pregabalin, Amitriptyline	7	19	4	3	7	3
8	59	Female	Angiolipomata	7	Gabapentin, Cocodamol 30/500, SI joint injection, Facet joint injections, TENS	Carbamazepine, Duloxetine, Amitriptyline, Pregabalin, Ropinirole	9	18	4	6	15	6
9	26	Female	Fibromyalgia	18	Amitriptyline 50 mg, Pregabalin, Gabapentin, Tramadol, psychotherapy	OxyContin, Ibuprofen, Amitriptyline, Duloxetine.	6	16	3	8	18	8

10	45	Female	Demyelination of nerves	6	Gabapentin, Pregabalin, Nabilone, Ketamine, Butranspatch, codeine, Capsaicin cream, Lidocaine patch, Fentanyl patch, Duloxetine, Topiramate, Carbamazepine, TENS	Amitriptyline 50 mg Codeine 60 mg at night	6.5	21.5	6.5	7	17.5	7
11	54	Female	Stump pain	4	Paracetamol , Oramorph prn, Oxycodone MR, Pregabalin, Lidocaine patches, Acupuncture, TENS, carbamazepine	Paracetamol , Oramorph prn, Oxycodone MR, Pregabalin, Lidocaine patches	9	26	12	9	27	9



**Figure 4.1:** Box plot showing the McGill SF somatic score, affective score and visual analogue score (VAS), before (B) and after (A) lignocaine infusion in chronic pain subjects. Data are mean  $\pm$  SD;  $n=11$ , \*  $p<0.05$  for somatic score and affective score. \*  $p=0.053$  for VAS score.

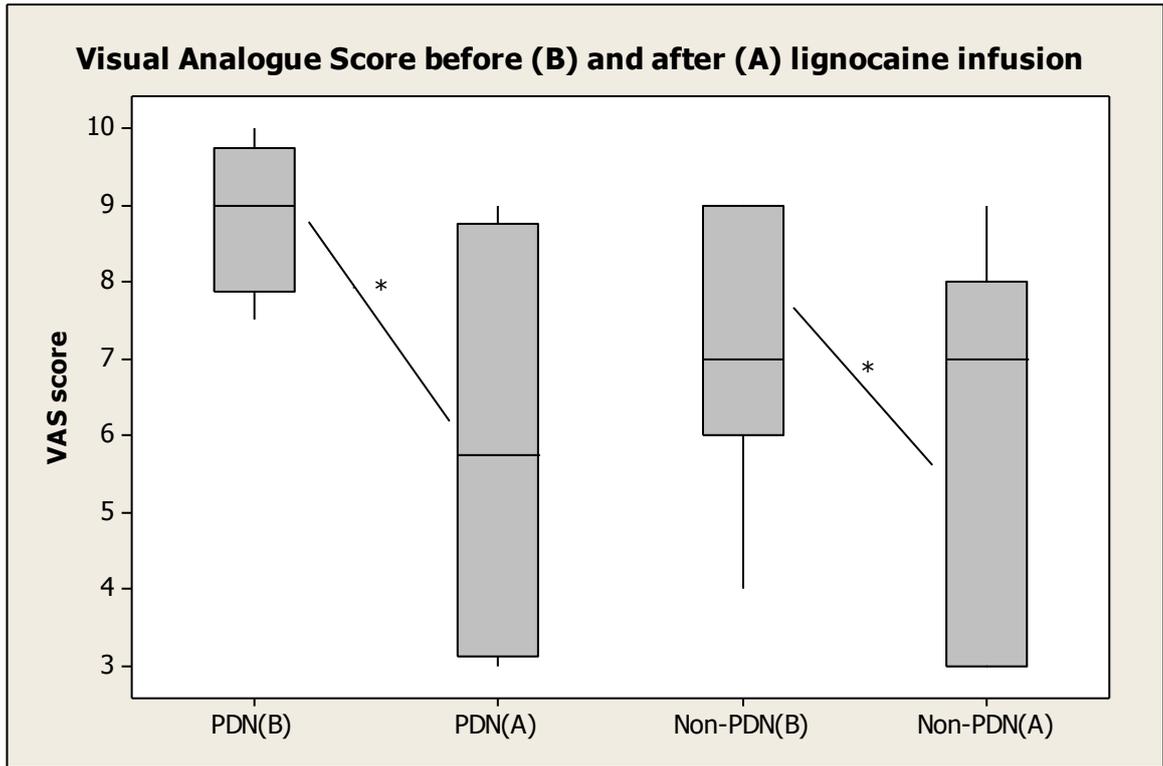
The box plot in figure 4.1 shows the McGill pain scores in all 3 sub-categories, including somatic score, affective score and visual analogue scores (VAS), before (A) and after (B) lignocaine infusion in all subjects. Before lignocaine infusion, the mean somatic score was  $20.4 \pm 7.16$  SD (median 20) compared to a mean somatic score after lignocaine infusion of  $16.5 \pm 9.52$  SD (median 17.5) ( $P < 0.014$ ). Before lignocaine infusion, the mean affective score was  $5.5 \pm 3.09$  SD (median 5) compared to a mean affective score after lignocaine infusion of  $4.0 \pm 3.13$  SD (median 3.0) ( $P < 0.013$ ). Before lignocaine infusion, the mean VAS score was  $7.72 \pm 1.75$  SD (median 8) compared to a mean VAS score after lignocaine infusion was  $6.13 \pm 2.53$  SD (median 7) ( $P = 0.053$ ). The plot also shows the median score (dark band) along with minimum

and maximum score. The box represents the lower (Q1=25%) and upper (Q3=75%) quartile range of score.

All PDN patients were male and all non-PDN patients were female. The ages in both genders were similarly distributed ( $P > 0.05$ ). The mean duration of pain (+/- SD) in the PDN group was 6.5 +/- 3.42 years compared to 7.75 +/- 4.77 years in non-PDN group. The duration of pain in both groups were similarly distributed ( $P > 0.05$ ). All participants had tried a combination of medications including antidepressants, antiepileptic medications, and opioid agonists, and moreover, were currently on a combination of medications with unsatisfactory response.

The results show a 33% reduction of visual analogue pain score after lignocaine infusion in the PDN group compared to an 11% reduction in non-PDN group. The data were statistically significant ( $P < 0.05$ ; see Figure 4.2). Similarly, there was a significant ( $p < 0.05$ ) reduction in affective pain score (41%) after lignocaine infusion in the PDN group compared to 21% in the non-PDN group (see Figure 4.3). In contrast, the somatic pain score reduction after lignocaine infusion was similar between groups, with 23% reduction in the PDN group and 17% in non-PDN group. These data were not statistically significant ( $P > 0.05$ ; see Figure 4.4)

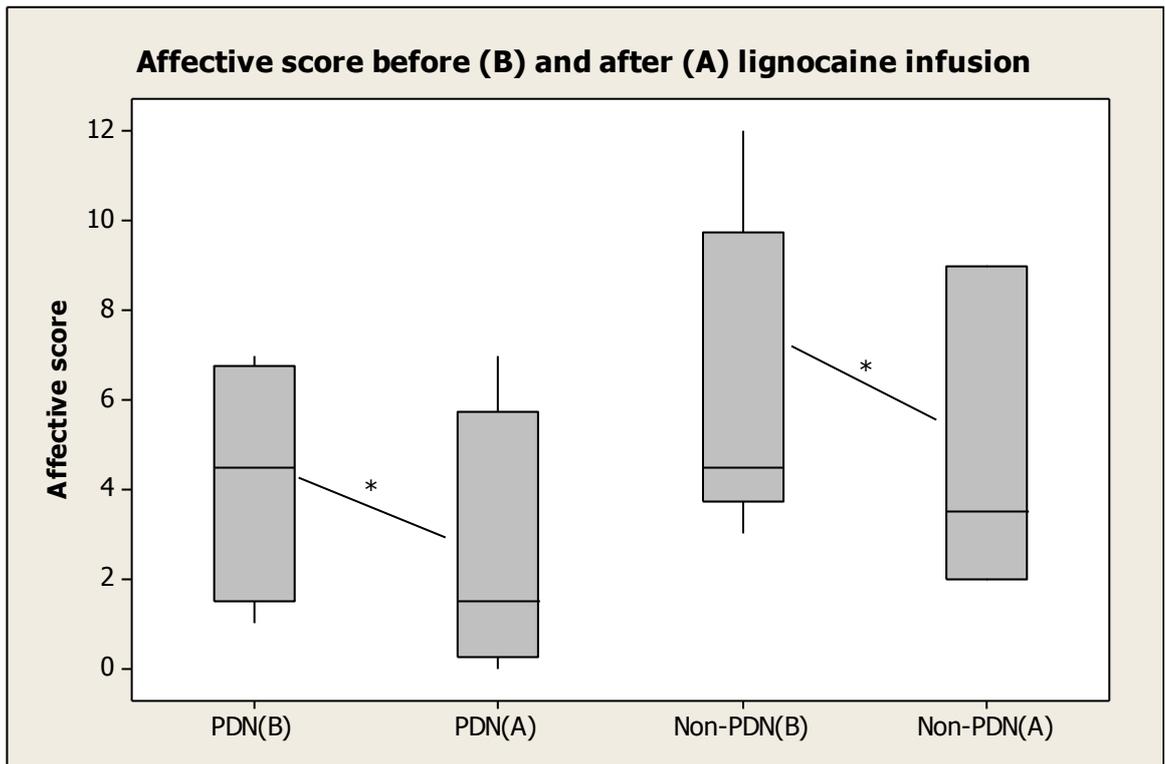
All 11 patients reported no adverse effects and their observations, including electrocardiograms, pulse, blood pressure and oxygen saturation, were within normal limits throughout the lignocaine infusion.



**Figure 4.2:** Box plot showing visual analogue scores before (B) and after (A) lidocaine infusion in the PDN and non-PDN groups. Data are mean  $\pm$  SD;  $n=4$  for PDN and  $n=7$  for non-PDN. \*  $p<0.05$  for PDN group compared to non-PDN group. In this and subsequent figures, PDN(B) = Painful diabetic neuropathy group score before lignocaine infusion; PDN(A) = Painful diabetic neuropathy group score after lignocaine infusion; Non-PDN(B) = Non-PDN group score before lignocaine infusion; Non-PDN(A) = Non-PDN group score after lignocaine infusion; VAS = Visual analogue score

The box plot analysis in Figure 4.2 shows the visual analogue score (VAS) before (A) and after (B) the lignocaine infusion in PDN and non-PDN groups. In the PDN group, the VAS mean score before lignocaine infusion was  $8.87 \pm 1.03$  SD (median 9.0) compared to a VAS mean score of  $5.87 \pm 3.06$  SD (median 5.75) after lignocaine infusion (33% pain reduction). In the Non-PDN group ( $n=7$ ), the mean VAS score before lignocaine infusion was  $7.07 \pm 1.7$  SD (median 7) compared to a VAS mean score of  $6.28 \pm 2.43$  SD (median 7) after lignocaine infusion (11% pain reduction). The pain

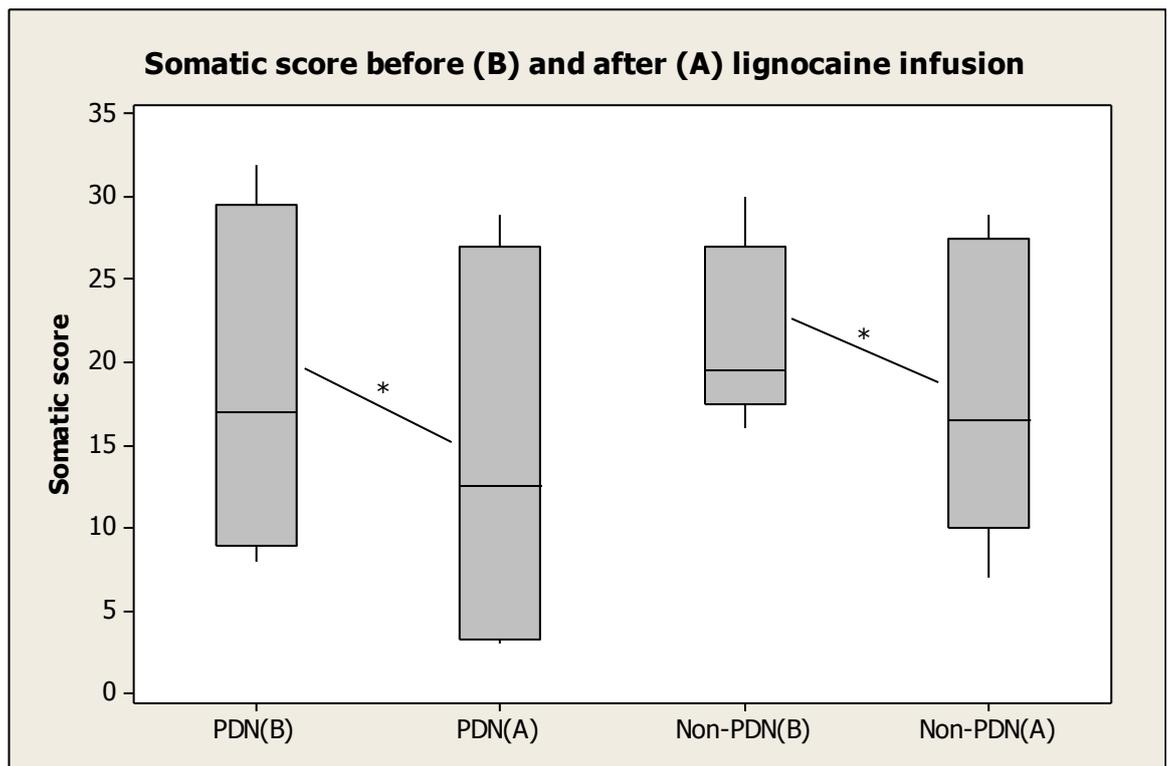
reduction in the PDN group compared to the non-PDN group was statically significant ( $P<0.0015$ ). The plot also shows the median score (horizontal band) along with the minimum and maximum score. The box represents the lower (Q1=25%) and upper (Q3=75%) quartile range of the score.



**Figure 4.3:** Box plot showing affective score before (B) and after (A) lidocaine infusion. Data are mean  $\pm$  SD; n=4 PDN group and n=7 for non-PDN group. \*  $p<0.05$  for PDN group compared to non-PDN group.

The box plot analysis in Figure 4.3 shows the McGill SF affective score before (B) and after (A) the lignocaine infusion in the PDN and non-PDN groups. The results show that in the in PDN group, the affective mean score was  $4.25 \pm 2.75$  SD (median 4.5) before lignocaine infusion compared to an affective mean score of  $2.50 \pm 3.11$  SD (median 1.5) (41% pain reduction) after lignocaine infusion. In the non-PDN group (n=7),

before lignocaine infusion, the mean affective score was 6.17 +/- 3.54 SD (median 4.5) compared to an affective mean score of 4.83 +/- 3.31 SD (median 3.5) (21% pain reduction) after lignocaine infusion was. The pain reduction in the PDN group compared to the non-PDN group was statistically significant ( $P < 0.0036$ ). The plot shows the median score (horizontal band) along with the minimum and maximum score. The box represents the lower (Q1=25%) and upper (Q3=75%) quartile range of the score.



**Figure 4.4:** Box plot showing McGill SF somatic score before (B) and after (A) lidocaine infusion. Data are mean +/- SD; n=4 for PDN group and n=7 for non-PDN group. \*  $p < 0.05$  for PDN group compared to non-PDN group.

The box plot analysis in Figure 4.4 shows the McGill SF somatic score before (B) and after (A) lignocaine infusion in the PDN and non-PDN groups. In PDN group, the somatic mean score was 18.5 +/- 10.75 SD (median 17.0) before lignocaine infusion compared to a somatic mean score of 14.25 +/- 12.84 SD (median 12.5) (23% pain

reduction) after lignocaine infusion. In the non-PDN group, before lignocaine infusion, the mean somatic score was 21.50 +/- 5.36 SD (median 19.5) compared to a somatic mean score of 17.83 +/- 8.73 SD (median 16.5) (17% pain reduction) after lignocaine infusion. The pain reduction in PDN group compared to the non-PDN group was not statically significant ( $P=0.3769$ ). The plot shows the median score (horizontal band) along with the minimum and maximum score. The box represents the lower (Q1=25%) and upper (Q3=75%) quartile range of the score.

#### **4.5 Discussion**

Painful diabetic neuropathy (PDN) is a common complication of diabetes mellitus (DM), with about 1/3 of all DM patients suffering from diabetic neuropathic pain (Tesfaye, 2009). Moreover, the condition has a huge impact on the quality of life (QoL) of the patient (Galer et al., 2000; Gardner and Shoback, 2007; Quattrini and Tesfaye, 1996). Several trials have reported some improvement of PDN symptoms with various antidepressants, anticonvulsants, opioids and topical medications (Kaur et al., 2011; Goldstein et al., 2005; Kadiroglu et al., 2008, Rosenstock et al., 2004; Lesser et al., 2004; Richter et al., 2005; Freyhagen et al., 2005; Backonja, 1999; Vinik et al., 1998; Badran et al., 1975; Edwards et al., 2000; Donofrio et al., 2005; Harati et al., 1998; Rudroju et al., 2013; Vinik et al., 2014; Low et al., 1995; Yuen et al., 2002). However, follow-up studies have revealed that only 23% of patients show satisfactory improvement of PDN symptoms after conventional treatment (Boulton et al., 1983; Daousi et al., 2006). Most patients learn to tolerate the residual pain and live with it; however, severe cases of PDN can include constant unremitting neuropathic pain, disturbance of sleep, and even inability to walk due to the severity of the pain (Galer et al., 2000; Gardner and Shoback, 2007; Quattrini and Tesfaye, 1996). Lignocaine infusion has been used as a treatment in various challenging cases of chronic pain, including chronic pain syndrome, (Wallace et al., 2000;

Challapalli et al., 2005), chronic neuropathic pain (Tremont-Lukats et al., 2006) and PDN (Kastrup et al., 1987; Viola et al., 2006; Bach et al., 1990), when conventional treatments proved ineffective or intolerable.

The present data have shown a reduction in all 3 domains of the McGill SF questionnaire pain scores for the PDN group, including visual analogue score (33% reduction), affective score (41% reduction) and somatic scores of (23% reduction) after lignocaine infusion, compared to 11%, 21% and 17%, respectively, in the non-PDN group. The differences between groups were statistically significant for the VAS and affective scores, but not for the somatic scores. This could be due to the statistically significant response of lignocaine infusion on somatic scores in both groups of patients (see Figure 4.1).

#### ***4.5.1 Comparison with existing data***

The data from this study have clearly shown significant reduction of McGill SF affective pain score and visual analogue score after lignocaine infusion in patients with PDN compared to patients with non-PDN chronic pain. These results are consistent with the findings of Viola et al. (2006) and Kastrup et al. (1987), who demonstrated significant reduction in both affective scores and visual analogue scores after lignocaine infusion. The present study measured the effectiveness of lignocaine infusion as a treatment in PDN patients compared to patients with chronic pain from other causes. Viola et al. (2006) and Kastrup et al. (1987), on the other hand, measured the effectiveness of lignocaine infusion compared to saline infusion in patients with PDN. In our study, the reduction of the McGill SF somatic pain score was 23% in PDN group compared to 17% in the non-PDN group. Despite the higher reduction of somatic pain score in the PDN group, the data were not statistically significant. In contrast, Viola et al. (2006) and

Kastrup et al. (1987) showed a significant reduction of McGill somatic pain score in the PDN group compared to control. This discrepancy could be due to the fact that the lignocaine infusion response was nearly the same level in both the PDN and non-PDN groups, making the difference insignificant. The present study was similar to that of Viola et al. (2006) in that all participants had intractable pain and failure to respond to or tolerate conventional treatment. It is particularly noteworthy that in this study and the studies done by Viola et al. (2006) and Kastrup et al. (1987), no participants reported any adverse effects with lignocaine infusion of 5 m/kg bodyweight. This observation clearly suggests that this dosage of lidocaine is safe for the treatment of PDN. However, one investigation (Raphael et al., 2003) has reported that lignocaine infusion caused marked adverse effects resulting in hypotension and arrhythmia. The study was performed on fibromyalgia patients and lignocaine infusion was given consecutively for 6 days. Also, the dose was increased incrementally every day to maximum of 5 mg/kg bodyweight plus 150 mg or total maximum 550 mg (Raphael et al., 2003).

There are several studies reporting significant reduction in pain after lignocaine infusion in PDN as well as in a variety of non-PDN conditions including fibromyalgia (Raphael et al., 2003), headache (Rosen et al., 2009), back pain (Park et al., 2012), trigeminal neuralgia (Arai et al., 2013) and chronic pain syndrome (Cahana et al., 1998; Wallace et al., 2000). As with previous investigations, the present study showed a beneficial effect of lignocaine infusion in treating both the PDN and non-PDN groups. However, in patients with PDN, lignocaine infusion was statistically more effective than for other causes of chronic pain. PDN pathogenesis involves peripheral and central sensitization with neural plasticity (Aslam et al., 2014). The half-life of lignocaine infusion is only 2 hours; however, the effect of analgesia is reported for up to 28 days (Kastrup et al., 1987; Viola et al., 2006). This suggests that lignocaine infusion may affect

not only peripheral, but perhaps central neural plasticity as well. The possible central effect of lignocaine could have caused the increased effectiveness in the PDN group.

#### ***4.5.2 Strengths and limitations of the study***

The study population was well defined for both groups and assembled with minimal selection bias as the participants for the PDN and non-PDN groups were referred from the Foot Clinic or Pain Clinic, respectively. Moreover, both groups of participants completed the McGill SF pain questionnaires 100%. Both groups were similar in age; however, all participants in the PDN group were males and all in the non-PDN group were females. Recall bias could exist when participants completed the questionnaire. However, most questions from the McGill SF questionnaire were based on current or recent physical and mental well-being of person; hence, recall bias can be assumed to be minimal. The results also showed that lignocaine infusion had no significant effect on the ECG, BP, pulse rate or oxygen saturation in the both groups of patients. This was an observational study and all patients were well aware that they were having treatment with lignocaine infusion. Therefore, possible placebo effect cannot be ruled out. Also, the sample size was very small with only 4 in the PDN group and 7 in the non-PDN group. A further randomized controlled trial on a large sample is needed in order to verify the results.

#### **4.6 Conclusion**

Overall, the study has shown that lignocaine infusion is both effective and safe in reducing chronic intractable pain in both PDN and non-PDN patients when conventional treatments are intolerable or unhelpful. The study found that the treatment is more effective in PDN patients compared to patients with other causes of chronic pain. There

is a need for a multicentre randomized controlled trial to verify the effect of lignocaine infusion, especially in PDN. Chronic neuropathic pain, including PDN, causes the modulation of pain signalling at the spinal level and plasticity in the brain. As a result, it is more difficult to treat the refractory pain (Aslam et al., 2014). Perhaps clinicians need to consider introducing lignocaine infusion in the early stages when conventional treatments are not helpful.

## *Chapter 5*

*General discussion, conclusions and future scope of research*

## 5.1 General discussion

It was a wonderful experience to complete research projects as a part of MSc by Research degree. During my academic tenure at University of Central Lancashire (UCLAN), I learnt several new generic academic skills including academic writing, research methods, research designing, process of ethical clearance, statistics analyses and how to write a paper and get it published. During my MSc tenure at UCLAN, I was able to publish papers in leading journals. It was only possible with the help and support provided to me from my supervisors and excellent research environment provided by UCLAN and Lancashire hospitals NHS trust. Apart from generic skills, I have learnt enormously in the field of diabetes and in particularly PDN.

During my MSc by research, I contributed knowledge in the academic arena and completed three pilot research projects. The data was either published or is under review by leading journals. The prevalence and characteristics of PDN study under review in Canadian journal of diabetes, impact of PDN on quality of life study published in diabetes & primary care journal and lignocaine infusion as a treatment of PDN under review in journal of pain medicine.

The study found that about 1/3 of the diabetic subjects tested in Chorley and Whiston towns of Northwest England suffer from PDN, and that it was twice as prevalent in type 2 DM than in type 1. These results are similar to other prevalence studies in UK (Abbot et al., 2011; Davies et al., 2006). There was a significant correlation of PDN with various cardiovascular risk factors, including smoking, increasing age, duration of diabetes, poor glycaemic control and obesity. We used S-LANSS questionnaire in postal survey to diagnose PDN. A major limitation of the study was related to the selection bias of both Hospital group and GP group patients. Hospital group patients were selected from

the DARE database where patients had already volunteered for future diabetes research. Secondary care enrolment suggests severity of the disease with multiple comorbidities. Furthermore primary care group lies in the low socioeconomic community status area. Poor socioeconomic areas are known to have higher cardiovascular risks and comorbidities. Cardiovascular risks and comorbidities are known to have direct association with PDN. These discrepancies and lack of randomisation in the study could have led to selection bias which could have an impact on outcome. Recall bias could exist during completion of the questionnaire. Questions on the S-LANSS questionnaire were based on current or recent characteristics of pain; hence, recall bias in the best scenario is expected to be minimal. However it requires ability to read, understand the questions and physically able to write the response and post it to the researcher. The outcome was based only on those patients who responded with their best understanding of the questions hence recall bias could not be ruled out. There is a need of a large multicentre randomized controlled study to verify these results.

The study suggests PDN has a huge impact on quality of life of the patients, and moreover, it has strong association with symptoms of anxiety and depression. When encountering patients with PDN, clinicians should consider exploring more about the psychosocial and mental well-being of the patients and the overall impact of the condition on the patient's quality of life. A major limitation of the study relates to the selection of the control group. As mentioned above, the GP surgery from which the control group data were taken lies in an area of low socioeconomic status. It is known that low socioeconomic community status is positively associated with prevalence of depression (Murali and Oyeboode, 2004). Furthermore, the two groups were selected from healthcare

settings of different nature. These discrepancies and the lack of randomisation in the study could have led to selection bias, which in turn could have had an impact on outcomes. Data other than age and sex were not collected for comparison (duration of diabetes, presence of other complications, and treatment with antidepressants are among the other potential confounding factors). As with any non-randomised study, it is not possible to infer a causal relationship and thus our conclusions are tentative at best.

Treatment of PDN is often challenging for physicians and distressing for patients. Studies have found up to a 50% response rate with combination of treatment (Tesfaye et al., 2013; Boulton et al., 1983; Daousi et al., 2006). The results of this study has shown that lignocaine infusion is both effective and safe in reducing chronic intractable pain in PDN and non-PDN patients when conventional treatments are intolerable or not helpful. Lignocaine infusion is more effective in PDN patients than in those with other causes of chronic pain. This was an observational study and all patients were well aware that they were having treatment with lignocaine infusion. Therefore, possible placebo effect cannot be ruled out. Also, the sample size was very small with only 4 in the PDN group and 7 in the non-PDN group. A further multicentre randomized controlled trial on a large sample is needed in order to verify the results. Chronic neuropathic pain, including PDN, causes modulation of pain at the spinal level and plasticity of brain; as a result, it is more difficult to treat the refractory pain (Aslam et al., 2014). Physicians may thus need to consider introducing lignocaine infusion in early stages when conventional treatments are not helpful.

## **5.2 Conclusion**

The study found that about 1/3 of all diabetic subjects in the study suffered from PDN. It was twice as prevalent in type 2 DM as in type 1 DM. There was a significant correlation of PDN with smoking & height. Prevalence of PDN also increased with age, duration of diabetes, poor glycaemic control and obesity. The study also supports past findings that PDN has a huge impact on quality of life and moreover has a strong association with symptoms of anxiety and depression. The study has shown that lignocaine infusion is both effective and safe in reducing chronic intractable pain in both PDN and non-PDN patients when conventional treatments are intolerable or unhelpful. The study found that the treatment is more effective in PDN patients compared to patients with other causes of chronic pain. There is a need for a multicentre randomized controlled study on larger sample to verify these results.

## **5.3 Scope for future studies**

About 1/3 of all diabetes patients suffer from PDN, a distressing condition and has a huge impact on the patient's quality of life. Despite the development of newer medications, the treatment of this distressing condition is frequently challenging for physicians. This may be because we have a poor understanding of pathogenesis of PDN. In this thesis research, similar to several others, it was shown that various cardiovascular risk factors are associated with PDN including smoking, increasing age, increasing duration of diabetes, obesity and poor glycaemic control. So far there is no direct evidence linking the pathogenesis of PDN with these risk factors. It is assumed that these individual risk

factors alone or collectively damage the nerves but our understanding of the pathogenesis of PDN remains poor. This is an area worthy of extensive study.

The present study found that PDN patients infused with lignocaine responded better compared to patients suffering from other forms of chronic pain. Although the half-life of lignocaine infusion is only 2 hours, studies have reported an analgesic effect of up to 28 days, suggesting that lignocaine may act centrally as well as peripherally. The studies undertaken in this thesis were observational studies with small samples and lack of randomization which could have led to selection bias. This in turn could have had an impact on the outcome. As with any non-randomized study, it is not possible to infer a causal relationship accurately and, thus, the present conclusions remain tentative. There is a need for multicentre randomized study on large sample to verify these results. Also, there is a space for further research in exploring the pathogenesis of PDN. This may help us to understand the modes of action of current PDN treatments including lignocaine infusion and may help in creating newer treatments to help in this debilitating condition.

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## **Appendix**

**Appendix 1: S-LANSS Questionnaire**

Name: \_\_\_\_\_

Date of Birth: \_\_\_\_\_

Post Code: \_\_\_\_\_

**Sex:** Male \_\_\_ Female: \_\_\_\_\_ ,

Smoker: Yes \_\_\_ No \_\_\_

Ex smoker \_\_\_\_\_ (Which year did you stop \_\_\_\_\_)

What treatment do you take for diabetes:

1.....

2.....

3.....

4.....

5.....

6.....

Do you drink Alcohol: Yes \_\_\_ No \_\_\_,

If you drink alcohol how much do you drink in an average week?

Cider/Lager/ Bitter \_\_\_\_\_ pints per week

Wine: \_\_\_\_\_ Glasses per week

Spirit: \_\_\_\_\_ measures per week

Other (Please specify) \_\_\_\_\_ per week

\_\_\_\_\_ per week

How long you have had diabetes for? \_\_\_\_\_ (yrs)

Do you know your diabetes type: Type 1 \_\_\_ Type 2 \_\_\_ Don't know \_\_\_\_\_

Ethnicity: (Please tick one) 1. White \_\_\_ 2. Asian \_\_\_\_\_ (Pakistan \_\_\_\_, Bangladesh \_\_\_\_, Indian \_\_\_\_, other \_\_\_\_\_) 3. Black \_\_\_\_\_ 4. Other \_\_\_\_\_

Are you experiencing any pain in feet/legs or hands? Yes \_\_\_\_\_ No \_\_\_\_\_

If yes, kindly fill out the form below. It will help us to know more about diabetes related nerve problem. If not you can send back this page along with the empty form.

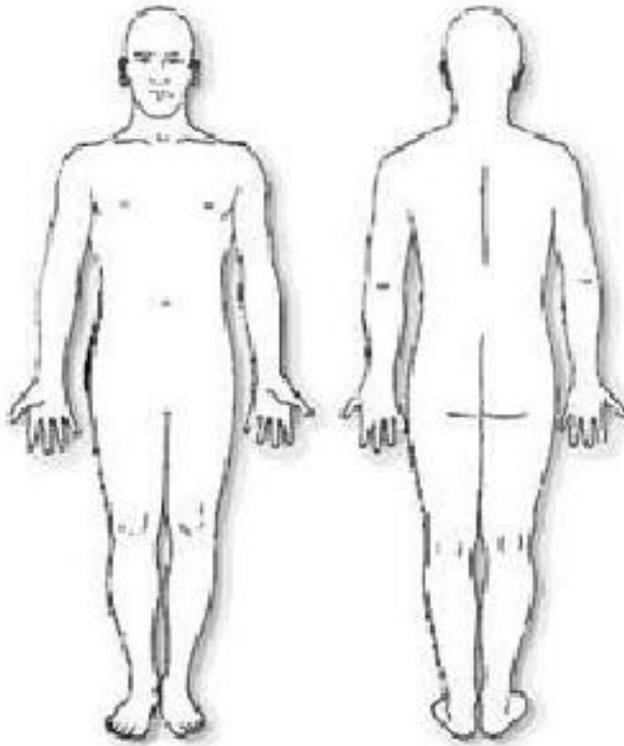
If you do not want us to access your blood results from Lancashire hospitals NHS trust database please indicate below:

\_\_\_\_\_

If for any reason you wish to withdraw from our list to receive information about future research projects please indicate below.

\_\_\_\_\_

This questionnaire can tell us about the type of pain that you may be experiencing. Please draw on the diagram below where you feel your pain. If you have pain in more than one area, only shade in the one main area where your worst pain is.



---

On the line below, please put a cross across or circle a number to indicate how bad your pain (that you have shown on the above diagram) has been in the last week.

NONE  SEVERE PAIN  
(0 1 2 3 4 5 6 7 8 9 10)

On an average day how many hours do you have very bad pain? \_\_\_\_\_ Hours

Below are 7 questions about your pain (the one in the diagram). Think about how your pain that you showed in the diagram has felt over the last week. Put a tick against the descriptions that best match your pain. These descriptions may, or may not, match your pain no matter how severe it feels. Only tick the responses that describe your pain in any question.

1. In the area where you have pain, do you also have 'pins and needles', tingling or prickling sensations?

-----a) NO - I don't get these sensations

-----b) YES - I get these sensations often

2. Does the painful area change colour (perhaps looks mottled or more red) when the pain is particularly bad?

-----a) NO - The pain does not affect the colour of my skin

-----b) YES - I have noticed that the pain does make my skin look different from normal

3. Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations or pain when lightly stroking the skin might describe this.

-----a) NO - The pain does not make my skin in that area abnormally sensitive to touch

-----b) YES - My skin in that area is particularly sensitive to touch

4. Does your pain come on suddenly and in bursts for no apparent reason when you are completely still? Words like 'electric shocks', jumping and bursting might describe this.

-----a) NO - My pain doesn't really feel like this

-----b) YES - I get these sensations often

5. In the area where you have pain, does your skin feel unusually hot like a burning pain?

-----a) NO - I don't have burning pain

-----b) YES - I get burning pain often

6. Gently rub the painful area with your index finger and then rub a non-painful area (for example, an area of skin further away or on the opposite side from the painful area). How does this rubbing feel in the painful area?

-----a) The painful area feels no different from the non-painful area

-----b) I feel discomfort, like pins and needles, tingling or burning in the painful area that is different from the non-painful area

7. Gently press on the painful area with your finger tip then gently press in the same way onto a non-painful area (the same non-painful area that you chose in the last question). How does this feel in the painful area?

-----a) The painful area does not feel different from the non-painful area

-----b) I feel numbness or tenderness in the painful area that is different from the non-painful area.

## Appendix 2. SHORT FORM-36 (SF36) SURVEY

Please answer the following questions about your health. Select ONLY ONE ANSWER for each question

1. In general, would you say your health is:

1. Excellent
2. Very Good
3. Good
4. Fair
5. Poor

2. Compared to one year ago, how would you rate your health in general now?

1. Much better now than one year ago
2. Somewhat better now than one year ago
3. About the same as one year ago
4. Somewhat worse now than one year ago
5. Much worse than one year ago

3. Does your health now limit you in this activity? If so, how much? Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

4. Does your health now limit you in this activity? If so, how much? Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

5. Does your health now limit you in this activity? If so, how much? Lifting or carrying groceries.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

6. Does your health now limit you in this activity? If so, how much? Climbing several flights of stairs.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

7. Does your health now limit you in this activity? If so, how much? Climbing one flight of stairs.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

8. Does your health now limit you in this activity? If so, how much? Bending, kneeling, or stooping.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

9. Does your health now limit you in this activity? If so, how much? Walking more than a mile.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

10. Does your health now limit you in this activity? If so, how much? Walking several blocks.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

11. Does your health now limit you in this activity? If so, how much? Walking one block.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

12. Does your health now limit you in this activity? If so, how much? Bathing or dressing yourself.

1. Yes, limited a lot
2. Yes, limited a little
3. No, not limited at all

13. During the past 4 weeks, have you had the following problem with your work or other regular daily activities as a result of your physical health? Cut down the amount of time you spent on work or other activities.

1. Yes
2. No

14. During the past 4 weeks, have you had the following problem with your work or other regular daily activities as a result of your physical health? Accomplished less than you would like.

1. Yes
2. No

15. During the past 4 weeks, have you had the following problem with your work or other regular daily activities as a result of your physical health? Were limited in the kind of work or other activities.

1. Yes

2. No

16. During the past 4 weeks, have you had the following problem with your work or other regular daily activities as a result of your physical health? Had difficulty performing the work or other activities (for example, it took extra effort).

1. Yes

2. No

17. During the past 4 weeks, have you had the following problem with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious). ?Cut down the amount of time you spent on work or other activities.

1. Yes

2. No

18. During the past 4 weeks, have you had the following problem with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious) ?Accomplished less than you would like.

1. Yes

2. No

19. During the past 4 weeks, have you had the following problem with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?Didn't do work or other activities as carefully as usual.

1. Yes

2. No

20. During the past 4 weeks, to what extent has your physical health OR emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

1. Not at all

2. Slightly

3. Moderately

4. Quite a bit

5. Extremely

21. How much bodily pain have you had during the past 4 weeks?

1. None
2. Very mild
3. Mild
4. Moderate
5. Severe
6. Very severe

22. During the past 4 weeks how much did pain interfere with your normal work (including both work outside the home and housework)?

1. Not at all
2. A little bit
3. Moderately
4. Quite a bit
5. Extremely

23. How much of the time during the past 4 weeks: Did you feel full of pep?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

24. How much of the time during the past 4 weeks: Have you been a very nervous person?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time

6. None of the time

25. How much of the time during the past 4 weeks: Have you felt so down in the dumps that nothing could cheer you up?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

26. How much of the time during the past 4 weeks: Have you felt calm and peaceful?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

27. How much of the time during the past 4 weeks: Did you have a lot of energy?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

28. How much of the time during the past 4 weeks: Have you felt downhearted and blue?

1. All of the time
2. Most of the time
3. A good bit of the time

4. Some of the time
5. A little of the time
6. None of the time

29. How much of the time during the past 4 weeks: Did you feel worn out?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

30. How much of the time during the past 4 weeks: Have you been a happy person?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

31. How much of the time during the past 4 weeks: Did you feel tired?

1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. None of the time

32. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

1. All of the time
2. Most of the time
3. Some of the time
4. A little of the time
5. None of the time

33. How true or false is the following statement? I seem to get sick a little easier than other people.

1. Definitely true
2. Mostly true
3. Don't know
4. Mostly false
5. Definitely false

34. How true or false is the following statement? I am as healthy as anybody I know.

1. Definitely true
2. Mostly true
3. Don't know
4. Mostly false
5. Definitely false

35. How true or false is the following statement? I expect my health to get worse.

1. Definitely true
2. Mostly true
3. Don't know
4. Mostly false
5. Definitely false

36. How true or false is the following statement? My health is excellent.

1. Definitely true

2. Mostly true
3. Don't know
4. Mostly false
5. Definitely false

37. Are you ...?

1. Male
2. Female

38. How old were you on your last birthday?

Age:

### Appendix 3: Hospital Anxiety and Depression Scale Scoring Sheet

	Yes definitely	Yes sometimes	No not much	No not at all
1) I wake early and then sleep badly for the rest of the night	3	2	1	0
2) I get very frightened or have panic feelings for apparently no reason	3	2	1	0
3) I feel miserable and sad	3	2	1	0
4) I feel anxious when I go out of the house on my own	3	2	1	0
5) I have lost interest in things	3	2	1	0
6) I get palpitations, or sensations of 'butterflies' in my stomach or chest	3	2	1	0
7) I have a good appetite	0	1	2	3
8) I feel scared or frightened	3	2	1	0
9) I feel life is not worth living	3	2	1	0
10) I still enjoy the things I used to	0	1	2	3
11) I am restless and can't keep still	3	2	1	0
12) I am more irritable than usual	3	2	1	0
13) I feel as if I have slowed down	3	2	1	0
14) Worrying thoughts constantly go through my mind	3	2	1	0

Anxiety 2,4,6,8,11,12,14

Depression 1,3,5,7,9,10,13

Scoring 3,2,1,0 (for item 7 & 10 the scoring is reversed)

GRADING: 0-7 =Non-case 8 and above +ve

**Appendix 4: McGill (SF) Pain Assessment Form**

Date:.....

Name:

Hospital No:

DOB:

Tick the level of pain for each word or tick none if it does not apply to you.

No	Type of pain	None	Mild	Moderate	Severe
1	Throbbing				
2	Shooting				
3	Stabbing				
4	Sharp				
5	Cramping				
6	Gnawing				
7	Hot-burning				
8	Aching				
9	Heavy				
10	Tender				
11	Splitting				
12	Tiring-Exhausting				
13	Sickening				
14	Fearful				
15	Cruel-punishing				

Put a cross on this line to show how bad your pain is. At the left end of line means no pain at all, at right end means worst-pain possible.

No ..... Worst Possible

<b>Please do not write in this box:</b>		
S ----- / 33	A ----- / 12	VAS ----- /10

***Presentations and Publications***

**Currently in press in the “International journal of diabetes and metabolism”**

**Diagnosis and treatment of atypical painful neuropathy due to “Insulin neuritis” in patients with diabetes**

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**Running title:** Insulin neuritis

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## **Abstract**

Diabetes is very common and its global prevalence is rising day by day. As a result we are seeing more complications related to diabetes. In order to prevent micro vascular and macro vascular complications such as retinopathy, nephropathy, erectile dysfunction, neuropathy, myocardial infarction and stroke health care professionals are keen to have better glycaemic control. When dealing with newly diagnosed or poorly controlled diabetes patients are encouraged to bring down glycated haemoglobin (HbA1c). Diabetic painful neuropathy (DPN) is one of the well-known complications associated with long-term poor glycaemic control. However, on the other hand rapid control of high blood sugar can precipitate painful neuropathy known as “insulin neuritis”. The rapid tight glycaemic control with either insulin or oral hypoglycaemic agents on poorly controlled diabetic patients cause flux of blood glucose and metabolic shift resulting in structural changes at nerve endings (endoneural blood vessels) which resemble the retinopathy changes in retina. It causes steal effect and hypoxia in the nerves and hence precipitates neuropathic pain. It lasts for about 6 months and responds well to standard treatment of painful neuropathy. Health professionals need to be aware of this condition and consider gentle glycaemic control when aiming for Target HbA1c. This review outlines the disease, the symptoms, the types and treatment.

**Words for index:** insulin neuritis, diabetes mellitus, glycaemic control, neuropathy, retinopathy, blood glucose

## **Introduction**

Diabetes mellitus (DM) is the commonest metabolic disease currently affecting more than 250 million people worldwide and it costs the Governments of the world more than £800 billion to diagnose, treat and care for diabetic patients. DM is associated with numerous long-term complications including cardiomyopathy, nephropathy, neuropathy and retinopathy. This review addresses diabetic painful neuropathy (DPN) which is one of the well-known complications of diabetes and it affects up to 53% of diabetic population<sup>1</sup>. It is the most common form of painful neuropathy<sup>2</sup>. It manifests with varying description from mild pins and needle sensation to the stabbing pain, burning, unremitting or even described as electric shock. The most common feature is cutaneous hypersensitivity leading to acute distress on contact with an external stimulus, such as clothing<sup>3</sup>. The pathogenesis of DPN is mainly caused by inflammatory process<sup>4</sup> and strongly correlates with longer duration of the diabetes and poor glycaemic control<sup>5-18</sup>

Treatment induces acute neuropathy due to rapid glycaemic control has been reported in literature as ‘insulin neuritis’ that usually manifests with severe excruciating neuropathic pain in the first month of initiation of insulin or oral hypoglycaemic agents. Symptoms usually last up to 6 months and respond to treatment that is usually needed up to 6 months<sup>3</sup>. Insulin neuritis was first described by Caravati in 1933. He reported a diabetic woman with numbness, tingling, and shooting pains in the lower extremities that appeared four weeks after the initiation of insulin. The pain increased despite the use of analgesics and sedatives, but resolved within 3 days of stopping insulin concurrent with severe hyperglycaemia. Further attempts at the use of insulin resulted in similar levels of pain. He called the condition “insulin neuritis”<sup>19</sup>. The word insulin neuritis is a misnomer, as it can also be induced by oral hypoglycaemic agent<sup>20</sup>. The cause is not directly by insulin

but mainly due to the change in flux of blood glucose caused by rapid change in blood glucose level following pharmacological treatment<sup>21</sup>.

### **Symptoms**

There are several studies and case reports in the literature about insulin neuritis with varying presentation after starting insulin or oral hypoglycaemic agents. These reports described the most common features as generalized pain bilaterally mainly distally in feet with burning sensation, hypersensitivity and contact discomfort of the skin within 2 to 4 weeks<sup>20,22,23</sup>. It may present with truncal neuropathy<sup>24,25,26,27</sup>, autonomic neuropathy<sup>28</sup>, worsening of retinopathy<sup>29</sup> and even with profound weight loss<sup>22,30,31,32</sup>

### **Generalize pain mainly distally.**

The most common presentation of Insulin neuritis is symmetrical and bilateral distal neuropathic pain mainly involving feet<sup>3</sup>. In one observational study on 6 patients with diabetes, all experienced severe excruciating bilateral neuropathic pain mainly in feet after 2-4 weeks of insulin treatment with rapid reduction of blood glucose up to one fifth of initial levels. This improved in all cases with symptomatic treatment allowing discontinuation of therapy in 3-8 months<sup>20</sup>. A case report on a newly diagnosed type 1 diabetes patient described development of severe pain in his feet, which prevented him from walking, after initiation of insulin. The HbA1c of that patient dropped from 14.1 to 7.6%, and 3 months after presentation, the patient showed dramatic improvement and regained his ability to walk<sup>33</sup>. There is another similar case report of painful neuropathy on 15<sup>th</sup> day of treatment with intense insulin therapy following poor glycaemic control period of 8 years. He responded well on symptomatic treatment on day 3 on venlafaxine.<sup>34</sup>

### **Diabetic neuropathic cachexia**

Painful neuropathy is sometimes associated with profound weight loss and called “Diabetic neuropathic cachexia”. This has also been reported with insulin neuritis that could last up to a year. The exact mechanism and cause is unknown<sup>3</sup>. It is observed that constant pain and discomfort can cause loss of appetite and low mood which results in patients not eating enough and start losing weight. Most patients respond well with neuropathic pain treatment which gives pain relief and regain weight. In one observational study, 9 diabetic patients experienced painful neuropathy with constant burning pain mainly in the legs, especially distally. There was marked troublesome allodynia associated with profound weight loss along with depression with impotence. These severe manifestations subsided in most cases in 6 months and in all cases in 10 months<sup>22</sup>. There is another case report in which patient presented with painful neuropathy, profound weight loss after initiation of insulin therapy within 3 months<sup>31</sup>

### **Truncal neuropathy**

Insulin neuritis may precipitate focal neuropathic pain called “Truncal neuropathy” on specific dermatome region. Truncal neuropathy in diabetes presents with neuropathic pain such as a hypoesthesia, regional hyperalgesia, allodynia and sometime focal weakness in specific dermatome region. It usually presents with unilateral abdominal or thoracic wall pain.<sup>3,25</sup> There was one case of insulin neuritis which presented with painful neuropathy with paraesthesia and hyperesthesia restricted to the abdomen and this was associated with profound weight loss. The haemoglobin A (1c) had dropped from 12% to 7.5% within 5 months, following rapid improvement in glycaemic control. On

investigation, there was no indication of disease in intra-abdominal area. The symptoms improved dramatically within 4 months after symptomatic treatment<sup>30</sup>

It is not uncommon that these patients have to undergo a number of investigations to determine the cause of pain before having the diagnosis of truncal neuropathy<sup>24-27,30</sup>. There are several cases of truncal neuropathy that were misdiagnosed initially as for example hernia due to focal weakness on abdominal wall<sup>26</sup>, angina due to left sided chest wall pain<sup>25</sup> and painless gall stones due to focal sensory deficit complicated with painless jaundice secondary gall stone<sup>27</sup>. The diagnosis of truncal neuropathy is essentially clinical and positive recognition of neuropathic element of pain is the key factor. Most people respond well on neuropathic treatment and usually settle in 3 to 12 months.

### **Autonomic neuropathy**

Autonomic dysfunction is one of the complications of diabetes<sup>3</sup>. It manifests with one or more of the following: erectile dysfunction, gastroparesis, neurogenic bladder, dry feet, depressed cough reflex, postural hypotension or high blood flow to foot<sup>35,36</sup>. Insulin neuritis has been reported to precipitate autonomic neuropathy. In one prospective study on 16 diabetic patients followed up for 18 months, all the patients develop severe painful neuropathy in 8 weeks of intense glycaemic treatment. All individuals with treatment for induced neuropathy had evidence of autonomic dysfunction on testing and exhibited symptoms of autonomic impairment. Approximately, 69% of cohort had systolic blood pressure falls > 20 mmHg. Symptoms of autonomic dysfunction were more prevalent and more severe in subjects with type 1 diabetes, particularly with respect to symptoms of orthostatic intolerance and gastrointestinal function. Urinary frequency, nocturia and anhidrosis were reported more frequently in individuals with type 2 diabetes<sup>28</sup>.

## **Retinopathy**

Retinopathy is a well-known complication of diabetes and directly related with poor glycaemia and duration of diabetes<sup>37</sup>. It is also proven that better glycaemic control prevent worsening of retinopathy<sup>38</sup>. Insulin neuritis with rapid flux of blood glucose causes structural changes at endoneural blood vessels of nerves which resemble with retinopathic changes in retina<sup>39</sup>. Rapid drop in blood glucose in poorly controlled diabetes may exert the same changes in retina, thus worsening the retinopathy. In one large observational study, 87 patients were divided in 3 groups of varying glycaemic control. These included a group of poor glycaemic control corrected rapidly, poor glycaemic control not corrected and good control group. The progression rate of diabetic maculopathy was significantly higher in the group that underwent rapid control than in the other 2 groups ( $P < 0.02$ ). Patients with moderate to severe non-proliferative diabetic retinopathy preoperatively in the rapid control group had significantly higher progression rates of diabetic retinopathy and maculopathy ( $P < 0.002$  and  $p < 0.008$ , respectively)<sup>40</sup>.

## **Pathogenesis**

In 1992 Boulton first described the observation that acute painful neuropathy might follow sudden change in glycaemia control suggesting that blood glucose flux could precipitate pain. Sudden changes in glycaemia may contribute to the generation of impulses or even induce relative hypoxia in nerve fibres, indicating that it is the combination of structural and functional changes in peripheral nerves which cause the pain<sup>21</sup>. This observation was experimentally tested by Kihara et al in 1994 on rats. In their study, they infused insulin under non-hypoglycaemic conditions and evaluated its effect on endoneurial oxygen tension, nerve blood flow, and the oxy-haemoglobin dissociation

curve of peripheral nerves in normal and diabetic rats. Their results showed that insulin administration could cause a reduction in nerve nutritive blood flow and an increase in arterio-venous shunt flow. When the latter was eliminated by the closure of arterio-venous shunts (infusion of 5-hydroxytryptamine), endoneurial oxygen reverted to normal. These findings clearly indicate a deleterious vasoactive effect of insulin and may explain the development of insulin neuritis<sup>41</sup>.

In 1996 Tesfaye et al observed neurovascular changes in vivo in five human diabetic patients with insulin neuritis. These patients presented with severe sensory symptoms but clinical examination and electrophysiological tests were normal except with one subject who had severe autonomic neuropathy and all tests were abnormal. On sural nerve exposure in vivo, epineural blood vessels showed severe structural abnormalities resembling the retinopathy changes normally seen in the retina, including arteriolar attenuation, tortuosity and arterio-venous shunting and proliferating new vessels formation. They hypothesized that the structural abnormalities with new vessels formation in epineural blood vessels cause steal effect and hence results in hypoxia and neuropathic pain<sup>39</sup>. It can now be postulated that sudden change in glycaemic control can cause flux effect resulting in structural and functional changes at the epineural blood vessels of nerves which in turn can lead to neuropathic pain “Insulin neuritis (see figure 1)”<sup>21,39</sup>.

## **Treatment**

Management of neuropathic pain in “insulin neuritis” is symptomatic including first line medication tricyclic antidepressants (Amitriptyline) or selective serotonin uptake inhibitor (Duloxetine). Second line medications include anti-epileptic medications

(Gabapentin, Pregabalin, Carbamazepine and Topiramate) and Opioids. Most patients recover within 6 months of onset of insulin neuritis<sup>3</sup>

## **Conclusion**

The flow diagram in Figure 2 summarises the pathogenesis of insulin neuritis. With increasing prevalence of diabetes and its complications, both health professional and patients are keen to have good glycaemic control in order to prevent long term complications<sup>42</sup>. Most of the time it is not a problem but on several occasions intense treatment for rapid glycaemic control may cause insulin neuritis. This is presumed to be caused by change in glucose flux which can result in structural and functional changes at the nerves leading to hypoxia. This in turn can precipitate neuropathic pain and the whole phenomenon is called “insulin neuritis”. It usually manifests distally in feet and is bilateral with burning sensation, hypersensitivity and allodynia. It could affect focally – truncal neuritis and may present with neuropathic pain and/or weakness in dermatomal region. Similarly, it may present with autonomic symptoms. Constant pain may cause cachexia and loss of appetite which can result in significant weight loss. Most patients respond well with neuropathic treatment and recover within 6 months. It is very important to be aware that treatment induced insulin neuritis can have significant impact on the quality of the life of the diabetic patient. This can be easily prevented by gradual glycaemic control and by symptomatic treatment as necessary. Healthcare professionals need to be aware of this condition when managing poorly controlled diabetic patients and should consider gradual titration of the pharmacological agents employed to treat the patients.

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## PATHOGENESIS OF INSULIN NEURITIS

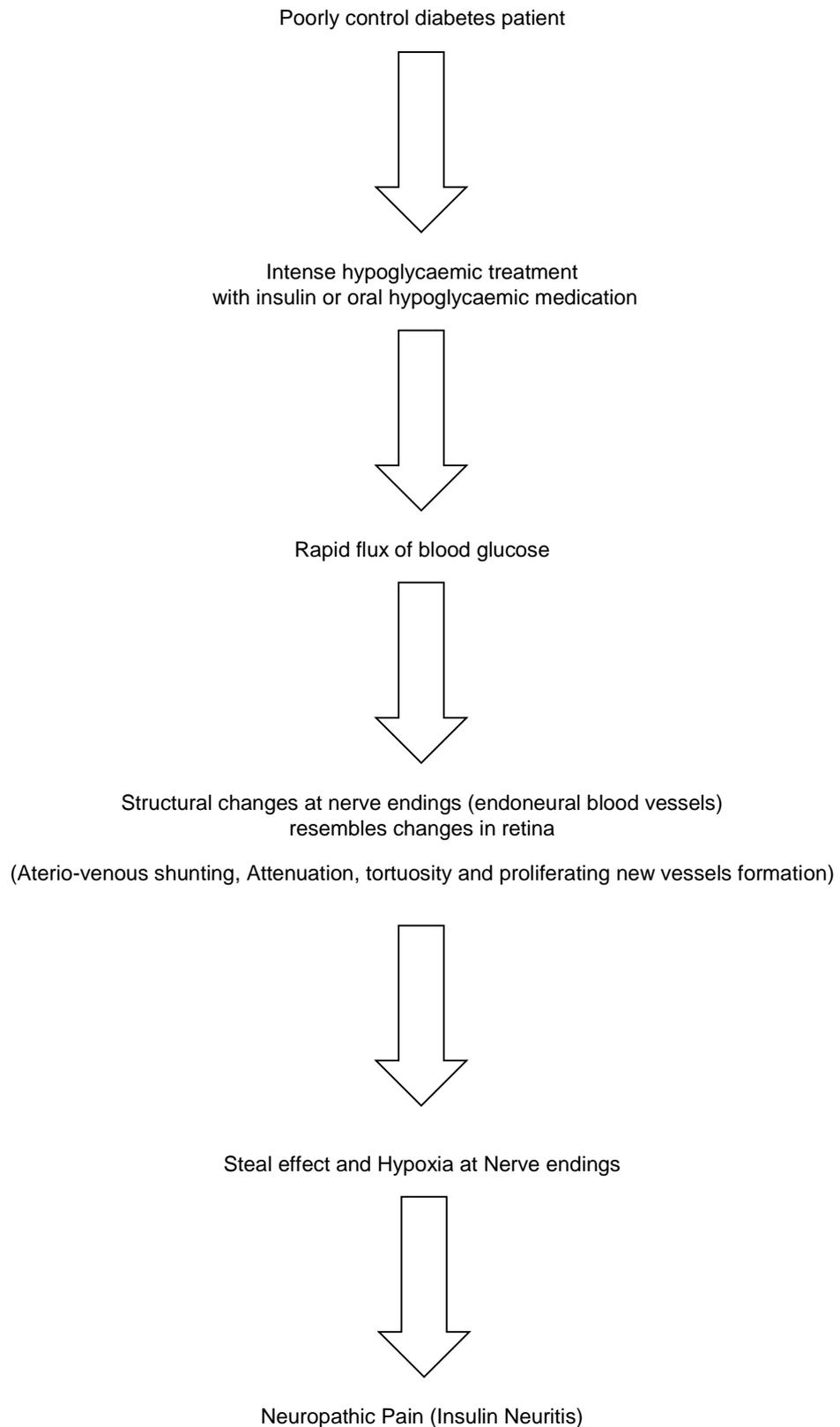


Figure 1: A flow diagram showing the pathogenesis of insulin neuritis



Figure 2: Arteriolar attenuation, tortuosity and arterio-venous shunting and proliferating new vessels formation of vasa nervosum seen in sural nerve of patient with insulin neuritis (photo courtesy of Tesfaye and Boulton <sup>9</sup>)

# The impact of painful diabetic neuropathy on quality of life: An observational study

Amir Aslam, Jaipaul Singh, Satyan M Rajbhandari

**About a third of people with diabetes experience PDN at some point in their lives, and it is a distressing condition affecting individuals both physically and emotionally. The aim of the study reported here was to assess quality of life, anxiety and depression in people with PDN using the 36-item Short Form Health Survey and the Hospital Anxiety and Depression Scale questionnaires, comparing these results against those in with people with diabetes who did not have PDN. The findings are presented in this article.**

Currently, over 380 million people worldwide are living with diabetes and it is estimated that this figure will rise up to 592 million in the year 2035 (International Diabetes Federation, 2013). The prevalence of diabetes-related complications is also rising. Painful diabetic neuropathy (PDN) is a common complication of diabetes, affecting about a third of all people with diabetes (Tesfaye, 2009). It is characterised by bilateral symmetrical distal neuropathic pain in the lower extremities with varied symptoms including mild pins and needles, a tingling sensation, a shooting pain similar to electric shock, a constant burning sensation with nocturnal exacerbation, and contact hyper-sensitivity (allodynia; Larsen et al, 2002). Relentless pain and allodynia can affect people both physically and mentally and can cause disturbance in sleep, low mood, impotence and social withdrawal. In some extreme cases, the affected individual is unable to walk (Quattrini and Tesfaye, 1996; Galer et al, 2000; Gardner and Shoback, 2007). PDN can significantly alter – and, moreover, has a huge impact on – individuals' quality of life (QoL).

Currently, there are only a few studies that have been performed specifically to measure the physical and mental impact of PDN on QoL. The study reported here was designed to assess QoL, anxiety and depression in people with PDN (PDN group) compared with those

with diabetes not known to have PDN (control group).

There are several health-related questionnaires available to assess QoL and physical and mental wellbeing (Healthmeasurement.org, 2014). Typically, researchers use the 36-item Short Form Health Survey (SF-36®) for the assessment of QoL and the Hospital Anxiety and Depression Scale (HADS) for the assessment of mood and anxiety. Ware and Sherbourne (1992) introduced SF-36, which was designed for use in clinical practice and research, health policy evaluations and general population surveys. SF-36 includes 36 subjective questions that assess eight health concepts of QoL from the patient's point of view:

- 1 Limitations in physical activities because of health problems.
- 2 Limitations in social activities because of physical or emotional problems.
- 3 Limitations in usual role activities because of physical health problems.
- 4 Bodily pain.
- 5 General mental health (psychological distress and wellbeing).
- 6 Limitations in usual role activities because of emotional problems.
- 7 Vitality (energy and fatigue).
- 8 General health perceptions.

SF-36 is a practical, reliable and valid measure of physical and mental health and has been

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## Article points

1. Painful diabetic neuropathy (PDN) is a common and potentially very serious complication of diabetes.
2. There is relatively little research aimed at quantifying the impact of PDN on quality of life (QoL) and mental health.
3. Here the authors report data from north-west England suggesting that PDN is associated with a negative impact on QoL and anxiety.

## Key words

- Anxiety
- Depression
- Painful diabetic neuropathy
- Quality of life

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### Page points

1. In this observational study, the 36-item Short Form Health Survey was used to assess the quality of life, while the Hospital Anxiety and Depression Scale was employed to explore specific aspects of mental health.
2. The painful diabetic neuropathy group was formed from attendees at the diabetic neuropathic pain clinic at Chorley and South Ribble District General Hospital, while the control group (comprising people with diabetes not known to have neuropathic pain) was formed from individuals visiting the Aston Healthcare GP surgery at Whiston (Merseyside) for diabetes review.
3. Each group consisted of 25 consecutive consenting patients at the respective sites.

used in a variety of chronic health conditions including diabetic neuropathic pain (Garratt, 1993; Ware et al, 1994; Rosenstock et al, 2004; Vinik et al, 2013) and published in more than 4000 documents, as of 2002 (Turner-Bowker et al, 2002).

The HADS questionnaire was originally developed by Zigmond and Snaith (1983) for psychometric evaluation. Since then, it has been widely used worldwide by health professionals, in both the community and hospital settings, and it has been found to be both a reliable and a valid measure of anxiety and depression (el-Rufai and Absood, 1987; Nortvedt et al, 2006). The HADS questionnaire is based on a total of 14 questions, seven for anxiety assessment and seven for depression. HADS provides clear cut-off scores for severity of anxiety and depression. We felt that HADS would serve as an ideal tool for screening and thus adopted it in our study.

### Methods

#### Study design

This was an observational study. The SF-36 and HADS questionnaires were used for data collection, based on the rationale described above. It takes approximately 15 minutes to fill in the SF-36 questionnaire and 5 minutes to fill in the HADS questionnaire, which meant that participants were able to fill these in while waiting for their appointment or to post them back to the research team after completing them at home.

#### Participants

The PDN group was formed from attendees at the diabetic neuropathic pain clinic at Chorley and South Ribble District General Hospital, while the control group (comprising people with diabetes not known to have neuropathic pain) was formed from individuals visiting the Aston Healthcare GP surgery at Whiston (Merseyside) for diabetes review. Each group consisted of 25 consecutive consenting patients at the respective sites. Individuals under 16 or over 80 years of age were excluded from participation. All individuals gave consent for participation. Institutional approvals were obtained at both centres for the study.

#### Assessment of QoL, anxiety and depression SF-36 (used for QoL assessment)

The SF-36 questions were scored from 0 (worst possible functioning) to 100 (highest level of function). The average scores from those questions that addressed each specific area of a functional health domain provided the final score for the domain. Aggregate scores were compiled as a percentage of the total points possible, using the RAND scoring system (RAND Health, 2014).

Of the eight domains (described earlier), four relate to physical health (physical functioning, physical health limitation, pain and general health) and four to mental health (social functioning, emotional wellbeing, fatigue and emotional problem limitation). Aggregate scores for physical health domains and for mental health domains were also calculated.

#### HADS questionnaire (used for the assessment of anxiety and depression)

Each HADS question was scored from 0 (excellent mental health) to 3 (worst mental health). Aggregate scores (with a maximum of 21) were calculated for the seven anxiety questions and the seven depression questions. Scores between 0 to 7 were considered "normal", for both anxiety and depression assessment. Scores of 8 and above were considered to be significant for the diagnosis of anxiety or depression (el-Rufai and Absood, 1987; Nortvedt et al, 2006).

#### Statistical analysis

Data were analysed using GraphPad software (GraphPad Software Inc, 2014). For the normally distributed continuous variables from SF-36 and HADS, means ( $\pm$  standard deviation [SD]) were calculated and analysed using the unpaired Student's *t*-test. Categorical data were also calculated, as a percentage of participants. The categorical data from HADS were analysed as a 2x2 table using Fisher's exact test.

For the purpose of visually summarising the data, box-plots were also created, using Minitab (2014) statistical software, and these represented median, minimum and maximum values, as well as the lower and upper quartiles.

**Table 1. Data for the eight domains of the 36-item Short Form Health Survey (SF-36®) in the study groups.**

SF-36 domain	Mean score in PDN group	Mean score in control group	95% confidence interval	P-value
Physical functioning	28.4	65.2	18.9 to 54.7	<0.0001*
Physical health limitation	17.0	61.0	22.0 to 66.1	<0.0002*
Pain	29.3	59.9	14.2 to 47.0	<0.0005*
General health	31.1	52.0	7.3 to 34.6	0.0034*
Social functioning	48.8	68.0	2.0 to 36.4	0.0292*
Emotional wellbeing	61.4	69.3	-7.0 to 22.6	0.292
Fatigue	25.4	42.4	4.8 to 29.3	0.0073*
Emotional problem limitation	41.3	72.0	5.3 to 56.0	0.0188*

\* $P < 0.05$ .

PDN=painful diabetic neuropathy.

## Results

The two groups were similarly distributed ( $P > 0.05$ ) in age and also in sex (PDN group, 60% male; control group, 56% male). Participants in the PDN group had significantly ( $P < 0.05$ ) lower scores in seven out of eight domains of SF-36 compared with the control group (Table 1). The exception was emotional wellbeing. Both physical health and mental health summary scores were significantly lower in the PDN group than the control group (Figure 1).

Individuals in the PDN group had significantly higher HADS anxiety scores, but HADS depression scores were not statistically significantly different from those in the control group (Figure 2).

Fourteen individuals (56%) out of 25 had anxiety in the PDN group (the mean score was  $7.32 \pm 3.42$ ). In the control group, five individuals (20%) met the criterion for a diagnosis of anxiety (the mean score was  $4.72 \pm 4.34$ ). The  $P$ -values calculated from comparisons of the continuous data and of the categorical data were 0.023 and 0.018, respectively (both statistically significant).

Fifteen people (60%) out of 25 had depression in PDN group (the mean score was  $8.36 \pm 4.05$ ). In the control group, 11 people (44%) met the criterion for a diagnosis of depression (the mean score was  $6.6 \pm 4.16$ ). The  $P$ -values calculated from comparisons of the continuous data and of the categorical data were 0.136 and 0.396, respectively (neither being statistically significant).

## Discussion

Few studies have specifically reported the impact of PDN on QoL and psychological wellbeing of people with diabetes (Benbow et al, 1998; Quattrini and Tesfaye, 1996; Galer et al, 2000; Gore et al, 2005; Argoff et al, 2006; Van Acker et al, 2009). Our data reveal a significant association of PDN with poor QoL and anxiety symptoms but not with depression. This last observation could be because a number of people with PDN were treated with antidepressants for their neuropathic pain, and the underlying symptoms of depression might have thus been reduced to some extent, or it could be down to insufficient power.

### Comparison with existing data

The data from our study hint at a significant impairment of QoL associated with PDN within both the physical and mental health areas of the SF-36 questionnaire. The results are consistent with similar research reported using a shorter (12-item) version of the questionnaire. Van Acker et al (2009) found significant impairment in both the physical and mental health components of QoL. In another study, by Benbow et al (1998), the Nottingham Health Profile questionnaire was used, and it was found that there were significant impairments in QoL in five of the six domains (emotional reaction, energy, pain, physical mobility and sleep). The exception was the social isolation domain. Similarly, in the present study, the data showed significant impairment in all of the domains but one (emotional wellbeing).

## Page points

1. Few studies have specifically reported the impact of painful diabetic neuropathy (PDN) on quality of life (QoL) and psychological wellbeing of people with diabetes
2. The authors' data hint at an association of PDN with poor QoL and anxiety symptoms.

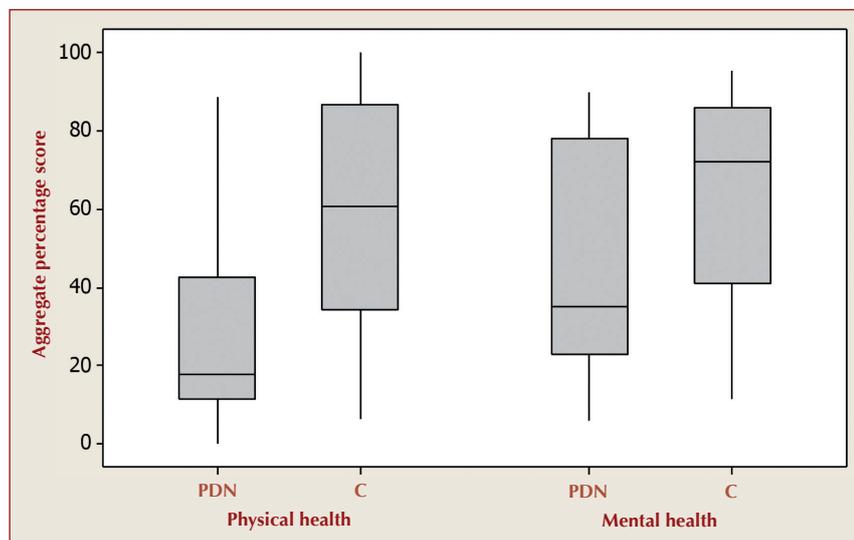


Figure 1. A box-plot of the overall physical and mental health scores from the 36-item Short Form Health Survey in the painful diabetic neuropathy (PDN) and control (C) groups (boxes for median and lower and upper quartile values [with bars for minimum and maximum score]; n=25).

As mentioned earlier, there are reports of severe PDN with constant unrelenting neuropathic pain, disturbance of sleep and even the loss of the ability to walk, owing to the severity of pain (Quattrini and Tesfaye, 1996; Galer et al, 2000; Gardner and Shoback, 2007). This can in turn lead to withdrawal from routine activity of life, including employment, and can also affect emotional wellbeing and contribute to social isolation. The data for the emotional wellbeing domain in our study and the social isolation

domain of Benbow et al (2000) study were not significant, perhaps owing to the presence of only a small number of the severe type of PDN case associated with extreme symptoms.

HADS data in the present study showed that more than half (56%) of the participants in the PDN group had anxiety symptoms, with this proportion (and the summarised continuous data) being statistically significantly different from those of the control group. The data were broadly consistent with those reported by Gore et al (2005), using the HADS questionnaire. They reported that 35% of their participants had anxiety symptoms. However, they used a threshold score on HADS of 11 or above (moderate-to-severe symptoms), while we used a threshold score of 8 and above. Our data for depression symptoms showed that more than half (60%) of the individuals in the PDN group had symptoms of depression (a score above 7). However, comparisons of the differences from the control group were not statistically significant. In contrast, Gore et al (2005) showed a significant association between PDN and depression. In their study, the prevalence of depression in people with PDN was 28% (a score of 11 or above).

A large systematic review and meta-analysis reported the prevalence of depression in people with diabetes to be around 17.5% (Ali et al, 2006). In our study, the control group of people with diabetes was found to have an unusually high prevalence of depression (44%). This may be down to random factors or could have resulted from the control group having been taken from an area of relatively low socioeconomic status.

### Strengths and limitations of the study

The study population was well defined, and both groups of participants had a 100% response in completing the two questionnaires. The groups were similar in age and in the ratio of males to females.

Recall bias could potentially exist when participants are completing questionnaire. However, most questions from both questionnaires used were based on current or recent physical and mental wellbeing of the person, and hence recall bias is considered to have been minimal.

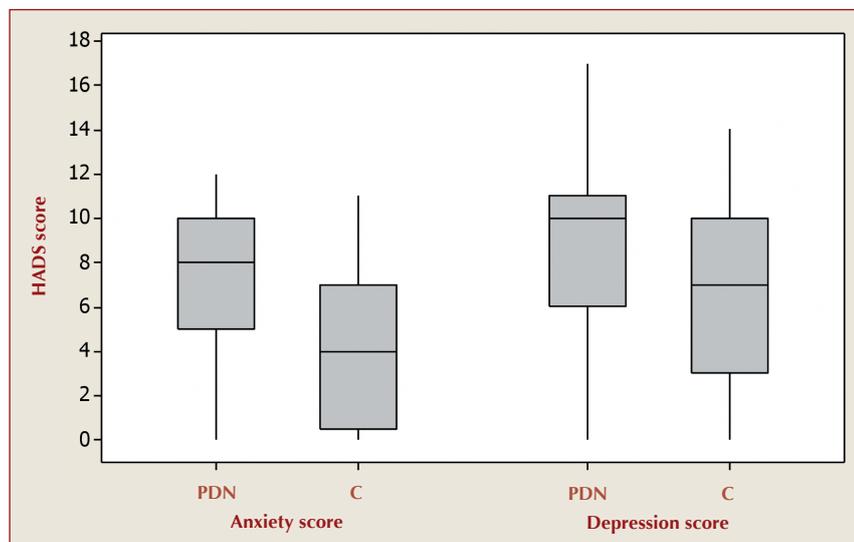


Figure 2. A box-plot of the Hospital Anxiety and Depression Scale (HADS) scores in the painful diabetic neuropathy (PDN) and control (C) groups (boxes for median and lower and upper quartile values [with bars for minimum and maximum score]; n=25).

A major limitation of the study relates to the selection of the control group. As mentioned above, the GP surgery from which the control group data were taken lies in an area of north-west England with a low socioeconomic status. It is known that low socioeconomic community status has a positive association with prevalence of depression (Murali and Oyeboode, 2004). Furthermore, the two groups were selected from healthcare settings of a different nature. These discrepancies, and the lack of randomisation in the study, could thus have led to selection bias, which in turn could have had an impact on outcomes. Data were not collected to compare factors other than age and sex (duration of diabetes and the presence of other complications are among the other potential confounding factors). As with any non-randomised study, it is not possible to infer a causal relationship and thus our conclusions can only be tentative at most.

## Conclusion

Overall, we believe our study tentatively suggests that, in a population in north-west England, PDN has a clinically significant impact on QoL and is also associated with symptoms of anxiety. Further research would be needed to shed more light on depression and to draw firmer conclusions on the potential causal nature of the association observed.

In light of our findings, we suggest that, when caring for people with PDN, clinicians should consider exploring psychosocial wellbeing and the overall impact of the condition on QoL. ■

## Declaration of competing interests

The authors reported no conflict of interests regarding the publication of this paper.

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**“When caring for people with painful diabetic neuropathy, clinicians should consider exploring psychosocial wellbeing and the overall impact of the condition on quality of life.”**

## Review Article

# Pathogenesis of Painful Diabetic Neuropathy

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The prevalence of diabetes is rising globally and, as a result, its associated complications are also rising. Painful diabetic neuropathy (PDN) is a well-known complication of diabetes and the most common cause of all neuropathic pain. About one-third of all diabetes patients suffer from PDN. It has a huge effect on a person's daily life, both physically and mentally. Despite huge advances in diabetes and neurology, the exact mechanism of pain causation in PDN is still not clear. The origin of pain could be in the peripheral nerves of the central nervous system. In this review, we discuss various possible mechanisms of the pathogenesis of pain in PDN. We discuss the role of hyperglycaemia in altering the physiology of peripheral nerves. We also describe central mechanisms of pain.

## 1. Introduction

Diabetes affects 382 million people worldwide and its prevalence is expected to increase to 592 million by the year 2035 [1]. Diabetic neuropathy, a well-known, long-term complication of diabetes, can affect almost half of the diabetic population [2] and is associated with higher morbidity and mortality [3]. Diabetic neuropathy encompasses a variety of clinical or subclinical presentations. Painful diabetic neuropathy (PDN) is a common type of diabetic neuropathy and the most common cause of neuropathic pain [4]. The reported prevalence of PDN varied from 11% in Rochester, Minnesota, USA [5], to 53.7% in the Middle East [6]. One UK study published in 2011 reported that the prevalence of PDN was 21.5% in type 2 diabetes patients and 13.4% in type 1 diabetes patients, resulting in an overall prevalence of 21% [7]. In the large, prospective EURODIAB study in 16 European countries, almost one-quarter of type 1 patients developed new onset painful diabetic neuropathy over a seven-year period [8]. A prospective study in Finland followed newly diagnosed diabetes patients between the ages of 45 and 64 years for 10 years. It found a 6% prevalence at the time of diagnosis of diabetes and a 26.4% prevalence at the 10-year follow-up [9]. In a large UK-based community diabetic

population, Abbot et al. [7] observed that increasing age was directly related to painful symptoms of neuropathy. Most studies found no significant difference in gender; however, Abbot et al. [7] reported a slightly higher prevalence of painful symptoms of neuropathy in females (38%) than males (31%). The same study also found a higher prevalence of painful symptoms in South Asians (38%) compared to Europeans (32%).

Painful diabetic neuropathy (PDN) symptoms exhibit a symmetrical “stocking and gloves” distribution and are often associated with nocturnal exacerbation. It can be presented from a mild pins and needle sensation to stabbing, burning, unremitting, or even unpleasant electric shock sensation. There can be allodynia in the form of cutaneous hypersensitivity leading to acute distress on contact with an external stimulus, such as clothing [10]. The pain is often worse at night and often disturbs sleep, causing tiredness during the day. Some patients present with distressing allodynia and severe pain in the legs. This may be so painful that it prevents them from performing their daily activities, thereby impacting their employment and social life. The constant, unremitting pain and withdrawal from social life often result in depression [11]. In extreme cases, patients lose their appetite and experience significant weight loss, which is

reported in the literature as “diabetic neuropathic cachexia” [10].

## 2. Physiology of Pain

Pain is the body’s perception of actual or potential damage to the nerve or tissue by noxious stimuli. The sensory afferent nerves carry sensations from the skin, joints, and viscera via large and small fibres. Large fibres, such as A-alpha, are responsible for limb proprioception and A-beta fibres carry sensations of limb proprioception, pressure, and vibration. Large A-delta myelinated fibres and small C unmyelinated fibres are mainly responsible for carrying nociceptive sensations. Superficial pain is often a sharp or pricking sensation and is transmitted by A-delta fibres. A deep-seated, burning, itching, aching type of pain is often accompanied with hyperalgesia and allodynia and is transmitted via slow, unmyelinated C fibres. Tissue damage results in the release of inflammatory chemicals, such as prostaglandins, bradykinins, and histamines, at the site of inflammation, which triggers the depolarization of nociceptors, thereby generating an action potential. The action potential transmits the nociceptive sensation, via the dorsal root ganglion (DRG), to the dorsal horn of the spinal cord. The release of glutamate and substance P results in the relay of nociceptive sensations to the spinothalamic tract, thalamus, and, subsequently, the cortex, where pain is interpreted and perceived [12].

Nociceptive pain is the normal response to noxious insult or injury of tissues such as skin, muscles, visceral organs, and joints. Nociceptive pain usually subsides upon the healing of the tissue injury. On the other hand, neuropathic pain arises as a direct consequence of a lesion or disease affecting the somatosensory system without any noxious stimuli. Neuropathic pain is caused by damage or pathological change and is characterised by the activation of abnormal pathways of pain at the peripheral nerves and posterior roots (peripheral neuropathic pain) or spinal cord and brain (central pain) [13]. Neuropathic pain manifestation can be focal, multifocal, or generalized depending on the involvement of peripheral or central origin and cause of the disease. A few examples of neuropathic pain are listed in Table 1.

## 3. Neuropathic Pain Generation Pathogenesis

The origin of pain in PDN is not fully understood. The abnormalities in the peripheral or central nervous system could be related to hyperglycaemia, as this is the key metabolic abnormality of diabetes. There are many other conditions that produce pain similar to that of PDN and they may also aid our understanding of the pathophysiology of PDN.

**3.1. Ectopic Electrical Impulses.** Chronic hyperglycemic damage to the nerves can cause regeneration of nerve sprouts, called neuromas, at the stump. The sprouting of the new nerves in all directions causes collateral damage of otherwise undamaged nerves and expands the sensitized area [14]. Hyperexcitability in the neuroma generates ectopic impulses that affect neighbouring intact afferents and the cell bodies

TABLE 1: Examples of neuropathic pain.

Origin of pain	Structure	Example
Peripheral nervous system	Nerve	Diabetic painful neuropathy
		Neuroma
		Phantom limb pain Trigeminal neuralgia Lumbosacral plexopathy
Central nervous system	Dorsal root	Postherpetic neuralgia Brachial plexus avulsion
	Spinal cord	Spinal cord injury Spinal cord infarction Multiple sclerosis
	Thalamus	Infarct Tumour Parkinson’s disease

of the DRG. It leads to spontaneous, exaggerated, abnormal hyperexcited responses, along with increased sensitivity to a given stimulus [15]. This phenomenon is called peripheral sensitization. Electrical impulses from the axon of small fibres at the dorsal horn of the spinal cord are increased and, hence, it alters the “gate” (described below) and causes the release of substance P and glutamate. This causes a relay of the impulses to the ascending track, which is perceived as pain [16].

**3.2. Change in Glucose Flux and Pain.** Treatment of induced acute neuropathy due to rapid glycemic control in the first month of the initiation of insulin or oral hypoglycemic agents has been reported in the literature as “insulin neuritis.” In 1992, Boulton [17] first described the observation that acute painful neuropathy might follow a sudden change in glycaemia control, suggesting that blood glucose flux could precipitate pain. This observation was experimentally tested in rats by Kihara et al. in 1994 [18]. In their study, they infused insulin under nonhypoglycemic conditions and evaluated its effect on endoneurial oxygen tension, nerve blood flow, and the oxyhaemoglobin dissociation curve of peripheral nerves in normal and diabetic rats. Their results showed that insulin administration caused a reduction in nerve nutritive blood flow and an increase in arteriovenous shunt flow. When the arteriovenous shunts were obliterated by the infusion of 5-hydroxytryptamine, endoneurial oxygen reverted to normal. Sudden changes in glycaemia may induce relative hypoxia in nerve fibres, which contributes to the generation of impulses, thereby indicating that it is the combination of structural and functional changes in peripheral nerves that cause the pain.

In 1996, Tesfaye et al. [19] observed neurovascular changes in vivo in five human diabetic patients with insulin neuritis. These patients presented with severe sensory symptoms but clinical examination and electrophysiological tests were normal, except in one subject who had severe autonomic neuropathy. On sural nerve exposure in vivo, epineurial blood vessels showed severe structural abnormalities resembling the retinopathy changes normally seen in the retina,

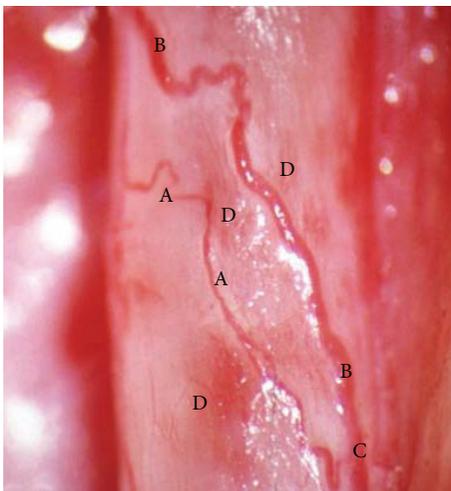


FIGURE 1: Arteriolar attenuation (A), tortuosity (B), arteriovenous shunting (C), and proliferation of newly formed vessels (D) of the vasa nervosum seen in the sural nerve of a patient with insulin neuritis (photo courtesy of Tesfaye).

including arteriolar attenuation, tortuosity, arteriovenous shunting, and the proliferation of newly formed vessels. They hypothesized that the structural abnormalities in epineural blood vessels, together with the formation of new vessels, caused a steal effect and, hence, resulted in hypoxia and neuropathic pain. It can now be postulated that a sudden change in glycemic control can cause flux effects that result in structural and functional changes in the epineural blood vessels of nerves, which, in turn, can lead to neuropathic pain or “insulin neuritis” [17, 19] (Figure 1). Symptoms can be mild and often go unreported but may present with severe, excruciating neuropathic pain. Symptoms usually last up to six months and respond to treatment that is usually needed for up to six months [10].

### 3.3. Role of the Dorsal Root Ganglion in Neuropathic Pain.

The expression of voltage-gated sodium and calcium channels and voltage-independent potassium channels in the DRG has a significant role in the generation of nociceptive sensation and peripheral sensitization that leads to central sensitization. Hyperexcited ectopic impulses are generated by the expression of various voltage-gated sodium channels, such as Nav1.3, Nav1.7, and Nav1.8 [20]. The voltage-gated sodium channel Nav1.3 probably plays a key role in the development of neuropathic pain [21]. Amir et al. described after nerve injury, in the DRG, the fact that there is a sustained phasic discharge that results in repeated firing [22]. The voltage-dependent sodium channel alternates with a voltage-independent potassium leak to oscillate membrane potentials. When these oscillations reach the threshold amplitude, they result in the generation of ectopic impulses and, hence, lead to sustained peripheral sensitization [23]. In addition to the voltage-gated sodium channels, the expression of voltage-gated calcium channels was also found in neuropathic pain [24]; specifically subtype Cav 3.2 is highly expressed in

DRG neurons and showed strong correlation with allodynia [25]. Calcium entry through voltage-gated calcium channels causes the release of substance P and glutamate, which results in the modulation of pain at the dorsal horn [26]. The upregulation of transient receptor potential expression is also found to be associated with neuropathic pain. Studies found a direct relationship between TRPV1 (transient receptor potential vanilloid 1) and neuropathic pain. A few animal studies suggest that hyperalgesia does not develop in TRPV1-deficient mice and TRPV1 antagonists reduce pain behaviour in mice [27, 28].

**3.4. Methylglyoxal and Pain.** Methylglyoxal (MG) is a reactive intracellular by-product of several metabolic pathways. However, the most important source of MG is glycolysis and hyperglycaemia [29]. Studies found that PDN patients had significantly higher concentration of plasma MG (>600 nM) compared to healthy control or diabetes patients without pain [30, 31]. MG depolarizes the sensory neuron by activating TRPV1 in the DRG [32] and also induces posttranslational modification of the voltage-gated sodium channel Nav1.8 [30]. These changes are associated with increased electrical excitability and facilitate firing of nociceptive neurons.

**3.5. Sympathetic Modulation of Pain.** Nociceptive A-delta and C fibres are normally not directly connected to sympathetic nervous system. Several experiments using  $\alpha$ -adrenoreceptor agonists found that it did not activate sympathetic neurons at nociceptor fibres under normal conditions [33, 34]. It is widely accepted that the sympathetic nervous system does not activate the sensory nervous system under normal conditions.

Neuropathy causes hypersensitivity in nerves as a result of an abnormal epinephrine-mediated transmission from one axon to another. This unusual connection is called ephaptic transmission or cross-talk [35]. It was also noted that damaged nerves in the periphery also cause basket formation, called sympathetic sprouting in the DRG, which results in the release of noradrenaline [36]. Both sympathetic sprouting and ephaptic transmission release adrenaline and cause sympathetic-sensory coupling. This leads to an increase in ectopic and spontaneous firing. This unusual connection is called sympathetically maintained pain.

Several studies proved this hypothesis and showed dramatic improvement in pain relief after sympathetic blockage [37], sympathectomy [38], or temporary blockage with  $\alpha$ -adrenergic antagonists with intravenous phentolamine [39].

**3.6. Gate Control Theory.** In 1965, Melzak and Wall [40] described, for the first time, the fact that nervous connections from the peripheral to central nervous system and to the brain are not a seamless transmission of information. They described the gate mechanism at the dorsal horn of the spinal cord, which inhibits or facilitates the flow of afferent impulses from peripheral nerves to the spinal cord before it evokes pain perception. The activity at the gate is primarily dependent on the transmission of impulses along small or large nerve fibres.

Small nerve fibres, unmyelinated C fibres, and myelinated A-delta fibres tend to open the gate and large A-beta fibres tend to close the gate. Opening and closing of the gate depend on the number of input impulses. Thus, if nociceptive input from C- and A-delta fibres exceeds A-beta fibre input, then the gate is open and nociceptive impulses ascend to the spinal cord. On the other hand, if A-beta fibre input (touch, vibration, and pressure) exceeds that of C- and A-delta fibre input (pain), then the gate is closed; nociceptive impulses only pass through when the gate is open. The classic example of this phenomenon is the rubbing of an injured site immediately after suffering from trauma, which results in gate closure.

**3.7. Central Sensitization.** Central sensitization was first described by Woolf in 1983. Nonnoxious stimuli transmitted from the periphery with A-beta fibres (touch) were perceived as painful by patients with allodynia [41]. A-delta fibres and C fibres are innervated in laminae I-II and A-delta fibres also are innervated in lamina V of the dorsal horn. The majority of spinal cord neurons that express the substance P receptor are located in lamina I or have their cell bodies in laminae III-IV but extend their dendrites to lamina I. The pain mediation of noxious stimuli occurs by releasing substance P, mainly in lamina I of the dorsal horn. A-beta fibres are innervated deep in laminae III to V and are responsible for touch mediation [42–44]. Peripheral sensitization and sustained hyperexcited impulses at the dorsal horn cause an increase in responsiveness to noxious and nonnoxious stimulation. This was believed to be due to the structural plasticity of sprouting of A-beta fibres, which leads to “rewiring” of the dorsal horn laminae in the central nervous system (CNS) [44]. As a result, the CNS pathway, which is responsible for transmitting only nonnoxious stimuli (touch), was replaced by sprouting A-beta fibres that transmit nonnoxious impulses and release substance P in the dorsal horn, thereby mediating allodynia [45]. This hypothesis was mainly based on experiments that showed that the uptake of the cholera toxin B (CTB) subunit, which is a selective tracer for large myelinated A-fibres, terminated in lamina II [46]. The selectivity of this toxin after peripheral nerve injury is somewhat controversial. Experiments demonstrated that uptake of the CTB tracer was not selective, that CTB was found in axons of all types, including A-delta fibres and C fibres, and that the CTB tracer incorporated in C fibres that terminated in lamina II [47]. This contradicts the hypothesis of structural plasticity and A-beta fibres sprouting in lamina II. However, studies with immunostaining and electrophysiological recordings have clearly established that peripheral nerve injury causes large myelinated fibres to begin to drive nociceptive neurons in superficial lamina [48, 49]. The persistent incoming nerve impulses lead to activation of N-methyl-D-aspartate (NMDA) receptors on postsynaptic membranes in the dorsal horn of the spinal cord. This leads to the release and binding of glutamate (an excitatory neurotransmitter), which causes an influx of sodium and calcium and an efflux of potassium. This generates a larger postsynaptic action potential and augments the perception of normal stimuli, thereby resulting in allodynia [50].

**3.8. Central Inhibition.** Impulses from the brainstem nuclei descend to the spinal cord and influence the transmission of pain signals at the dorsal horn. The periaqueductal grey matter (PAG), locus coeruleus, the nucleus raphe magnus, and several bulbar nuclei of reticular formation give rise to descending modulatory pathways. These pathways dampen or enhance the pain signal. The projections from the nucleus raphe magnus to the spinal cord are the major source of serotonin in the spinal cord. Exogenous opioids imitate the endogenous opioids and induce analgesia by acting upon the PAG, reticular formation, and the spinal dorsal horn [12]. The antidepressant serotonin and norepinephrine reuptake inhibitors (SNRIs) [51] and opioids [52] have been found to be beneficial in the treatment of neuropathic pain as these medications increase the availability of these neurotransmitters and, hence, increase inhibition at the spinal cord. Psychological factors, such as fear and anxiety, can influence the inhibitory mechanism through the modulatory system. Cognitive behavioural therapies are thought to be beneficial in modulating the pain by reducing the fear and anxiety [53].

**3.9. Thalamic Abnormalities.** The nociceptive hyperexcited impulse generated within primary afferent nerves is modulated and amplified not only at the DRG-spinal cord level but also at the thalamic ventral posterolateral (VPL) level, before being relayed to the cerebral cortex. This was experimentally proved in streptozosin rat model with PDN. The experiment demonstrated hyperexcitability in thalamic VPL neurons, with increased responses to phasic brush, press, and pinch stimuli applied to peripheral receptive fields. VPL neurons from diabetic rats also displayed enhanced spontaneous activity, independent of ascending afferent impulses, and enlarged receptive fields [54]. Selvarajah et al. [55] investigated this further in humans using a magnetic resonance (MR) perfusion scan in patients with PDN. This study demonstrated increased thalamic vascularity and sluggish blood flow. Similar vascular perfusion findings were also observed at the sural nerve in patients with PDN [56]. It was suggested that increased perfusion at thalamus VPL neurons in PDN patients causes an increase in neuronal activity and, hence, further modulates pain and central sensitization.

**3.10. Chronic Neuropathic Pain and Plasticity of Brain.** Neuroplasticity or plasticity of the brain is the term used to describe the adaptive change in structure, chemical balance, and function of the brain in response to changes within the body or in the external environment. In response to chronic neuropathic pain, neuroplasticity is associated with somatosensory cortex remodelling, reorganization, and hyperexcitability in the absence of external stimuli. A study of patients with chronic neuropathic and nonneuropathic pain using functional and anatomical magnetic resonance imaging found cortical reorganization and changes in somatosensory cortex activity only in the neuropathic pain group [57]. Provoked pain and spontaneous stimuli may reverse the remodelling and reorganization at the somatosensory cortex. Studies have shown a beneficial effect of pain relief with transcranial magnetic stimulation (TMS) and transcranial

direct current stimulation (tDCS), which suggests a reversal of plasticity [58, 59].

#### 4. Conclusion

In summary, the exact mechanism of pain in PDN is far from being clear. The source of pain could be anywhere in the pathway from the damaged nerves to the somatosensory cortex or it could be due to a combination of pathologies. PDN is a distressing condition and, as a result, adversely affects a patient's quality of life, both physically and mentally. Despite significant advances in therapeutics, the treatment of chronic symptoms of pain in PDN is still suboptimal and challenging for clinicians [11, 60]. This may be due to a poor understanding of the pathogenesis of PDN. There is an increasing body of evidence that suggests that the central nervous system is primarily responsible for maintaining painful symptoms. In recent years, there have been significant advances in the neuroimaging of pain. Further research is needed to have a better understanding of the disease process of PDN, which will help to tackle this enormous challenge.

#### Conflict of Interests

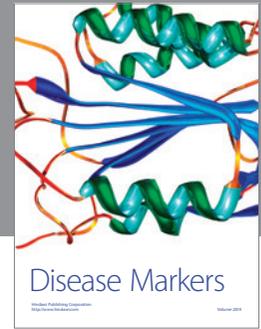
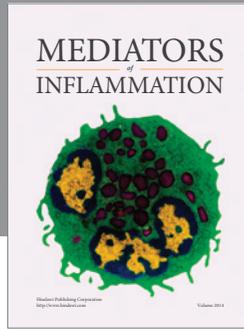
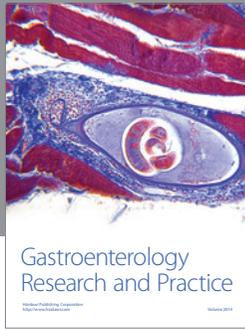
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#### References

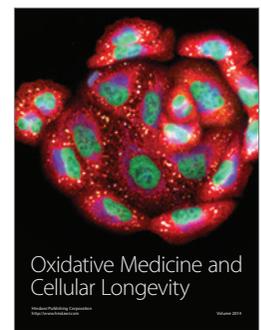
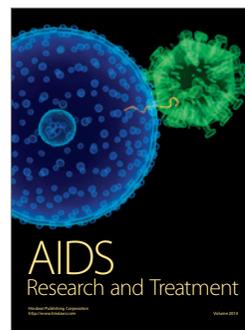
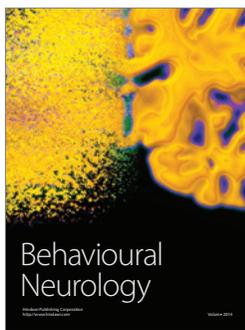
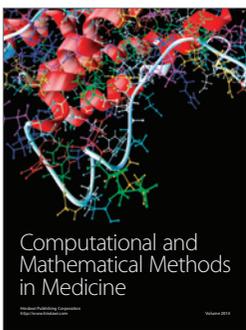
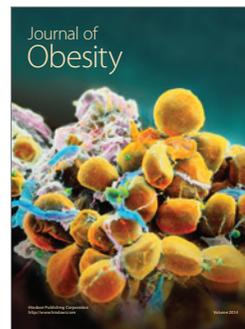
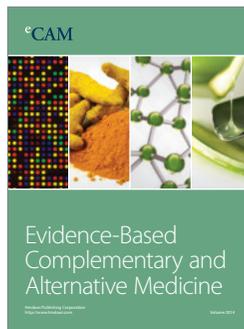
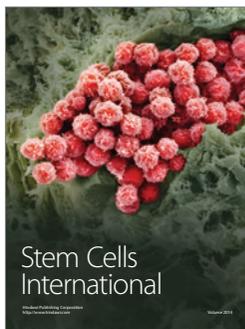
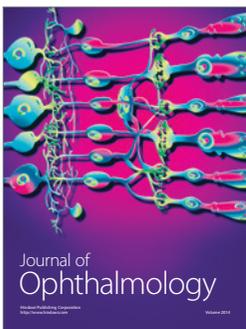
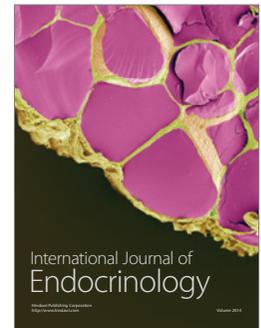
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# Abdominal Pain and Weight Loss in New-Onset Type 1 Diabetes

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and Satyan M. Rajbhandari, MBBS, MD, FRCP London, FRCP Edin

**P**atients who are newly diagnosed with type 1 diabetes are routinely counseled by their health care professionals to make lifestyle changes and take other measures to improve their glyce-mic control and prevent long-term complications. However, the rapid achievement of metabolic control can lead to unforeseen consequences. We recently identified one such case, in which rapid improvement in metabolic control precipitated insulin neuritis with associated weight loss, resulting in extensive and unnecessary investigations.

## PRESENTATION

A 31-year-old man presented to our hospital emergency department with new-onset type 1 diabetes complicated by ketoacidosis. He responded to intravenous fluids and insulin and was discharge on day 2 on a basal-bolus insulin regimen using premeal insulin aspart three times daily and insulin detemir at bedtime.

Under the supervision of a diabetes specialist nurse, his metabolic control improved, with self-monitoring of blood glucose results between 90 and 126 mg/dl. The patient did, however, develop severe right-side lower abdominal pain that was associated with weight loss and was accordingly referred to a gastroenterologist. Testing was performed to exclude celiac disease, and the patient also underwent numerous tests including urine culture, abdominal ultrasound, CT scan of the abdomen, colonoscopy, and barium

meal follow-through, all of which yielded normal or negative results.

The patient was seen in the diabetes clinic 2 months after the episode of ketoacidosis and still complained of sharp pain over his right side. There was no aggravating factor, but he reported nocturnal exacerbation of pain that disturbed his sleep.

It transpired that his appetite had reduced, and he had lost ~ 15 lb in weight since his diagnosis, despite having good glyce-mic control. His A1C had fallen from 14.4 to 7.1% within that 2-month period. During the consultation, he denied body image problems or excessive exercise or self-induced vomiting. On further examination, he had mild tenderness over the right iliac fossa region and had altered sensation in the dermatome supplied by the right T12 and L1 nerve root. He was diagnosed with “truncal neuropathy” due to “insulin neuritis” causing pain and cachexia.

The patient was prescribed amitriptyline, 25 mg at night, with the dose gradually increasing to 75 mg. His pain and appetite improved, and he gained 13 lb within a month.

## QUESTIONS

1. Should blood glucose be lowered gradually in all cases to avoid “insulin neuritis?”
2. Is there any association between weight loss and “truncal neuropathy?”
3. Could the patient in this case have had an underlying behavior disorder?

4. Were all of the invasive investigations performed in this case necessary for a 31-year-old man?

## COMMENTARY

Acute neuropathy resulting from rapid glyce-mic control has been reported in literature as “insulin neuritis” that usually manifests with severe excruciating neuropathic pain in the first month of insulin therapy. Symptoms can last up to 6 months and respond to treatment, which is usually required for a similar period.<sup>1</sup> In one observational study,<sup>2</sup> six patients with diabetes experienced severe neuropathic pain, mostly in their feet. The pain started within 2–4 weeks of initiation of intensive diabetes therapy, during which blood glucose levels dropped up to one-fifth of initial levels.

The patient in this case developed localized pain in his abdominal wall within 4 weeks of rapid correction of blood glucose. Similar abdominal wall pain has been reported after rapid reduction of A1C from 12 to 7.5% in a patient with type 2 diabetes.<sup>3</sup>

Development of acute painful neuropathy after rapid glyce-mic control suggests that blood glucose flux is responsible for the pain.<sup>4</sup> Tesfaye et al.<sup>5</sup> elegantly demonstrated several structural abnormalities in the sural nerve, including arteriolar attenuation, tortuosity, and arterio-venous shunting with new vessel formation in patients with insulin neuritis. The combination of structural and

functional changes in the nerves is possibly the cause of neuropathic pain in insulin neuritis.<sup>4</sup>

Our patient experienced weight loss associated with neuropathic pain, which resulted in a number of clinical investigations. Weight loss associated with painful diabetic neuropathy has been reported in the literature as “diabetic neuropathic cachexia,” which can last up to 1 year. Most patients respond well to neuropathic pain treatment, which provides pain relief and assists in increasing weight. The exact mechanism and cause are unknown.<sup>1</sup>

In one observational study,<sup>6</sup> nine patients with diabetes reported to have painful neuropathy with constant discomfort, and profound weight loss was noted, along with depression and impotence. The severe manifestation subsided in all cases within 10 months and in most cases within 6 months. One case has been reported<sup>7</sup> in which the patient presented with profound weight loss associated with painful neuropathy in the abdomen, as was the case with our patient.

The abdominal pain in our case resulted from truncal neuropathy, a condition that manifests with neuropathic pain such as a hypoesthesia, regional hyperalgesia, allodynia, and sometime focal weakness in a specific dermatome region.<sup>1,8</sup> The onset is sub-acute, and symptoms are usually unilateral but can be bilateral.

There are many possible causes of pain in the abdominal or thoracic wall; thus, patients with such symptoms often undergo numerous investigations.<sup>8–10</sup> There are several

cases in which investigations led to a misdiagnosis of hernia, angina, or cholelithiasis, with patients subsequently failing to respond to treatment for those conditions.<sup>8,9,11</sup>

The diagnosis of truncal neuropathy is made on clinical grounds with a good history and physical examination. The pain is neuropathic in character (i.e., burning and stabbing), localized to a dermatome, and often associated with altered sensation.<sup>8</sup> Most people respond well to neuropathic treatment within 3–12 months.

#### CLINICAL PEARLS

- Rapid correction of blood glucose can cause insulin neuritis that can present as neuropathic pain.
- Neuropathic pain can be associated with weight loss.
- Neuropathic pain localized to the thoracic or abdominal wall on one side is due to truncal neuritis. This is often missed and leads to extensive investigations, the results of which are usually normal.
- Most patients with insulin neuritis and truncal neuropathy respond well to specific treatment for painful neuropathy.

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# Depression is more common in subjects with diabetes amongst general practice attendees

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## Background and Aim:

- Globally the mortality from heart attack and stroke has declined due to better treatments as a result we are living longer with chronic health conditions (CHC).
- Diabetes is a major chronic health condition currently affecting more than 350 million people worldwide and its prevalence is rising day by day.
- The main aim of this study was to compare the frequency of depression between subjects attending diabetes clinic (DM group) and other clinic (C group) in a busy general practice.

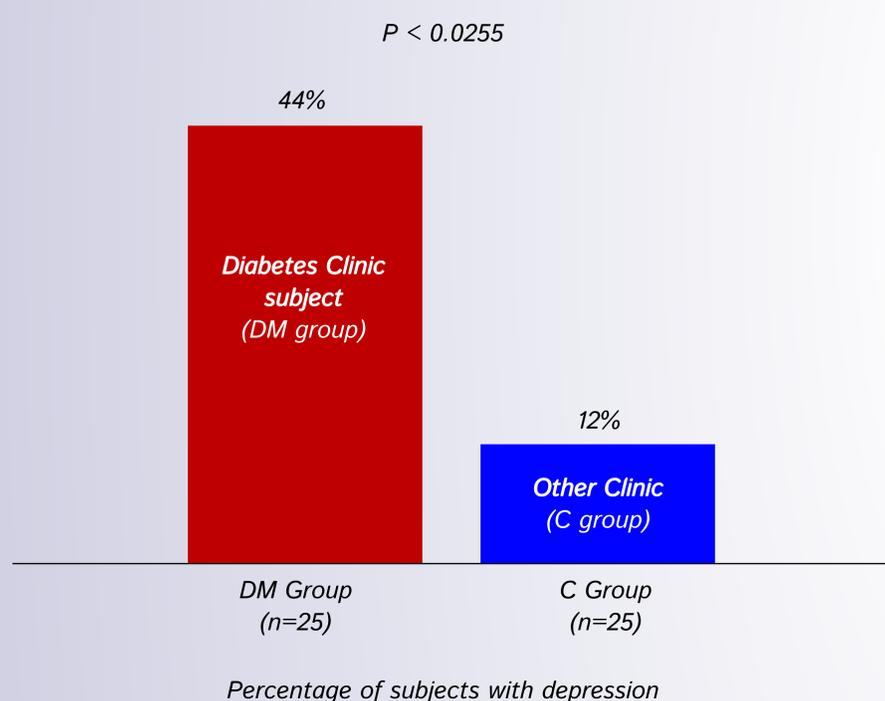
## Method:

- This was a prospective audit to study prevalence of depression using Hospital Anxiety and Depression Scale (HADS) in general practice setting. 25 adult subjects with diabetes [mean age 51 +/-14 years standard deviation (SD); 56%: Males], who attended for diabetes review and 25 adult subjects who attended other clinic [mean Age 49, +/- 13 years (SD); 52% Males] self-completed HADS questionnaire.
- The results were analysed using Fisher's exact test.

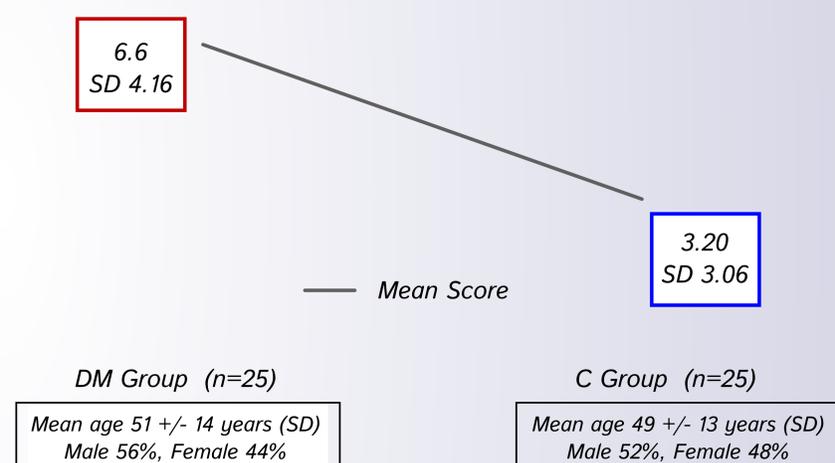
## Results:

- 11 subjects (44%) out of the 25 were diagnosed with depression in DM group (mean score 6.60 and SD 4.16) compared to only 3 subjects (12%) in the C group (mean score 3.20 and SD 3.06 (P < 0.0255).

Comparison of frequency of depression



HADS score comparison



## Conclusions:

- It is estimated about 1/3rd of CHC people are suffering from underlying depression.
- The frequency of depression was significantly higher in DM group and found to be more than 3 times compared to C group.
- Clinicians should consider screening for underlying depression when diabetes patients attend surgery.

# Deprivation of liberty to safeguard against recurrent ketoacidosis

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## Abstract

Advances in medical treatment have resulted in prolonged survival of people with diabetes, with multiple complications. Vascular dementia is one of these and is increasingly seen due to a reduction in mortality from cardiovascular causes. People suffering from dementia are often not capable of weighing up the advantages and disadvantages of proposed treatment in order to give an informed decision. In most cases, this incapacity does not cause problems as patients and their carers agree with the recommendation made by their health care professionals. However, we encountered a challenging case where we had to apply for deprivation of liberty safeguards (DoLS) to treat in the patient's best interests.

We report the case of a patient with vascular dementia who had repeated admissions with life-threatening diabetic ketoacidosis (DKA) as she refused to comply with the insulin treatment because of her lack of insight regarding her diabetes care. In order to prevent harm to her, an application was successfully made for DoLS. This allowed treatment with once-daily, long-acting analogue insulin under supervision even against her wishes. This prevented further admission to hospital with DKA.

DoLS was introduced in the UK in April 2009 to safeguard some of the most vulnerable people in our society for their own safety. People with type 1 diabetes are increasingly surviving longer and may suffer from dementia. The majority will manage with some help from family or health care worker, but in a small proportion DoLS may be needed, as in our case, to prevent recurrent life-threatening complications. Copyright © 2013 John Wiley & Sons.

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## Key words

DoLS; dementia; type 1 diabetes; recurrent DKA; deprivation of liberty safeguards

## Case history

A 66-year-old woman with childhood onset type 1 diabetes, complicated by blindness due to retinopathy and early vascular dementia following cerebrovascular accident, had challenging behaviour towards health care professionals. She lived alone with family support and was independently mobile. She managed her own blood glucose testing and insulin injections, but had an inappropriately fixed idea about the dose and type of insulin. She was admitted to the hospital six times with diabetic ketoacidosis (DKA) in one year. On one occasion when admitted due to DKA, she needed intensive treatment in the critical care unit.

After one of her admissions for DKA treatment she was discharged with an increased package of care, which included diabetes specialist nurse input in the community and district nurses administering long-acting insulin on a daily basis. Unfortunately, she was admitted again with DKA because she refused to open the door to district nurses

and so missed her insulin injections. Following that episode, she was discharged to a care home for all insulin to be administered by staff. In the care home, she became verbally abusive and screamed, wanting to go home. She was assessed by a psychiatrist and it was found that she had some degree of dementia, with no insight regarding diabetes, but was deemed to have capacity to make her own decision about going home. She was therefore allowed home, and it took only a few days before she was readmitted with DKA. After recovering, she wanted to go home against medical advice.

On questioning, she was found to have no capacity to understand about the life-threatening consequences of not taking insulin. In her best interests, she had to be deprived of her liberty and was started on once-daily treatment with long-acting insulin against her wishes. In view of this, the treating team applied to the local primary care trust (PCT) for authorisation for deprivation of liberty safeguards (DoLS) assessment. She had the

DoLS assessment including mental capacity and best interests assessment, and, later on, a best interests meeting with the medical team, the nursing team, a family representative, PCT representative, social worker, best interests assessor, and general practitioner. It was agreed that she had no capacity to make decisions about her treatment and care needs. The local authority authorised the DoLS in the patient's best interests for once-daily, fixed-dose, long-acting analogue insulin along with finger prick blood test for glucose even against her wishes. She was transferred to a care home where nursing staff injected daily insulin which she could not refuse, and she did not have any further admissions with DKA.

### Deprivation of liberty

Depriving liberty from someone who lacks the capacity to consent to the arrangements made for their care or treatment is a serious matter. The DoLS makes it clear that a person may only be deprived of their liberty: in their own best interests to protect them from harm if it is a proportionate response to the likelihood and seriousness of the harm; and if there is no less restrictive alternative. DoLS must not be used as a form of punishment, or for the convenience of professionals, carers or anyone else. It should not be extended due to delays in moving people between care or treatment settings. DoLS does not occur in every case where an individual lacks capacity to make decisions. In deciding whether or not application is necessary, the managing authority (hospital or care home) should carefully consider whether any restrictions that will be needed to provide ongoing care or treatment amount to a deprivation of liberty.<sup>1</sup>

DoLS was introduced to prevent breaches of the ECHR (European Convention on Human Rights) after a court case of HL vs United Kingdom.<sup>2</sup> HL, an autistic man with learning disability, had no capacity to make any decision about his treatment or hospital admission. He was admitted to a psychiatric hospital on an informal basis under common law but was prevented from leaving the hospital with his carers. His carers

challenged this in the European Court of Human Rights; the judgement held that the informal hospital admission constituted a deprivation of HL's liberty and, further, that the deprivation of liberty had not been in accordance with the procedure prescribed by law, therefore in breach of Article 5(1) of the ECHR.<sup>3</sup> This led to the introduction of DoLS in the UK in April 2009.<sup>4</sup>

### Deprivation of liberty safeguards: application process

The managing authority (hospital or care home) has to apply to the supervisory body (PCT, local authority or Welsh minister) for the assessment to get lawful authorisation to deprive liberty. A standard authorisation can be applied for when the managing authority feels that it is highly likely that the patient's liberty will be deprived in the next 28 days. However, in circumstances where there is no time to wait for standard authorisation, the managing authority can issue urgent authorisation themselves, which lasts for seven days, and at the same time apply for standard authorisation. This should be assessed within the timeframe of urgent authorisation. Standard authorisation assessment must be completed by the supervisory body within 21 days of application, and urgent authorisation assessment should be completed before its expiry. The supervisory body only authorises deprivation of liberty when they are satisfied with the following:<sup>1</sup>

- The person should be at least 18 years of age or older.
- The person should have a mental disorder – including dementia, learning disability, or certain neurological brain disorders (e.g. as a result of brain injury).
- The person lacks capacity to decide treatment or residence.<sup>5</sup>
- It should be in the best interests of the person to deprive liberty in order to prevent the likelihood and seriousness of the harm. The best interests assessor should seek the views of those interested in the care and welfare of the person such as family carers or close relatives; if no-one can represent on the patient's behalf, then the managing authority should apply for an Independent Mental Capacity Advocate to represent and

provide help about continued use of safeguards.

- The person is not eligible for deprivation of liberty authorisation if they need treatment for mental health for which they should be detained under the Mental Health Act 1983.
- There is no existing authority for decision making for that person which would conflict with deprivation of liberty authorisation such as an advanced directive made by the person for refusal of particular treatment.

If all of the above assessments support the authorisation of DoLS, then the best interests assessor recommends authorisation to the person's appointed representative. If there is any doubt or contradiction regarding the decisions, there is the right to apply for Court of Protection which has the power to terminate authorisation or vary conditions. If there is no conflict, the managing authority implements DoLS. The maximum duration of authorisation is 12 months. Reapplication by the managing authority is necessary before the authorisation expires if it is still deemed to be necessary.<sup>1</sup>

### Discussion

People with diabetes have a 2.5 times higher risk of developing dementia.<sup>6</sup> In one prospective study of 1262 patients followed up for 4.3 years, the adjusted relative risk of stroke-associated dementia in patients with diabetes was 3.4 times higher.<sup>7</sup> Various neurophysiological and structural changes have been described in subjects with type 1 diabetes;<sup>8,9</sup> however, there is a paucity of literature regarding an association between type 1 diabetes and dementia. The Rotterdam study on 6330 participants found a 3.2 times higher prevalence of dementia in diabetes subjects treated with insulin.<sup>10</sup> This problem is likely to increase as the survival of people with type 1 diabetes is improving.<sup>11,12</sup> Patients with dementia often fail to remember to take their prescribed medications. One of the consequences of missing insulin in type 1 diabetes could be life-threatening DKA. This can be prevented by special reminders, supervision by

# Case report

## Deprivation of liberty to safeguard against recurrent ketoacidosis

family members or administration by health care professionals. Most of the time, dementia patients and their families concur with the treatment plan; however, if a situation arises when either the patient or their family disagree, the treating team needs to consider applying DoLS in order to prevent harm in the best interests of the patient. Therefore, health care professionals managing type 1 diabetes need to be aware of DoLS and related legal issues.

We applied for DoLS in our patient as she was neither taking her insulin nor allowing anyone to give it to her, which resulted in multiple episodes of life-threatening DKA. Due to vascular dementia, she did not have any insight into the dangers of not taking insulin. Both the treating team and her family agreed on DoLS, and there were no advanced directives. Consequently, DoLS was authorised for the use of long-acting insulin once a day along with daily blood glucose monitoring,

### Key points

- Patients with type 1 diabetes are increasingly surviving longer and developing complications such as vascular dementia
- Vascular dementia makes it difficult for the patient to understand the need for insulin to prevent diabetic ketoacidosis
- Deprivation of liberty safeguards (DoLS) can be applied for from the local authority in order to ensure these patients take insulin under supervision, thus preventing diabetic ketoacidosis

which prevented further admissions with diabetic ketoacidosis.

### Declaration of interests

There are no conflicts of interest declared.

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## Diary

### ■ 5th International Conference on Advances in Diabetes and Insulin Therapy

11–14 April 2013  
Sofia, Bulgaria  
Email: [info@adit-conf.org](mailto:info@adit-conf.org)  
Website: <http://adit-conf.org>

### ■ PsychoSocial Aspects of Diabetes (PSAD) Spring Meeting

12–14 April 2013  
Croatia  
Website: [www.psad-easd.eu](http://www.psad-easd.eu)

### ■ Association of British Clinical Diabetologists (ABCD) Spring Meeting

18–19 April 2013  
St John's Hotel, Solihull, West Midlands, UK  
Email: [eliseharvey@redhotirons.com](mailto:eliseharvey@redhotirons.com)  
Website: [www.diabetologists.org.uk](http://www.diabetologists.org.uk)

### ■ 5th International Congress on Prediabetes and the Metabolic Syndrome

18–20 April 2013  
Vienna, Austria  
Email: [tlessick@kenes.com](mailto:tlessick@kenes.com)  
Website: [www2.kenes.com/prediabetes/](http://www2.kenes.com/prediabetes/)

### ■ British Renal Society Conference

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18 May 2013  
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### ■ The Royal College of Ophthalmologists Annual Congress

21–23 May 2013  
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### ■ Hot Topics in Obesity

23 May 2013  
Postgraduate Medical Centre, Derriford Hospital, Plymouth, UK  
Email: [k.godley-mcavoy@nhs.net](mailto:k.godley-mcavoy@nhs.net)

### ■ ADA 73rd Scientific Sessions

21–25 June 2013  
Chicago, USA  
Website: [www.diabetes.org](http://www.diabetes.org)

### ■ Heart UK 27th Annual Conference

5–7 July 2013  
UWE Exhibition and Conference Centre, Bristol, UK  
Website: [www.heart.org.uk](http://www.heart.org.uk)

### ■ Foundation of European Nurses in Diabetes Annual Conference

20–21 September 2013  
Barcelona, Spain  
Website: [www.fend.org](http://www.fend.org)

### ■ EASD Annual Meeting

23–27 September 2013  
Barcelona, Spain  
Email: [secretariat@easd.org](mailto:secretariat@easd.org)  
Website: [www.easd.org](http://www.easd.org)

### ■ International Society for Paediatric and Adolescent Diabetes Annual Meeting

16–19 October 2013  
Gothenburg, Sweden  
Email: [secretariat@ispad.org](mailto:secretariat@ispad.org)  
Website: [www.ispad.org](http://www.ispad.org)