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Diabetic peripheral neuropathy may not be as its name suggests: evidence from magnetic resonance imaging

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Abstract

Diabetic peripheral neuropathy (DPN) affects up to 50% of patients with diabetes and is a major cause of morbidity and increased mortality. Its clinical manifestations include distressing painful neuropathic symptoms and insensitivity to trauma that result in foot ulcerations and amputations. Several recent studies have implicated poor glycemic control, duration of diabetes, hyperlipidemia (particularly hypertryglyceridaemia), elevated albumin excretion rates, and obesity as risk factors for the development of DPN. However, similar data are not available for painful DPN. Moreover, although there is now strong evidence for the importance of peripheral nerve microvascular disease in the pathogenesis of DPN, peripheral structural biomarkers of painful DPN are lacking. However, there is now emerging evidence for the involvement of the central nervous system in both painful and painless DPN afforded by magnetic resonance imaging. This review will focus on this emerging evidence for central changes in DPN, hitherto considered a peripheral nerve disease only.

Keywords: Diabetic peripheral neuropathy, Neuropathic pain, Neuroimaging, Magnetic resonance imaging, Magnetic resonance spectroscopy, Central nervous system

1. Introduction

The prevalence of diabetes mellitus is increasing by epidemic proportions world-wide and is predicted to reach 642 million by 2040.[25] This will unfortunately mean a similar increase in diabetic complications including diabetic peripheral neuropathy (DPN), which is one of the long-term complications of diabetes and is associated with considerable morbidity, mortality, and diminished quality of life.[57] The Toronto Consensus meeting defined DPN as a symmetrical and length-dependent sensori-motor polyneuropathy that may involve motor, sensory, and autonomic nerves as a result of chronic hyperglycemia and vascular risk factors.[58] Diabetic peripheral neuropathy is prevalent in around 50% of all diabetic people and is characterized by neuropathic pain, and insensitivity to trauma that often results in foot ulcerations and amputations. There is a high health care burden associated with DPN as neuropathic pain is often unresponsive to pharmacotherapy,[17,66] and the direct and indirect costs of lower limb amputations are also considerable. In a recent report from the US, the total annual direct per patient medical costs were $6632 for diabetes only, whereas costs for DPN ($12,492), painful DPN ($27,931), and severe painful DPN ($30,755) are considerably higher.[43] Thus, from these epidemiologic data, it is clear that DPN and the associated problems are far from rare and far from benign, and will increasingly pose major health care challenges to the medical profession and to society.

Approximately 16% to 26% of all diabetic patients or 50% of those with DPN have painful neuropathic symptoms (painful DPN).[1,10,11] Pain is the most distressing symptom of DPN and the main reason for seeking medical attention. Affected patients often have a progressive build-up of unpleasant sensory symptoms, including tingling (paraesthesias); burning pain; shooting pains (like "electric shock") down the legs; lancinating (also likened as "stabbing or knife-like" pains); contact pain often with day-time clothes and bedclothes (allodynia); pain on walking often described as "walking barefoot on marbles," or "walking barefoot on hot sand"; sensations of heat or cold in the feet; persistent achy feeling in the feet and cramp-like sensations in the legs.[57] With advanced disease, the pain can extend above the feet and may involve the whole of the legs, and when this is the case there is often upper limb involvement also. Painful DPN is characteristically more severe at night, and often prevents sleep.[77] Some patients may be in a constant state of tiredness because of sleep deprivation.[77] Others are unable to maintain full employment. Severe painful neuropathy can occasionally cause marked reduction in exercise threshold so as to interfere with daily activities. This is particularly the case when there is an associated disabling, severe postural hypotension due to autonomic involvement. Thus painful DPN has a major negative impact on quality of life and is associated with depression and anxiety.[24,45]

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Insensitivity to trauma, often as a result of ill-fitting shoes can lead to foot ulceration and a host of unintentional but serious injuries. Patients who have lost feeling in their hands cannot sense temperature and often burn themselves while, for example, cooking or ironing and also have difficulty handling small objects. Those who have lost sensation in their feet often sustain puncture wounds, friction wounds, and burns that can become infected and/or ulcerated and lead to amputation. However, with appropriate foot care, a significant number of ulcerations can be prevented.[3]

2. Risk factors for diabetic peripheral neuropathy

In the Rochester Diabetic Neuropathy Study cohort where clinical parameters and nerve conduction (NC) were used, the prevalence of DPN was 54% in patients with type 1 diabetes mellitus (T1DM) and 45% in patients with type 2 diabetes mellitus (T2DM).[13] Where NC assessment is not used, clinic- and population-based studies show surprisingly similar prevalence rates for DPN, affecting about 30% of all diabetic people.[50] The European Diabetes Prospective Complications Study (EURODIAB Study) which involved the examination of 3250 type 1 patients, from 16 European countries, found a prevalence rate of 28% for DPN at baseline,[65] very strongly related to poor glycolic control. The follow-up study also showed that over a 7-year period, about one quarter of T1DM patients developed DPN; age, duration of diabetes, and poor glycemic control being major factors.[62] The development of neuropathy was also associated with potentially modifiable cardiovascular risk factors, such as hypertension, hyperlipidaemia, obesity, and cigarette smoking[62] (**Fig. 1**). More, recently, other studies have also implicated cardiovascular risk factors, such as obesity[79] and triglycerides,[69] in the pathogenesis of DPN. Wiggin et al.,[70] in a cohort of participants with mild to moderate diabetic neuropathy, also found that elevated triglycerides correlated with myelinated fibre loss, independent of disease duration, age, diabetes control, or other variables. These data support the evolving concept that hyperlipidemia may be instrumental in the progression of diabetic neuropathy. Based on recent epidemiological studies, correlates of DPN include, increasing duration of diabetes, poor glycemic control, retinopathy, albuminuria, and vascular risk factors.[59] In T2DM, waist circumference, peripheral arterial disease and increasing age were found to be significant risk factors for the development of DPN.[79] Diabetic peripheral neuropathy is also a major risk factor (predictor) for mortality even more so than microalbuminuria and HbA1c.[19] Elevated vibration threshold has also been found to be a risk factor for mortality in diabetic patients.[8] However, when risk factors for painful DPN were evaluated in the EURODIAB and other studies, there are no clear metabolic risk factors identified. This may be due to the underlying complexity of chronic neuropathic pain with potential influences from social, psychological, cultural, and other factors.

There is now little doubt that good blood sugar control prevents/delays the onset of diabetic neuropathy in T1DM. The Diabetes Control and Complications Trial conclusively showed that intensive diabetes control could both prevent and retard the development of DPN and autonomic neuropathy.[12] More recently, the Epidemiology of Diabetes Interventions and Complications study showed that the benefits of 6.5 years of intensive therapy on neuropathy status extended for at least 8 years beyond the end of the Diabetes Control and Complications Trial despite similar HbA1c levels.[34] However, in T2DM patients, the results are not clear cut with only modest slowing down of the progression of DPN.[68] A recent meta-analysis of randomized control trials found no significant benefit of intensive glycemic control in reducing the incidence of DPN in patients with T2DM.[4] This conclusion was supported by a Cochrane review which demonstrated no significant improvement in markers of neuropathy in patients with T2DM managed through intensive glycemic control.[6] However, most studies conducted in patients with T2DM were not specifically designed to investigate the effect of intensive glycaemic control on the development of neuropathy as primary end point and used inappropriate (insensitive) measures for neuropathy. For example in the Steno 2 study, intensive multifactorial intervention significantly reduced the progression of autonomic neuropathy but not DPN.[20] However, the end point used to define DPN (vibration perception threshold)[20] is now well recognised not be sensitive enough for such a study as it has great variability.[58] Moreover, although they were not carefully phenotyped, the participants probably had advanced DPN as

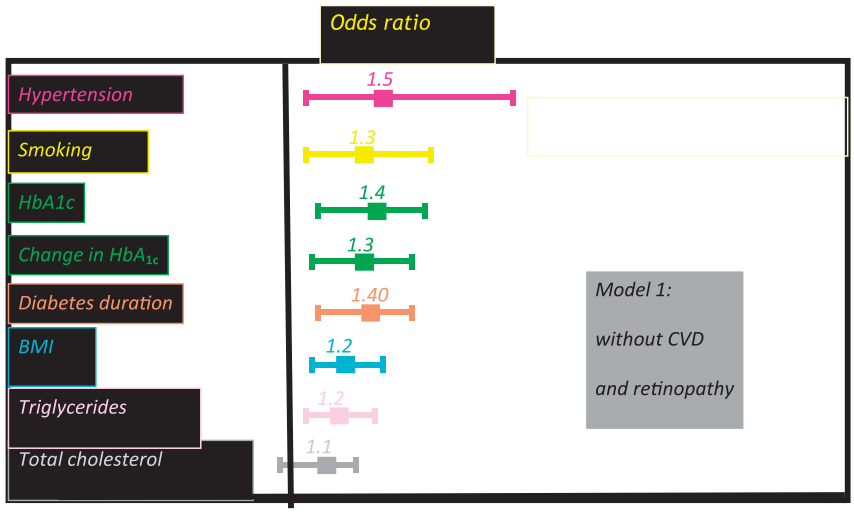

Figure 1. Risk factors for incident neuropathy: the EURODIAB Prospective Complications Study showing odds ratios for the various risk factors for DPN in a cohort of 1101 type 1 subjects followed for 7.3 ± 0.6 years (Tesfaye et al. 2005).[59] BMI, body mass index; CVD, cardiovascular disease. Reprinted with permission.

they were all microalbuminuric, at which point DPN would be irreversible. There is now emerging evidence that the neuropathic process is already present in recently diagnosed T2DM patients that have reduced peripheral NC velocity and intraepidermal nerve fibre density.[78] Moreover, recent studies have shown a significant prevalence of DPN even in prediabetes,[28,39] and that these can be reversed by life-style intervention and an exercise program.[51,53] In one study of patients with impaired glucose tolerance and painful DPN, life-style intervention resulted in the reversal of both small fibre neuropathy with epidermal reinnervation and resolution of painful symptoms.[53] Thus current good clinical practice remains to intensively manage hyperglycemia and other cardiovascular risk factors as part of the overall management of patients with DPN.

3. Pathogenesis of diabetic peripheral neuropathy

3.1. Peripheral mechanisms

Both vascular factors[64] and metabolic interactions (chronic hyperglycaemia, oxidative stress, nitrosative stress, poly (ADP-ribose) polymerase (PARP) activation, polyol pathway hyperactivity, protein kinase C hyperactivity, nonenzymatic glycation, abnormalities of nerve growth) are involved at all stages of DPN (**Fig. 2**). A detailed review of metabolic factors in the pathogenesis of DPN[36] is beyond this review. Morphometric studies have demonstrated that DPN is characterised by pathological changes including: (1) axonal loss distally, with a "dying-back" phenomenon,[44] (2) a reduction in myelinated fibre density,[29] and (3) focal areas of demyelination on teased fibre preparations.[44] Sural nerve biopsies also reveal microvascular defects in the endoneurial vessels, such as gross basement membrane thickening, endothelial cell proliferation, hypertrophy, and vessel occlusion.[23,30] The severity of endoneurial vessel pathology has been related to both the severity of clinical neuropathy and degree of nerve fibre loss.[30] The end result of this process is endoneurial hypoxia in patients with DPN.[30] Photography of surgically exposed sural nerve in vivo showed microvascular abnormalities, including arterial attenuation and tortuosity and arterio-venous shunting.[60] The arterio-venous shunting is likely due to endoneurial capillary blockage, with blood flow taking the route of least resistance and opening A-V shunts, that further exacerbates nerve hypoxia (**Fig. 3**). Direct sural nerve fluorescein angiography confirms arteriosclerosis on the surface of the nerve and impaired nerve blood flow[60] in patients with DPN compared with those with diabetes but no DPN (**Fig. 4**). Moreover, exercise-induced conduction velocity increment is impaired in DPN compared with subjects with no DPN indicating that the neuropathic nerve does not increase its blood flow in response to the demands of exercise.[61] Finally, subjects with acute insulin neuritis have a fine network of epineurial "new vessels" and retinal proliferating new vessels, indicating that similar processes are taking place on the surface peripheral nerve as on the retina.[63]

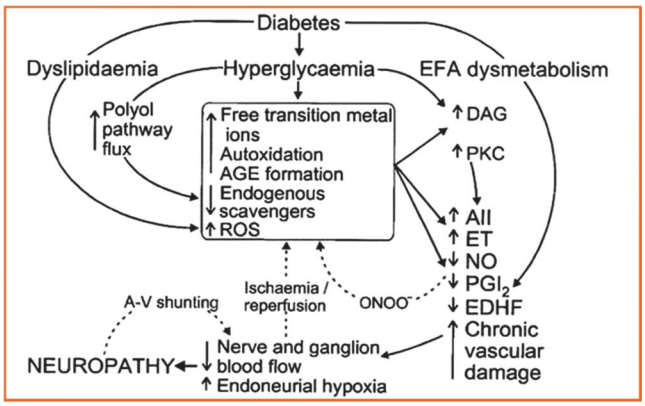

Figure 2. Pathogenesis of DPN. Schematic of the metabolic and vascular interactions that alter neurovascular function in diabetes. AII, angiotensin 2; AGE, advanced glycation end product; A-V, arterio-venous; DAG, diacylglycerol; DPN, diabetic peripheral neuropathy; EDHF, endothelium-derived hyperpolarizing factor; EFA, essential fatty acid; ET, endothelin-1; NO, nitric oxide; ONOO-, peroxynitrite; PGI2, prostacyclin; PKC, protein kinase C; ROS, reactive oxygen species (Ref. 46). Reprinted with permission.

However, none of the above peripheral nerve morphometric studies and microvascular defects in DPN showed consistently unique features for painful DPN. Indeed, the exact pathophysiological mechanisms of neuropathic pain in diabetes remain elusive although several mechanisms have been postulated (**Table 1**). Other potential mechanisms include the association of increased blood glucose instability in the genesis of neuropathic pain,[37] an increase in peripheral nerve epineurial blood flow,[15] altered foot skin microcirculation,[38] reduced intraepidermal nerve fibre density in the context of early neuropathy,[54] increased axonal regeneration and swellings in intraepidermal nerve fibers,[7] increased thalamic vascularity,[48] and autonomic dysfunction.[21]

3.2. Central mechanisms

Dysfunction and dysregulation in systemic glycaemic control leads to multisystem, multiorgan changes to both physiological and functional in vivo processes. It would seem most likely that, although very well protected from a variety of potential insults, the brain is susceptible to risks associated with diabetes. Indeed, stroke risk increases by a factor of 2 to 3 times, the ability to recover function after stroke is known to be impaired, and a general early brain-aging process is believed to be associated with mild cognitive decline.[16,32] In terms of the spinal cord that connects many levels and the periphery to the brain, post-mortem evidence gathered in the 1960s and 70s showed generalised atrophy, demyelination, and gliosis in patients with diabetes.[42,52] All of the previous brain and spinal complications have been reported in studies involving people with diabetes but without knowledge of the presence or absence of neuropathy.

Modern in vivo imaging modalities, including magnetic resonance imaging (MRI) and spectroscopy (MRS) can yield evidence of many different aspects of central nervous system (CNS) involvement in a large number of diseases that affect the brain or spine.

3.3. Magnetic resonance imaging: structure, pathology, and function

In vivo applications have developed dramatically since it was first demonstrated[27] that the phenomenon of nuclear magnetic resonance could be adapted to produce images depicting the spatial distributions of water molecules. Magnetic resonance imaging is very often the diagnostic modality of choice in the clinical setting when searching for the presence or absence of many different types of pathology, having applications in all organ systems.[74] The fundamental contrast mechanisms in standard clinical imaging are based on relative proton densities, T1- and T2-relaxation time properties, the latter 2 of which are reliant on tissue structure and chemical environment. Initial developments in MR focused on the ability to depict anatomy and, due to localised changes in T1, T2, and proton density, the presence of pathology. In addition to the variation in these 3 fundamental parameters in disease, a further multitude of contrast

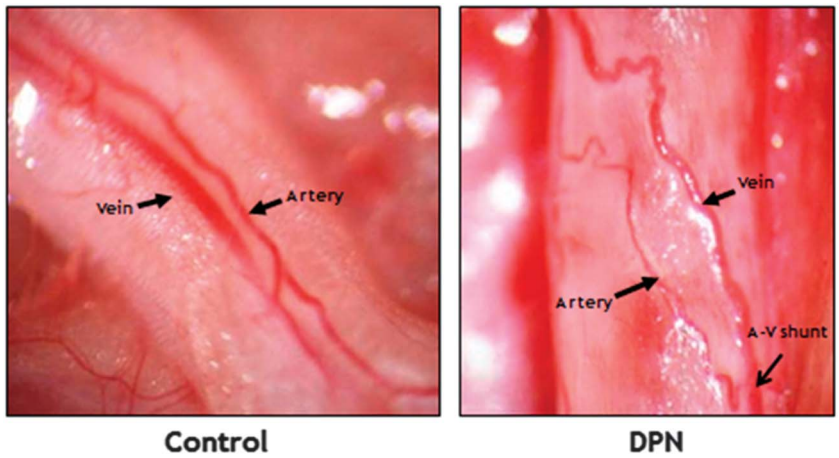

Figure 3. Sural nerve epineurial, arterial attenuation, and arterio-venous (A-V) shunting leading to increased venous pressure in human sural nerve. DPN, diabetic peripheral neuropathy.[60] Reprinted with permission.

mechanisms have more recently enabled further developments (eg, localised magnetic susceptibility/T2*, blood flow/phase-contrast detection, diffusion mapping/random molecular movement). The major advance that these different contrast mechanisms provide is the ability of MR to demonstrate and often quantify many aspects of physiological function. The relative noninvasive nature of MR points to its suitability for use in follow-up studies and, with scanning resources permitting, studies involving large sample sizes in multicentre settings. Many of these new "functional" techniques capable of both physiological monitoring and the ability to study mechanistic properties associated with histopathological development have been initially introduced as applications to imaging of the brain and spine, making MR a potential ideal candidate in the search for CNS abnormalities associated with neuropathy.

Detailing the vast number of contrast mechanisms that can be harnessed in the context of studying the CNS is beyond this article and can be found elsewhere.[9,71,74] Over the past 15 years, a number of MR findings have implicated the CNS in the pathogenesis of DPN.

3.3.1. Spinal cord involvement in diabetic peripheral neuropathy

Although spinal abnormalities had been reported findings at autopsy,[42,52] details were nonspecific to the presence or absence of neuropathy. These documented abnormalities could, thus, be due to diabetes per say or, alternatively they could have been associated with neuropathy, the latter indicating possible extension of the disease beyond the peripheral nerves. The absence of any sensation to electrical spinal cord stimulation in 20% of patients with severe painful DPN[67] led to a pilot MR study of the spinal cord in diabetes. The study obtained axial, T2-weighted 2-D images through the spinal cord (giving good cord/cerebrospinal fluid differentiation) in patients with DPN, without DPN, and healthy controls, and cross-sectional cord areas were calculated at 3 levels: lower cervical, upper, and lower thoracic. Significantly smaller cord areas were found at C4/5 and T3/4 in DPN, the article concluding that data provided evidence for involvement of the spinal cord on MRI.[14] A larger cohort follow-up study confirmed the findings.[46] In addition, when compared with controls (including a hereditary sensory motor neuropathy disease-control group), subclinical DPN patients who were clinically asymptomatic but had abnormalities on peripheral neurophysiological assessment showed significantly lower mean cord area compared with those without evidence of DPN. This article concluded that implied cord atrophy (it was a cross-sectional study) seemed to be an early phenomenon, present even in subclinical DPN.[46] Lesions in the spinal cord may result in pain syndromes. In some patients with severe painful DPN, there may be little in the way of abnormalities on clinical examination or electrophysiological assessment despite evidence of marked abnormalities in somatosensory evoked potentials within the spinal cord.[56] Thus the caudal aspect of the CNS does appear to demonstrate abnormalities that are concomitant with the presence of both early and established DPN.

Table 1

Mechanisms of neuropathic pain.

Peripheral mechanisms
Changes in sodium channel distribution and expression
Changes in calcium channel distribution and expression
Altered neuropeptide expression
Sympathetic sprouting
Loss of spinal inhibitory control
Altered peripheral blood flow
Axonal atrophy, degeneration or regeneration
Damage to small fibres
Increased glycemic flux
Central mechanisms
Central sensitization
Changes in the balance of facilitation/inhibition within descending pathways
Increased thalamic vascularity

Adapted from Tesfaye and Kempler 2005.[62]

3.3.2. Spinocortical axonal pathways

As the spinal cord forms the caudal portion of the CNS, involvement in the neuropathic process raises the question as to whether abnormalities terminate at that level or extend further via the spinothalamic tracts through the brainstem towards the thalamus and then onwards to the sensory cortex and associated intracranial pathways. Very preliminary data from small sample sizes (8 subjects with painless DPN and 6 nondiabetic volunteers) have illustrated the use of MR tractography based on high angular-resolution diffusion tensor imaging (DTI) as a potential method of investigating the integrity and extent of axonal fibre tracts in the context of DPN.[76] Data suggested that the total number of

modelled fibres connecting the brainstem with the somatosensory cortex showed a trend towards a decrease in the DPN group. However, it must be noted that the very small sample size reported indicates that larger subject numbers are necessary to determine whether this technique can provide evidence of involvement of spinothalamic and/or thalamocortical axonal pathways, thereby shedding light on the nature and extent of the neuronal tract degeneration previously observed within the cervical spine.[46]

3.3.3. Thalamic sensory "gateway" to the brain

The ascending spinothalamic neurons terminate in the ventroposterior lateral (VPL) thalamic subnucleus, which then projects input to the cranial aspects of the brain, including the somatosensory cortex. The thalamus is thus often believed of as the sensory gateway to the brain and as such, its function plays a crucial role in sensory processing and signal modulation (see, eg, Ref. 35). Information provided by ^{1}H-MRS regarding the resonance attributed to N-acetyl-aspartate (NAA) has been shown to be a useful marker of neuronal integrity and function.[74] Studies have used ^{1}H-MRS to interrogate the neurochemistry within the thalamus in the context of DPN.[22,47,55] In one of these studies, spectra were acquired from the thalamus in 18 subjects with Type-1 diabetes (8 with no DPN and 10 with DPN) and 6 age and sex-matched nondiabetic healthy controls.[47] Two spectra were acquired using different acquisition parameters: (1) at short echo time giving peak areas that reflect metabolite concentrations and (2) at long echo time giving peak areas that are subject to T2-weighting (which has been shown in other pathologies to be a marker of neuronal function[75]). Significantly lower mean thalamic NAA/Cho resonance area ratio was observed at long echo time in the DPN group compared with those from patients without DPN and healthy controls. No significant group differences were present at short echo time, although a significant correlation between NAA level and neuropathy score was identified. In a larger follow-up study comprising 110 patients with type-1 diabetes (20 no DPN, 30 subclinical DPN, 30 painful DPN, and 30 painless DPN) and 20 nondiabetic healthy controls, spectra were again acquired at both short and long echo time in the thalamus and additionally in the primary somatosensory cortex (S1).[22] As in the previous study, thalamic long echo time spectra identified abnormalities involving NAA in the painless DPN group (compared with other groups), whereas at short echo time, no group differences were identified. Conversely, in the sensory cortex, there were no significant between-group differences in any metabolite ratios at long echo time, whereas at short echo time there was significantly lower mean NAA in the painless DPN group (when compared with both no-DPN and nondiabetic groups). These findings underline that differences can be detected using different spectroscopic acquisition techniques (with, eg, long and short echo time) and care needs to be taken in realising the methodology used when subsequently judging inferences. The findings from this study are consistent with the occurrence of thalamic neuronal dysfunction and cortical loss including those of neuronal cell bodies (atrophy) in the same groups with painless DPN. In terms of the lack of significant thalamic depletion in NAA density within the thalamus, data from small numbers (7 patients with DPN vs 7 nondiabetic patients) from a study performed at a different centre is in agreement.[40] However, in a further study, short echo time spectra were acquired from 3 regions including the thalamus from 26 diabetic subjects (12 with and 14 without chronic pain), a lower mean thalamic NAA was found in the diabetic group with pain compared with the diabetic group without pain.[55] These conflicting findings between ^{1}H-MRS studies may reflect sample size considerations or perhaps highlight the aforementioned need for standardisation of spectroscopic data acquisition techniques.

Perfusion can also reflect metabolism and baseline vascular supply. Data from a dynamic susceptibility contrast-based perfusion assessment in a cohort of 18 subjects with T1DM (No DPN = 6, painful DPN = 5, painless DPN = 7), and 5 nondiabetic volunteers showed that the VPL region of the thalamus was associated with lower relative cerebral blood volume (rCBV) in painless DPN and higher rCBV in painful DPN compared with no-DPN and nondiabetic groups[48] (**Fig. 4**). This may imply that hypervascularity is present in patients with painful DPN while hypovascularity is a feature of the thalamus in patients with painless DPN. Of particular note is that animal models of painful DPN reporting electrophysiological hyperexcitability to various peripheral stimuli (in-keeping with allodynic or hyperalgesic states) also show high thalamic VPL electrical impulse activity even when nerve input to the brain has been terminated by transection of the cervical spinal cord.[18] The latter supports the hypothesis that the brain may generate activity in the absence of peripheral input that may lead to the sensation of a pain state. Further in vivo data are required to support this in the clinical context.

3.3.4. Higher brain areas—the pain-processing matrix

Studies based on fMRI and positron emission tomography have led to the characterisation of a normative network of brain areas that consistently activate in response to pain.[33] These cortical and subcortical brain network nodes include the thalamus as well as the primary and secondary somatosensory cortices (S1 & S2), the insular cortex, the anterior cingulate cortex (ACC), and the prefrontal cortex.[2] These regions are believed to be responsible for discriminating location and intensity of painful stimuli together with affective pain processing.[5,26] Activation of the lateral thalamus, S1, S2, and insular cortex are believed to be related to sensory-discriminative aspects of pain processing.[41] The basal ganglia, amygdala, cerebellum, hippocampus and other regions can also be involved and pain perception seems to be associated with a complex-connected matrix comprising many functional areas that may interact with each other and with the lower levels within the nervous system. Functional MRI may be a useful tool with which to investigate these complex, potentially interactive functional processes in normal subjects. The inclusion of potential neuropathic alterations to the pain matrix adds further to complex investigational demands, and these must be realised when inferences are being made.

Using fMRI, a preliminary study[72,73] comprising 18 T1DM subjects (6 no DPN, 6 painful DPN, and 6 painless DPN) tested the feasibility of monitoring the brain's response to the presentation of an acute thermal stimulus to the foot in the context of DPN. Preliminary analysis showed that subjects with no DPN had greater blood-oxygen-level dependent (BOLD) response than those with painless DPN. Subjects with painful DPN showed significantly greater response than those with painless DPN. The primary sensory cortex, lateral frontal, and cerebellar regions were involved. Negative correlation was also reported between BOLD response and overall neuropathy score in both the thalamus and left parietal lobe. Group differences occurred within the frontal lobe (high/level perception/cognitive function), the cerebellum (processing speed action), and the thalamus as well as in the sensory cortex. Although similar brain regions were activated in this study with those that comprise the "pain matrix," there were some clear differences in brain activation patterns. This suggests that the normal network is altered in painful DPN. A similar thermal stimulation fMRI study comprising subjects with Type-2 diabetes (11 painful DPN, 11

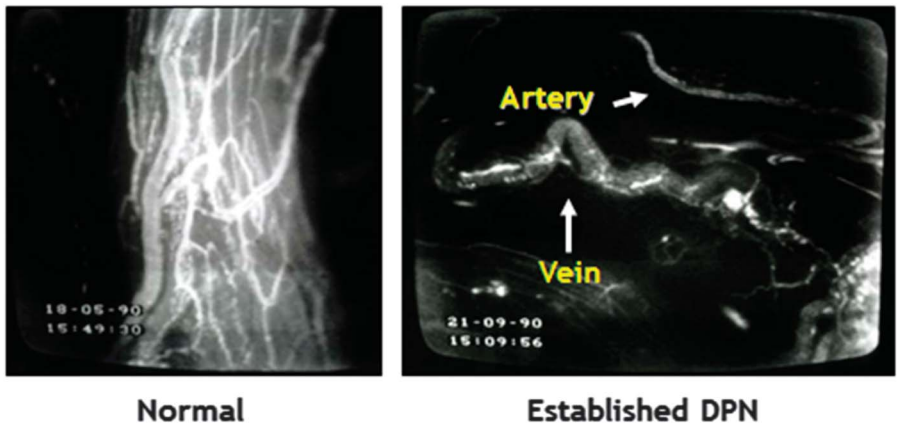

Figure 4. Impaired blood flow in the sural nerve of a subject with diabetic peripheral neuropathy (DPN) compared with a diabetic control without neuropathy. There is arterial attenuation and increased venous pressure due to arterio-venous shunting in the neuropathic subject.[60] Reprinted with permission.

painless DPN, and 11 nondiabetic controls) also reported differences between groups: increased BOLD response in the painful DPN group compared and reduced BOLD response in the painless DPN group.[74] In terms of pronounced activation in the painful group, areas identified included the ACC, medial thalamus, anterior insula, sensory cortices, and lentiform nucleus.

Subjectivity associated with pain perception and the different forms of clinical symptoms known to be present in DPN may lead to a high degree of between-subject variance, highlighting the need for careful characterization. The individuals' pain matrix, obtained through fMRI itself, may provide unique input to such approaches to the problem of neuropathy stratification.

In the ^{1}H-MRS study by[55] short echo time spectra acquired from the ACC showed no group differences, suggestive of no apparent neurochemical changes in this constituent of the pain matrix. In the dorsolateral prefrontal cortex, they reported lower NAA and Cr in those with diabetes compared with those without, with no specific differences assigned to the presence or absence of neuropathy.

The status of neurotransmitter balance may be important in DPN. Preliminary data from 7 patients with noninsensate DPN and 7 nondiabetic patients in a study that used spectral editing to investigate GABA-Glx resonances found lower GABA and higher Glx-levels in the posterior insula.[40] No such differences were observed in either the thalamus or the ACC. The authors inferred that the excitatory-inhibition neurotransmitter balance was altered within the posterior aspect of the insula, part of the overall pain matrix. The potential importance of this finding warrants further investigation.

3.3.5. Reduction in gray matter volume

Changes in parenchymal volume within the CNS are important as neuronal regeneration is not likely once atrophy has occurred. Strong relationships have been reported between brain volumes and walking outcomes in elderly patients with and without DPN.[31] Recently, detailed assessments of intracranial component volumes have been presented from a cohort of 54 subjects with T1DM (23 with no DPN, 16 with painful, and 15 with painless

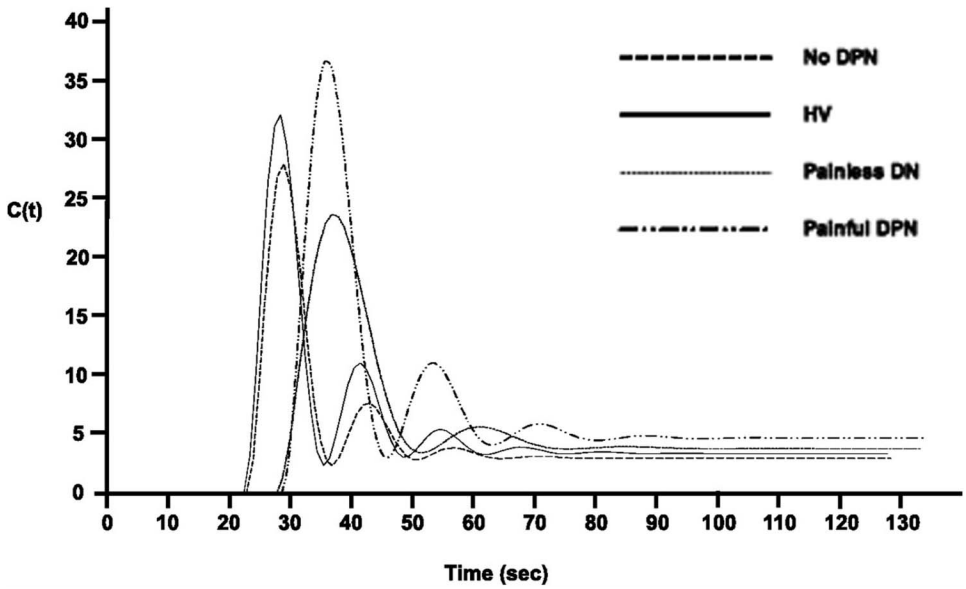

Figure 5. Increased thalamic vascularity in subjects with painful diabetic neuropathy and sluggish blood flow in those with painless diabtic neuropathy on MR perfusion imaging using gadolinium. DPN, diabetic peripheral neuropathy; MR, magnetic resonance.[48] Reprinted with permission.

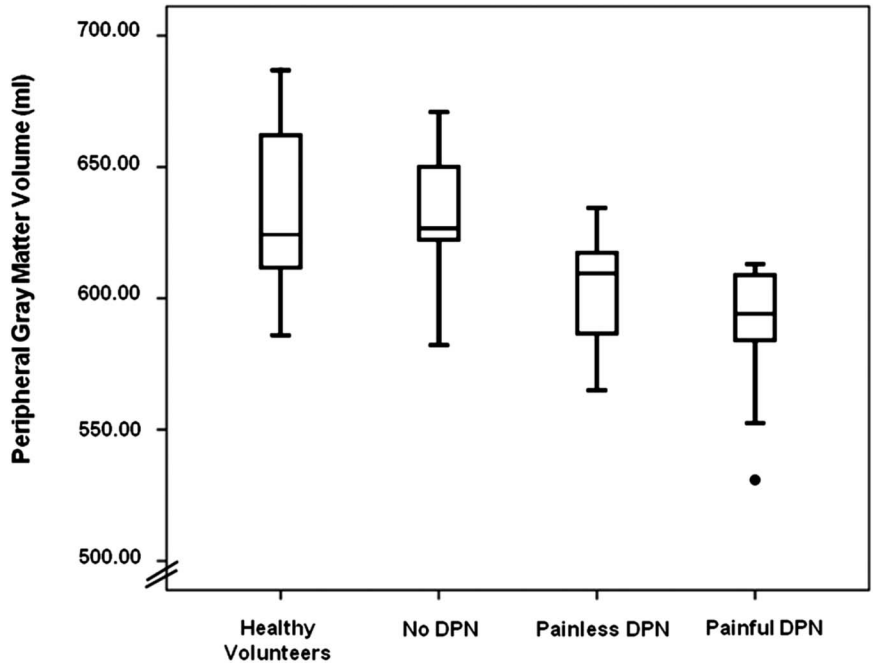

Figure 6. Reduced peripheral gray matter in diabetic subjects with painful and painless diabetic neuropathy. DPN, diabetic peripheral neuropathy.[49] Reprinted with permission. Copyright © 2014, American Diabetes Association.

DPN) and 18 nondiabetic controls.[49] Gray matter changes suggestive of atrophy were found in DPN compared with non-DPN groups. Cortical gray matter differences were found despite correcting for age, sex, and the degree of diabetic retinopathy, suggesting the DPN was the main factor (**Fig. 6**). Significant localised cortical gray matter differences were apparent in areas associated with somatosensory perception (precentral, postcentral, and supramarginal gyri). The inference of a sensory-cortical atrophy in DPN supports the previous observation of a lower NAA level (at short echo time) that was taken to imply an atrophic process observed in the sensory cortex, in patients with DPN.[22]

4. Summary and conclusion

Although DPN has been considered a disease of the peripheral nerve, from numerous studies it is becoming apparent that there are indeed changes within the CNS that, on a cross-sectional study basis, appear to be concomitant with the evolution of painful and painless DPN. Magnetic resonance imaging and spectroscopic studies have documented:

(1) spinal cord cross-sectional area differences, notably in subclinical DPN;
(2) volumetric differences and spectroscopic moiety density differences that suggest parenchymal atrophy in the primary sensory cortex;
(3) hyperperfusion in painful DPN and hypoperfusion in painless DPN within the thalamus;
(4) neurochemical changes that suggest abnormal neuronal thalamic function;
(5) alterations to GABA-Glx spectral resonances and the excitatory-inhibition neurotransmitter balance; and
(6) complex variability in the BOLD response to an external painful stimulus in DPN.

Magnetic resonance imaging and spectroscopy techniques have the potential to further elucidate the nature of CNS involvement in DPN. Imaging may help us to unravel one of the fundamental unanswered questions—where can the primary pathophysiology of the painful symptomatology of DPN be found? Magnetic resonance may also address the question of whether involvement at different CNS levels results from "die-back" phenomena after the development of peripheral pathology or is due to direct insults at the various levels, or a combination of both. Perhaps, the key to unlocking this lies in the acquisition of prospective, longitudinal, multilevel and multifunctional imaging data. It is believed that in vivo MR imaging may lead to the development of more rational therapies to help reduce the burden of DPN.[22]

Conflict of interest statement

The authors have no conflicts of interest to declare.

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