Magnetic Resonance Imaging as a Biomarker in Diabetic and HIV-Associated Peripheral Neuropathy: A Systematic Review-Based Narrative

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Background: Peripheral neuropathy can be caused by diabetes mellitus and HIV infection, and often leaves patients with treatment-resistant neuropathic pain. To better treat this condition, we need greater understanding of the pathogenesis, as well as objective biomarkers to predict treatment response. Magnetic resonance imaging (MRI) has a firm place as a biomarker for diseases of the central nervous system (CNS), but until recently has had little role for disease of the peripheral nervous system.

Objectives: To review the current state-of-the-art of peripheral nerve MRI in diabetic and HIV symmetrical polyneuropathy. We used systematic literature search methods to identify all studies currently published, using this as a basis for a narrative review to discuss major findings in the literature. We also assessed risk of bias, as well as technical aspects of MRI and statistical analysis.

Methods: Protocol was pre-registered on NIHR PROSPERO database. MEDLINE, Web of Science and EMBASE databases were searched from 1946 to 15th August 2020 for all studies investigating either diabetic or HIV neuropathy and MRI, focusing exclusively on studies investigating symmetrical polyneuropathy. The NIH quality assessment tool for observational and cross-sectional cohort studies was used for risk of bias assessment.

Results: The search resulted in 18 papers eligible for review, 18 for diabetic neuropathy and 0 for HIV neuropathy. Risk of bias assessment demonstrated that studies generally lacked explicit sample size justifications, and some may be underpowered. Whilst most studies made efforts to balance groups for confounding variables (age, gender, BMI, disease duration), there was lack of consistency between studies. Overall, the literature provides convincing evidence that DPN is associated with larger nerve cross sectional area, T2-weighted hyperintense and hypointense lesions, evidence of nerve oedema on Dixon imaging, decreased fractional anisotropy and increased apparent diffusion coefficient compared with controls. Analysis to date is largely restricted to the sciatic nerve or its branches.
INTRODUCTION

Diabetic peripheral neuropathy (DPN) is a condition associated with both type 1 (T1DM) and type 2 diabetes mellitus (T2DM), presenting as a distal symmetrical, length-dependent degeneration, usually affecting sensory more than motor nerves. Diabetes mellitus is common, affecting around 8.8% of adults worldwide (International_Diabetes_Federation, 2015), and around half of these are estimated to develop DPN at some point in their lives (Tesfaye, 2011). Neuropathic pain is a common symptom, affecting around a quarter of those with DPN (Van Hecke et al., 2014), and is poorly responsive to analgesic medications (Chung, 2012).

The pathophysiology of DPN remains incompletely understood, and numerous mechanisms have been proposed, including hyperglycaemia (Won et al., 2012; Xu et al., 2014), increased activity of the polyol pathway (Brownlee, 2001) and dyslipidaemia (Tesfaye et al., 1996) [an excellent review of this topic can be found in Calcutt (2020)]. The polyol pathway received significant attention in the field for some time (Chung, 2003) providing hope that aldose reductase inhibitors (ARIs) could modify disease in DPN. However, meta-analyses of commercially available ARIs to date have not been successful, so these have largely been abandoned in clinical practise (Chalk et al., 2007; Calcutt and Fernyhough, 2016). DPN is classically described as a small fibre neuropathy, with a reduction in intra-epithelial nerve fibre density (IENFD) shown on skin biopsy (Lauria et al., 2010) reflecting a “die-back” pattern of loss of unmyelinated C fibres. However, pathological studies have also shown loss of larger, myelinated fibres, even early in the natural history of the disease (Behse et al., 1977), and autopsies studies of DPN have shown that fascicular damage begins in the proximal sciatic nerve and can be found along the length of the affected nerve (Dyck et al., 1986), which is supported by recent imaging studies showing proximal sciatic involvement in DPN (Groener et al., 2020). The pathological mechanism of the peripheral predominance of symptoms in DPN remains unclear, with likely roles for metabolic dysfunction (Freeman et al., 2016) and neuroinflammation (Leinninger et al., 2004).

HIV infection also causes a symmetrical sensory-predominant polyneuropathy. HIV neuropathy is seen in 20–57% of patients infected with HIV, across low-, middle- and high-income countries (Cherry et al., 2016). The most common form of peripheral nerve lesion found in HIV is a length-dependent axonal degeneration of unmyelinated (C) and thinly myelinated (Aβ) fibres, much like DPN (Cherry et al., 2012b). Two distinct mechanisms appear to be involved in HIV neuropathy: (i) a direct toxic effect of anti-retroviral drugs (ARVs), particularly older di-deoxynucleotide agents (Cherry et al., 2012a; Kamerman et al., 2012), and (ii) an effect of the HIV virus itself, which seems to involve interaction of viral gp120 protein with macrophage CCR5/CXCR4, leading to an inflammatory cascade that results in axonal damage and degeneration (Lee et al., 2003; Moss et al., 2015). Other components of the HIV virus may also be involved in addition to gp120, including viral Transactivator of Transcription (Tat) (Wodarski et al., 2018). The biological mechanisms underlying pain in HIV neuropathy have been poorly elucidated, but various psychosocial factors have been identified (Scott et al., 2018; Scott, 2019).

Treatment of neuropathic pain (and other neuropathic symptoms) can be extremely difficult, with no true disease-modifying therapies for most underlying conditions, and meta-analyses demonstrating that existing therapies have modest efficacy, narrow therapeutic indices and that it is difficult to predict treatment responses at the individual patient level (Finnnerup et al., 2015). Part of the challenge of drug development and clinical trial design is the lack of robust biomarkers for neuropathy and neuropathic pain.

Electrophysiological techniques allow probing of the electrical properties of nerves, which help identify axonal and demyelinating processes. However, nerve conduction studies only involve the largest myelinated fibres, so dysfunction of smaller Aδ and C fibres will not be represented. Conversely, whilst skin biopsies can be used to assess epidermal nerve fibre density of the small, peripheral nerve fibres (Smith et al., 2005), this only provides information on structure but not function of nerves, and its application is anatomically limited in practise. The invasive nature of skin biopsy also precludes its use as a longitudinal biomarker. Therefore, we sorely need better, ideally non-invasive biomarkers of peripheral nerve damage, that are easily repeatable for longitudinal study.

Magnetic resonance imaging (MRI) would seem to be the ideal non-invasive biomarker and has found use with various diseases of the central nervous system. However, MRI has had limited application to the study of peripheral nerve disease. Until recently, technological challenges have impeded its use in this field, not of achieving sufficient resolution to provide useful information in structures with cross-sectional areas of 3–50 mm² (i.e., diameter of 2-8 mm). The increased availability of 3 Tesla (T) and 7T systems has changed the landscape in recent years. At higher field strength, MRI can offer fascicular
level resolution in larger peripheral nerves (Schmid et al., 2018), offering the possibility of a “virtual biopsy.” MR neurography uses structural \( T_1 \)-weighted, fat-suppressed \( T_2 \)-weighted and diffusion weighted sequences to image peripheral nerves. To date, this technology has found use mostly for compressive and traumatic neuropathies (Cudlip et al., 2002), immune mediated sensory and motor neuropathies (Kronlage et al., 2017), and degenerative diseases such as motor neurone disease (MND) (Gerevini et al., 2016).

In this systematic review we review the current state-of-the-art in applying MRI to understanding diabetic and HIV peripheral neuropathies, identifying the main findings in the field, assessing study quality, and suggesting areas for future research. We chose DPN as this is the most common cause of symmetrical polyneuropathy in the Western world. HIV neuropathy was chosen here because its clinical presentation is often indistinguishable from DPN, so would be an appropriate comparison. Also, given that it affects up to 57% of patients with HIV infection it is also not an uncommon condition in the west, but is of particular burden in areas of high HIV prevalence, such as Sub-Saharan Africa.

MATERIALS AND METHODS

Eligibility Criteria

We considered all original research studies relating to MRI in diabetic (T1DM or T2DM) or HIV polyneuropathy. Eligible imaging studies had to involve the peripheral nervous system, rather than the brain or spinal cord. We excluded studies restricted to the dorsal root ganglion, as whilst there is an emerging literature demonstrating pathological changes at this site, no studies to date have used MR neurography to investigate a link between MR changes and specific blood parameters (e.g., troponin T, cholesterol); these were additionally considered as “exposures” where relevant. “Outcome,” or “dependent variable(s)” corresponded to MRI outcomes. Finally, question 14 relates to the control of confounding variables. Based on an a-priori review of the literature for demographic effects on specific MR sequences, we identified 4 variables that should be considered confounds and controlled for accordingly: (i) age; (ii) gender; (iii) disease duration; (iv) BMI (Kollmer et al., 2018; Kronlage et al., 2018, 2019; Groener et al., 2020). This is discussed further in the Discussion section.

Information Search/Data Collection

We searched MEDLINE, Web of Science and EMBASE databases from 1946 to 15th August 2020. Search criteria were as follows:

**Diabetic Neuropathy**

(diabetes mellitus/ [MeSH term] OR “diabetes” OR “diabetic”)

AND

(diabetic neuropathies/ [MeSH term] OR polyneuropathies/ [MeSH term] OR small fibre neuropathy/ [MeSH term] OR “neuropathy” OR “neuropathic” OR “neuropathies” OR “polyneuropathy” OR “polyneuropathies”)

AND

(magnetic resonance imaging/ [MeSH term] OR “magnetic resonance imaging” OR “MRI” OR “nuclear magnetic resonance” OR “NMR”).

**HIV Neuropathy**

(HIV/ [MeSH term] OR HIV-1/ [MeSH term] OR HIV-2 OR “HIV” OR “human immunodeficiency virus”)

AND

(polyneuropathies/ [MeSH term] OR small fibre neuropathy/ [MeSH term] OR “neuropathy” OR “neuropathic” OR “neuropathies” OR “polyneuropathy”)

AND

(magnetic resonance imaging/ [MeSH term] OR “magnetic resonance imaging” OR “MRI” OR “nuclear magnetic resonance” OR “NMR”)
Other Outcome Measures

In addition to the above formal risk of bias assessment, given the relatively small number of studies meeting the inclusion criteria, we appraised each report in the discussion section according to pertinent quality outcomes for MRI studies specifically. These outcomes were: Sample size (whether power calculations have been performed); sample representativeness, and variables controlled for (age, gender, BMI, disease duration, medications, blood glucose and lipid measurements); any aspect of the MRI itself which limits interpretation of studies (field strength, spatial resolution, anatomy scanned); method of nerve segmentation (automated or manual: if automated, whether there is data presented in the paper or elsewhere demonstrating its accuracy; and if manual, whether data is provided on intra- and inter-rater reliability); statistical analysis. Study characteristics are shown in Table 1, and the main results summarised in Table 2.

RESULTS

Study Selection

Two thousand nine hundred seventy-five papers (duplicates excluded) were screened (by two independent reviewers) by reviewing titles and abstracts according to the inclusion/exclusion criteria itemised in the methods section above, of which 2,945 were deemed irrelevant, leaving 30 papers selected for full text screening. These papers were excluded largely because they involved conditions other than diabetic or HIV neuropathy (1635), or involved diabetic or HIV subjects but were either case reports, or on topics that fell outside of the review (e.g., imaging studies of Charcot arthropathy, or CNS imaging studies of HIV or infective complications of HIV). Twelve studies were excluded from full text screening, either because of study design not meeting inclusion criteria (letter to the editor, case reports, or studies not including any control group), patient population not being appropriate [investigating other forms of neuropathy such as chronic inflammatory demyelination polynévropathie (CIDP) rather than HIV or diabetic neuropathy], or because the result was a conference proceeding with limited data and with no peer review. Finally, we were left with 18 studies which met eligibility for systematic review (see PRISMA flow chart in Figure 1). All 18 studies were focused on diabetic neuropathy, with no studies found to date investigating HIV neuropathy with MRI. The remainder of the results section will therefore be dedicated to discussing studies of diabetic neuropathy.

Risk of Bias Assessment

The risk of bias assessment is shown for each study in Figure 2. This demonstrates that most (if not all) studies failed to satisfy questions 5 and 14, which relate to sample size justification and confounding variables. For this question we chose the following variables as most pertinent confounds: (i) age; (ii) gender; (iii) BMI; (iv) diabetes duration (if more than one diabetes group in the study).

Question 2 asks whether the populations studied were clearly defined. Many of the earlier studies did not distinguish between type 1 and 2 diabetes, and often did not make clear from the methods section the number of patients from each group, or which patients were on insulin treatment (Koechner et al., 1995; Shibata et al., 1998; Wu et al., 2017; Edward et al., 2020) (14/18 complied). Question 8 asks whether different “levels” of exposure were compared, which in this context relates to whether groups were stratified based on severity or duration of neuropathy or diabetes, to make a more convincing link between disease and MR biomarkers (9/18 complied). Question 10 relates to whether more than 1 time point was used (2/18 complied). Finally, question 12 asks whether outcomes were assessed in a blinded fashion; this was only clearly documented in 9/18 studies. However, of these 7/9 studies used (semi-)automated segmentation of MR images and DTI analysis pipelines which provide minimal opportunity to introduce bias (Pham et al., 2015; Vaeggemose et al., 2017a, 2020; Wu et al., 2017; Jende et al., 2019, 2020a; Edward et al., 2020).

The remaining questions demonstrated high compliance. However, it is worth noting that the three studies by Jende et al. (2018, 2019, 2020a) did not satisfy question 6, which pertains to whether the exposures were measured before the outcomes. In each of these studies, correlational relationships are made between specific MRI values and blood biomarkers (cholesterol and high sensitivity troponin T). As the authors themselves note in the discussion, the cross-sectional nature of the study limits causal relationships being made between variables.

NARRATIVE REVIEW

Dixon MRI

The earliest studies attempting to use MRI to non-invasively study peripheral nerves in DPN came from Eaton and Griffey in the late 1980s (Griffey et al., 1988; Koechner et al., 1995; Eaton et al., 1996). In a set of three papers, they used a proton-density-weighted Dixon sequence at 1.5 T as a measure of sural nerve water content. Dixon sequences capitalise on chemical shift, the phenomenon by which protons in fat and water have different resonant frequencies, and therefore over time their corresponding signal components alternate between being in- and opposed-phase. By acquiring two imaging (i.e., 2-point Dixon) or more and combining them mathematically, it is possible to derive water-only and fat-only images from these data. They used water-only Dixon images, normalised to a copper-sulphate (CuSO4) control to derive an estimate of water content from proton density. They demonstrated higher nerve water content in patients with DPN compared with either diabetes without DPN, or healthy controls (Griffey et al., 1988; Koechner et al., 1995; Eaton et al., 1996). In their earlier study, they showed that sural nerve water content positively correlated with deficits on nerve conduction studies. Later, in a larger study using 79 patients with DPN, 75 patients with diabetes without DPN, and 72 non-diabetic healthy controls, Eaton et al. (1996) demonstrated that there was a subset of patients with diabetes without DPN who demonstrated nerve “hyperhydration” (>30% water content of nerve) with nerve conduction values approaching those in the DPN cohort, but when stratifying the DPN patients according to duration of neuropathy, there was a trend towards decreasing nerve water...
| References          | Country conducted | Patient group                                                                 | Control group                                                                 | Variables controlled                      | Exclusion criteria                                                                 |
|---------------------|-------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------------------------------------|
| Griffey et al. (1988) | USA               | • Insulin-dependent diabetes with DPN (11) • Insulin-dependent diabetes with DPN taking aldose reductase inhibitor (6) | • Insulin-dependent diabetes without DPN (11) • Non-diabetic healthy control (11) | Nil                                       | • Women • Other causes polyneuropathy o Renal failure o Pernicious anaemia o Alcoholism o Heavy metal/toxin exposure o Hypothyroidism |
| Koechner et al. (1995) | USA               | • Diabetes with DPN (13)                                                     | • Non-diabetic healthy control (5)                                            | Nil                                       | Nil                                                                                 |
| Eaton et al. (1996)   | USA               | • Diabetes with DPN (79)                                                     | • Diabetes without DPN (75) • Non-diabetic healthy control (72)               | Statistically significant differences in age, gender, BMI., disease duration, and cardiovascular risk factors. No statistical control used. | • Other neuropathy risk factors: o Renal failure o Hypothyroid o Pernicious anaemia o Alcoholism o Neurosyphilis o Heavy metal/toxin exposure o Oedema in lower limbs |
| Shibata et al. (1998)  | Japan             | • Non-insulin-dependent diabetes mellitus (92)                              | • Non-diabetic healthy control (19)                                           | Age, retinopathy, nephropathy             |                                                                                     |
| Pham et al. (2011)    | Germany           | • T2DM with DPN (10) • T1DM with DPN (2)                                     | • T2DM without DPN (10) • T1DM without DPN (5) • Non-diabetic healthy control (10) | HbA1c, HTN, hyperlipidemia, CHD, myocardial infarction, smoking | Nil                                                                                 |
| Pham et al. (2015)    | Germany           | • Diabetes with mild-moderate DPN (25) • Diabetes with severe DPN (10)      | • Diabetes without DPN (15) • Non-diabetic healthy control (25)               | Age, sex, disease duration, Retinopathy, Nephropathy, CHD, HTN, Hypertension, Hyperlipidemia, Smoking, HbA1c, Cholesterol, Triglycerides, HDL, LDL, eGFR, BMI | • Age < 18 or > 75 • Contraindication (CI) to MRI • Symptomatic PAD or CVA • Other neuropathy risk factors o EtOH excess o Autoimmune o Systemic vasculitis o ESRF • Severe cardiac/lung disease o Acute or chronic MSK disorder o Lower-limb asymmetric weakness o CI to MRI • Other neuropathy risk factors o Acute metabolic dysregulation o Chronic neurologic diseases o Endocrine disorder |
| Vaeggemose et al. (2017a) | Denmark         | • T1DM with DPN (10)                                                        | • T1DM without DPN (10) • Non-diabetic healthy control (10)                   | Age, Disease duration, BMI, HbA1c         | (Continued)                                                                                     |
| References          | Country conducted | Patient group                                                                 | Control group                                      | Variables controlled                  | Exclusion criteria                                                                 |
|---------------------|-------------------|-------------------------------------------------------------------------------|-------------------------------------------------|--------------------------------------|----------------------------------------------------------------------------------|
| Wu et al. (2017)    | China             | Diabetic patients – type not specified (10)                                   | Non-diabetic healthy control (12)               | Sex, age                             | Pregnancy                                                                       |
|                     |                   |                                                                                |                                                 |                                      | CI to MRI                                                                         |
|                     |                   |                                                                                |                                                 |                                      | Hx of leg or knee surgery                                                        |
|                     |                   |                                                                                |                                                 |                                      | Severe cardiac/lung disease                                                       |
|                     |                   |                                                                                |                                                 |                                      | Other neuropathy risk factors                                                    |
|                     |                   |                                                                                |                                                 |                                      | Metabolic disorder                                                               |
|                     |                   |                                                                                |                                                 |                                      | Endocrine disorder                                                               |
|                     |                   |                                                                                |                                                 |                                      | Exposure to neurotoxic agents                                                     |
|                     |                   |                                                                                |                                                 |                                      | Chronic neurologic diseases                                                       |
|                     |                   |                                                                                |                                                 |                                      | Neuromuscular/MSK disorder                                                       |
| Felisaz et al. (2017)| Italy             | Diabetes with mild DPN (6)                                                    | Non-diabetic healthy control (15)               | Sex, age                             | Unilateral neuropathy                                                             |
|                     |                   | Diabetes with moderate/severe DPN (10)                                        |                                                 |                                      | Compressive radiculopathy                                                        |
|                     |                   | Symptomatic mild T1DM Polyneuropathy (13)                                     |                                                 |                                      | Posttraumatic radiculopathy                                                       |
|                     |                   | Symptomatic severe T1DM Polyneuropathy (11)                                   |                                                 |                                      | Other neuropathy risk factors                                                    |
| Vaeggemose et al. (2017b) | Denmark | Symptomatic mild T1DM Polyneuropathy (13)                                      | T1DM without DPN (25)                           | Age, gender, BMI, HbA1c             | Severe cardiac/lung disease                                                      |
|                     |                   | Symptomatic severe T1DM Polyneuropathy (11)                                   | Non-diabetic healthy control (30)               |                                      | Acute or chronic MSK disorder                                                     |
|                     |                   |                                                                                |                                                 |                                      | Lower-limb asymmetric weakness                                                   |
|                     |                   |                                                                                |                                                 |                                      | Contra-indications to MRI                                                        |
|                     |                   |                                                                                |                                                 |                                      | Other neuropathy risk factors                                                    |
|                     |                   |                                                                                |                                                 |                                      | Acute metabolic dysregulation                                                     |
|                     |                   |                                                                                |                                                 |                                      | Chronic neurologic diseases                                                       |
|                     |                   |                                                                                |                                                 |                                      | Endocrine disorder                                                               |
| Wang et al. (2018)  | China             | Diabetes with DPN (22) – 16 T2DM, 6 T1DM                                      | Diabetes with DPN (20) – 17 T2DM, 3 T1DM        | Age, sex, BMI, HbA1c               | Present or past foot osteomyelitis                                               |
|                     |                   |                                                                                | Non-diabetic healthy control (20)               |                                      | Present or past foot ulcer                                                       |
|                     |                   |                                                                                |                                                 |                                      | Known hx of foot fracture or surgery                                              |
|                     |                   |                                                                                |                                                 |                                      | Skin swelling/lesions                                                            |
|                     |                   |                                                                                |                                                 |                                      | Other neuropathy risk factors                                                    |
|                     |                   |                                                                                |                                                 |                                      | EtOH excess                                                                       |
|                     |                   |                                                                                |                                                 |                                      | Metabolic/toxic factors                                                          |
|                     |                   |                                                                                |                                                 |                                      | Inflammatory or hereditary                                                        |
| Jende et al. (2018) | Germany           | T2DM with DPN (66)                                                           | T2DM without DPN (19)                           | Age, BMI, HbA1c, Cholesterol, eGFR, albumin/creatinine ratio | Age < 18                                                                         |
|                     |                   | T1DM with DPN (18)                                                           | T1DM without DPN (17)                           |                                      | Pregnancy                                                                       |
|                     |                   |                                                                                |                                                 |                                      | CI to MRI                                                                        |
|                     |                   |                                                                                |                                                 |                                      | Hx of lumbar surgery                                                              |
|                     |                   |                                                                                |                                                 |                                      | Disc protrusion                                                                  |
|                     |                   |                                                                                |                                                 |                                      | Other neuropathy risk factors                                                    |
|                     |                   |                                                                                |                                                 |                                      | EtOH excess                                                                       |
|                     |                   |                                                                                |                                                 |                                      | Malignancy                                                                       |
|                     |                   |                                                                                |                                                 |                                      | Infection                                                                        |
|                     |                   |                                                                                |                                                 |                                      | Chronic bowel disease                                                            |
|                     |                   |                                                                                |                                                 |                                      | Hypovitaminosis                                                                  |
|                     |                   |                                                                                |                                                 |                                      | Exposure to neurotoxic agents                                                    |
|                     |                   |                                                                                |                                                 |                                      | Chronic neurologic diseases                                                      |
|                     |                   |                                                                                |                                                 |                                      | Micro- or macrocytic anaemia                                                     |
|                     |                   |                                                                                |                                                 |                                      | Monoclonal gammopathy                                                            |

(Continued)
| References | Country conducted | Patient group                                      | Control group                                       | Variables controlled                  | Exclusion criteria                                                                 |
|------------|------------------|--------------------------------------------------|----------------------------------------------------|---------------------------------------|-------------------------------------------------------------------------------------|
| Jende et al. (2019) | Germany          | • T2DM with DPN (64)                             | • T2DM without DPN (36)                            | Age, BMI, HbA1c, eGFR                | • Age < 18                                                                          |
|            |                  | • Painful DPN (64) – mixture T1DM and T2DM       |                                                    |                                       | • Pregnancy                                                                         |
|            |                  | • Non-painful DPN (37) - mixture T1DM and T2DM   |                                                    |                                       | • CI to MRI                                                                         |
|            |                  |                                                  |                                                    |                                       | • Hx of lumbar surgery                                                                |
|            |                  |                                                  |                                                    |                                       | • Disc protrusion                                                                    |
|            |                  |                                                  |                                                    |                                       | • Other neuropathy risk factors                                                        |
|            |                  |                                                  |                                                    |                                       | • ETOH excess                                                                        |
|            |                  |                                                  |                                                    |                                       | • Malignancy                                                                         |
|            |                  |                                                  |                                                    |                                       | • Hypervitaminosis                                                                   |
|            |                  |                                                  |                                                    |                                       | • Monoclonal gammopathy                                                               |
|            |                  |                                                  |                                                    |                                       | • Exposure to neurotoxic agents                                                       |
|            |                  |                                                  |                                                    |                                       | • Chronic neurologic diseases                                                        |
|            |                  |                                                  |                                                    |                                       | • Renal insufficiency                                                                |
|            |                  |                                                  |                                                    |                                       | • Microangiopathy                                                                   |
| Jende et al. (2020a) | Germany         | • Painful DPN (64) – mixture T1DM and T2DM       | • Diabetes without DPN (30) - mixture T1DM and T2DM | Age, sex, HbA1c, diabetes duration, cholesterol, eGFR | • Age < 18                                                                          |
|            |                  | • Non-painful DPN (37) - mixture T1DM and T2DM   |                                                    |                                       | • Pregnancy                                                                         |
|            |                  | • Diabetes without DPN (30) - mixture T1DM and T2DM |                                                    |                                       | • CI to MRI                                                                         |
|            |                  |                                                  |                                                    |                                       | • Hx of lumbar surgery                                                                |
|            |                  |                                                  |                                                    |                                       | • Disc protrusion                                                                    |
|            |                  |                                                  |                                                    |                                       | • Other neuropathy risk factors                                                        |
|            |                  |                                                  |                                                    |                                       | • ETOH excess                                                                        |
|            |                  |                                                  |                                                    |                                       | • Malignancy                                                                         |
|            |                  |                                                  |                                                    |                                       | • Hypervitaminosis                                                                   |
|            |                  |                                                  |                                                    |                                       | • Monoclonal gammopathy                                                               |
|            |                  |                                                  |                                                    |                                       | • Exposure to neurotoxic agents                                                       |
|            |                  |                                                  |                                                    |                                       | • Chronic neurologic diseases                                                        |
|            |                  |                                                  |                                                    |                                       | • Pain disorder other than DPN                                                        |
| Groener et al. (2020) | Germany         | • T2DM with DPN (48)                             | • T2DM without DPN (13)                            | Age, BMI, HbA1c, diabetes duration, protein:creatinine ratio, eGFR                  | • Age < 18                                                                          |
|            |                  | • Non-diabetic healthy control (12)              |                                                    |                                       | • Pregnancy                                                                         |
|            |                  |                                                  |                                                    |                                       | • CI to MRI                                                                         |
|            |                  |                                                  |                                                    |                                       | • Other neuropathy risk factors                                                        |
|            |                  |                                                  |                                                    |                                       | • ETOH excess                                                                        |
|            |                  |                                                  |                                                    |                                       | • Malignancy                                                                         |
|            |                  |                                                  |                                                    |                                       | • Rheumatic autoimmune dx                                                             |
|            |                  |                                                  |                                                    |                                       | • Spinal lesions                                                                     |
|            |                  |                                                  |                                                    |                                       | • Chronic neurologic diseases                                                        |
|            |                  |                                                  |                                                    |                                       | • Renal insufficiency                                                                |

(Continued)
| References          | Country conducted | Patient group       | Control group             | Variables controlled | Exclusion criteria                                      |
|---------------------|-------------------|---------------------|---------------------------|----------------------|---------------------------------------------------------|
| Edward et al. (2020) | Egypt             | T2DM with DPN (30)  | Non-diabetic healthy controls (15) | Age                  | Evidence of nerve entrapment                           |
|                     |                   |                     |                           |                      | Evidence of other neuropathies:                          |
|                     |                   |                     |                           |                      |   o Drug-induced/toxic                                   |
|                     |                   |                     |                           |                      |   o Hereditary                                           |
| Jende et al. (2020b)| Germany           | T2DM with DPN (28)  | T1DM without DPN (23)     | Disease duration, HbA1c, BMI, eGFR | Age < 18                                                 |
|                     |                   |                     | Non-diabetic healthy controls (10) |                      | Pregnancy                                               |
|                     |                   |                     |                           |                      | CI to MRI                                               |
|                     |                   |                     |                           |                      | Other neuropathy risk factors                           |
|                     |                   |                     |                           |                      | EtOH excess                                             |
|                     |                   |                     |                           |                      | Malignancy                                              |
|                     |                   |                     |                           |                      | Infectious diseases                                     |
|                     |                   |                     |                           |                      | Rheumatic autoimmune dx                                 |
|                     |                   |                     |                           |                      | Spinal lesions                                          |
|                     |                   |                     |                           |                      | Chronic neurologic diseases                             |
|                     |                   |                     |                           |                      | Renal insufficiency                                     |
| Vaeggemose et al. (2020) | Denmark           | T2DM with DPN (10)  | T1DM without DPN (10)     | Age, diabetes duration, HbA1c | Acute metabolic dysregulation                           |
|                     |                   |                     | Non-diabetic healthy controls (20) |                      | Severe cardiac or lung disease                          |
|                     |                   |                     |                           |                      | Musculoskeletal disorders                               |
|                     |                   |                     |                           |                      | Other endocrine/neurological disorders                   |
|                     |                   |                     |                           |                      | Present or previous asymmetric weakness in the lower limbs |
|                     |                   |                     |                           |                      | CI to MRI                                               |
## TABLE 2 | Results summary.

| References         | Magnetic field strength (T) | Nerve/Segment | Measurement (spatial resolution) | Mean ± standard error (* indicates that values have been converted from the original standard deviation to standard error) | P-value |
|--------------------|-----------------------------|---------------|----------------------------------|-----------------------------------------------------------------------------------------------------------------|---------|
| Griffey et al. (1988) | 1.5                         | Sural nerve   | Proton density Dixon sequence, water ratio with CuSO4 phantom (0.312 x 0.615 x 3.0 mm³) | A: Diabetes with “Symptomatic” DPN 0.33 ± 0.11  
B: Diabetes with “Treated Symptomatic” DPN 0.26 ± 0.02  
C: “Neurologically Asymptomatic Diabetes” 0.27 ± 0.11  
D: Non-diabetic healthy control 0.23 ± 0.04 | A vs. D: p < 0.001  
B and C N.S. compared with D |
| Koechner et al. (1995)   | 1.5                         | Sural nerve   | Proton density Dixon sequence, nerve hydration coefficient with CuSO4 phantom (0.312 x 0.615 x 3.0 mm³) | A: Diabetes with “Symptomatic” DPN 31.4 ± 2.4  
B: Non-diabetic healthy controls 24.6 ± 1.2 | No statistical comparison |
| Eaton et al. (1996)     | 1.5                         | Sural nerve   | Proton density Dixon sequence, nerve hydration coefficient with CuSO4 phantom (0.312 x 0.615 x 3.0 mm³) | A: Diabetes with “Symptomatic” DPN 30.4 ± 5.8%  
B: “Neurologically Asymptomatic Diabetes” 27.6 ± 5.0%  
C: Non-diabetic healthy control 24.8 ± 3.5% | A vs. C: p < 0.05  
A vs. B: p < 0.05  
B vs. C: p < 0.05 |
| Shibata et al. (1998)   | 1.5                         | Sural nerve   | T₁ relaxometry, ms (resolution not specified) | A: Non-insulin-dependent diabetes mellitus 831 ± 495  
B: Non-diabetic healthy controls 472 ± 258  
C: Non-insulin-dependent diabetes mellitus: pre-ARI treatment (N = 12) 1,056 ± 530  
D: Non-insulin-dependent diabetes mellitus: post-ARI treatment (N = 12) 575 ± 335 | A vs. B: p < 0.001  
C vs. D: p < 0.001 |
|                      |                             |               | Nerve cross-sectional area, mm² | Non-insulin-dependent diabetes mellitus 2.8 ± 1.8  
Non-diabetic healthy controls 3.3 ± 1.5 | N.S. |

Other correlations:
- T₁ relaxometry and MNCV  
- T₁ relaxometry and CVI  
- T₁ relaxometry and FPG  
- T₁ relaxometry and HbA1c  

(Continued)
### TABLE 2 | Continued

| References | Magnetic field strength (T) | Nerve/Segment | Results |
|------------|-----------------------------|----------------|---------|
|            |                             |                | Measurement (spatial resolution) | Mean ± standard error (* indicates that values have been converted from the original standard deviation to standard error) | P-value |
|            |                             | Sciatic nerve  | T₂-weighted MRI (0.25 × 0.52 × 5.0 mm³) | | |
|            |                             | Tibial nerve   | Number of patients with observable lesions | | |
|            |                             | Common peroneal nerve (above knee) | T₂DM with DPN | 3/10 | No statistical comparison |
|            |                             |                | T₁DM with DPN | 1/2 | |
|            |                             |                | T₂DM without DPN | 0/10 | |
|            |                             |                | T₁DM without DPN | 0/10 | |
|            |                             |                | Non-diabetic healthy controls | 0/10 | |
|            |                             |                | Mean contrast ratio between nerve and adjacent muscle | | |
|            |                             |                | A: Diabetic (T₁DM/T₂DM) with DPN and observable lesions as above (N = 4) | 4.2 ± 0.9 | A vs. B: p = 0.003 |
|            |                             |                | B: Diabetic control subjects without DPN (N = 15) | 2.1 ± 0.3 | A vs. C: p = 0.004 |
|            |                             |                | C: Non-diabetic healthy controls (N = 10) | 1.9 ± 0.2 | |
|            |                             | Full length of sciatic/tibial/common peroneal nerve (nerve root to ankle) | T₂-weighted MRI (0.4 × 0.3 × 3.5 mm³) | | |
|            |                             |                | Number of proximal lesions | | |
|            |                             |                | A: DM with severe DPN | 57 ± 18.4 | A vs. D: p < 0.0022 |
|            |                             |                | B: DM with mild-moderate DPN | 35 ± 4.0 | B vs. D: p < 0.0005 |
|            |                             |                | C: DM without DPN | 21 ± 5.5 | C vs. D: N.S |
|            |                             |                | D: Non-diabetic healthy controls | 18 ± 3.6 | |
|            |                             |                | Number of distal lesions | | |
|            |                             |                | E: DM with severe DPN | 22 ± 8.1 | E: p < 0.0174 |
|            |                             |                | F: DM with mild-moderate DPN | 12 ± 1.8 | F vs. H: N.S |
|            |                             |                | G: DM without DPN | 8 ± 2.9 | G vs. H: N.S |
|            |                             |                | H: Non-diabetic healthy controls | 8 ± 1.4 | |
|            |                             |                | Average common peroneal vol per slice (mm³) | | |
|            |                             |                | I: DM with severe DPN | 29.2 ± 3.0 | F = 5.61(3.71), p = 0.001 |
|            |                             |                | J: DM with mild-moderate DPN | 24.6 ± 1.4 | No pairwise comparisons given |
|            |                             |                | K: DM without DPN | 23.6 ± 1.2 | |
|            |                             |                | L: Non-diabetic healthy controls | 23.5 ± 1.1 | |
|            |                             |                | Average tibial vol per slice (mm³) | | |
|            |                             |                | F: DM with severe DPN | 74.4 ± 6.0 | F = 5.61(3.71), p = 0.001 |
|            |                             |                | J: DM with mild-moderate DPN | 62.5 ± 2.7 | No pairwise comparisons given |
|            |                             |                | K: DM without DPN | 60.4 ± 3.3 | |
|            |                             |                | L: Non-diabetic healthy controls | 52.8 ± 1.4 | |
|            |                             |                | Divide by slice thickness 3.5 mm to get average cross sectional area (mm²) | | |

(Continued)
### TABLE 2 | Continued

| References       | Magnetic field strength (T) | Nerve/Segment | Results                                                                 |
|------------------|-----------------------------|---------------|-------------------------------------------------------------------------|
| Wu et al. (2017) | 3                           | Tibial nerve  | **Logistic regression by disease group**                                 |
|                  |                             | Common Peroneal nerve (knee) | T<sub>2</sub> relaxometry                                               |
|                  |                             |               | Proton density                                                          |
|                  |                             |               | **Regressions/correlations with proton density**                        |
|                  |                             |               | Presence of symptomatic DPN                                              |
|                  |                             |               | NDS                                                                     |
|                  |                             |               | NSS                                                                     |
|                  |                             |               | Disease duration, HbA1c, BMI, presence of nephropathy/neuropathy, smoking, hyperlipidaemia |
|                  |                             |               | **Measurement (spatial resolution)**                                    |
|                  |                             |               | Mean ± standard error (* indicates that values have been converted from the original standard deviation to standard error) |
|                  |                             |               | **P-value**                                                             |
|                  |                             |               |                                                                         |
| Logistic regression by disease group |                             |               |                                                                         |
| T<sub>2</sub> relaxometry |                             |               |                                                                         |
| Proton density |                             |               |                                                                         |
| Regressions/correlations with proton density |                             |               |                                                                         |
| Presence of symptomatic DPN |                             |               |                                                                         |
| NDS |                             |               |                                                                         |
| NSS |                             |               |                                                                         |
| Disease duration, HbA1c, BMI, presence of nephropathy/neuropathy, smoking, hyperlipidaemia |                             |               |                                                                         |
| **Other correlations** |                             |               |                                                                         |
| FA vs. motor nerve conduction velocity |                             |               |                                                                         |
| ADC vs. motor nerve conduction velocity |                             |               |                                                                         |
| **Mean ± standard error** |                             |               |                                                                         |
| **P-value** |                             |               |                                                                         |
| **Other correlations** |                             |               |                                                                         |
| FA vs. motor nerve conduction velocity |                             |               |                                                                         |
| ADC vs. motor nerve conduction velocity |                             |               |                                                                         |
| **Other correlations** |                             |               |                                                                         |
| FA vs. motor nerve conduction velocity |                             |               |                                                                         |
| ADC vs. motor nerve conduction velocity |                             |               |                                                                         |

**T<sub>2</sub> relaxometry**

### Diffusion tensor imaging (1.25 × 1.28 × 3.0 mm<sup>3</sup>)

|                     | Tibial nerve | Common peroneal (CP) |
|---------------------|-------------|----------------------|
| Fractional anisotropy (FA) |             |                      |
| A: Diabetic neuropathy (10) | 0.534 ± 0.165* | 0.553 ± 0.022*       |
| B: Non-diabetic healthy controls (12) | 0.593 ± 0.185* | 0.623 ± 0.172*       |
| Apparent diffusion coefficient (ADC; × 10<sup>3</sup> mm<sup>2</sup>/s) |             |                      |
| A: Diabetic neuropathy |             |                      |
| B: Non-diabetic healthy controls | 1.173 ± 0.277* | 1.128 ± 0.058*       |
| ADC | 1.080 ± 0.217* | 0.993 ± 0.040*       |
| Tibial: p = 0.001 | CP: p = 0.009 |
| r = 0.469, p < 0.05 | r = 0.479, p < 0.05 |

(Continued)
| References                | Magnetic field strength (T) | Nerve/Segment | Measurement (spatial resolution) | Results | P-value |
|---------------------------|----------------------------|---------------|----------------------------------|---------|---------|
| Vaeggemose et al. (2017a) | 3                          | Sciatic nerve (thigh) | Diffusion tensor imaging (1.36 x 1.36 x 3.0 mm$^3$) | Sciatic |                      |
|                           |                            |               | Fractional anisotropy (FA)       |         |         |
|                           |                            |               | A: T1DM with DPN                 | 0.37 ± 0.02* | 0.31 ± 0.02* |
|                           |                            |               | B: T1DM without DPN              | 0.47 ± 0.03* | 0.41 ± 0.02* |
|                           |                            |               | C: Non-diabetic healthy controls | 0.49 ± 0.01* | 0.43 ± 0.03* |
|                           |                            | Tibial nerve (calf) | Apparent diffusion coefficient (ADC; x1$^0$3 mm$^3$/s) |         |         |
|                           |                            |               | D: T1DM with DPN                 | 1.69 ± 0.08* | 1.87 ± 0.14* |
|                           |                            |               | E: T1DM without DPN              | 1.50 ± 0.02* | 1.59 ± 0.06* |
|                           |                            |               | F: Non-diabetic healthy controls | 1.42 ± 0.04* | 1.57 ± 0.08* |
|                           |                            |               | Multi-echo turbo spin echo sequence (0.3 x 0.3 x 3.0 mm) | | |
|                           |                            |               | $T_2$ relaxometry (ms)            |         |         |
|                           |                            |               | G: T1DM with DPN                 | 86 ± 5.1*  | 65 ± 4.7*  |
|                           |                            |               | H: T1DM without DPN              | 86 ± 3.8*  | 63 ± 3.2*  |
|                           |                            |               | I: Non-diabetic healthy controls | 79 ± 3.2*  | 58 ± 3.8*  |
|                           |                            |               | Proton density                   |         |         |
|                           |                            |               | J: T1DM with DPN                 | 314 ± 24.3* | 429 ± 39.8* |
|                           |                            |               | K: T1DM without DPN              | 346 ± 18.0* | 512 ± 35.4* |
|                           |                            |               | L: Non-diabetic healthy controls | 302 ± 16.8* | 492 ± 26.6* |
|                           |                            |               | Nerve cross-section area (m$^2$)  |         |         |
|                           |                            |               | M: T1DM with DPN                 | 29 ± 2.2*  | 8 ± 0.9*  |
|                           |                            |               | N: T1DM without DPN              | 29 ± 2.8*  | 6 ± 0.6*  |
|                           |                            |               | O: Non-diabetic healthy controls | 26 ± 1.6*  | 7 ± 0.8*  |
| References          | Magnetic field strength (T) | Nerve/Segment                        | Measurement (spatial resolution) | Results                  | $P$-value       |
|---------------------|-----------------------------|--------------------------------------|---------------------------------|--------------------------|-----------------|
| Felisaz et al. (2017) | 3                           | Tibial nerve (ankle)                 | IDEAL (Dixon) sequence ($0.117 \times 0.143 \times 2.0$ mm$^3$) | Nerve volumes (mm$^3$) -NV: 383.0 ± 30.6 326.7 ± 48.4 286.8 ± 18.0 \*Fascicles volume (mm$^3$) -FV: 251.4 ± 20.3 218.7 ± 29.7 198.4 ± 12.8 \*Fascicles to nerve ratio -FNR: 0.659 ± 0.014 0.677 ± 0.018 0.699 ± 0.11 \*Cross-sectional areas (mm$^2$) -CSA: 12.97 ± 0.91 12.62 ± 1.27 10.22 ± 0.45 \* | NV/FV/FNR A vs. C; p < 0.03 CSA A vs. C; p < 0.01 B vs. C; p < 0.04 Others N.S. |
| Vaeggemose et al. (2017b) | 3                           | Sciatic nerve (thigh) Tibial (calf) 1 | Diffusion tensor imaging ($1.36 \times 1.36 \times 3.0$ mm$^3$) | Fractional anisotropy (FA): A: T1DM with severe DPN (11) 0.38 ± 0.01* 0.31 ± 0.02* B: T1DM with mild-moderate DPN (13) 0.41 ± 0.02* 0.34 ± 0.02* C: T1DM without DPN (25) 0.47 ± 0.01* 0.41 ± 0.01* D: Non-diabetic healthy controls (30) 0.48 ± 0.01* 0.42 ± 0.01* Apparent diffusion coefficient (ADC; $10^{-3}$mm$^2$/s): E: T1DM with severe DPN 1.62 ± 0.05* 1.78 ± 0.06* F: T1DM with mild-moderate DPN 1.62 ± 0.07* 1.74 ± 0.12* G: T1DM without DPN 1.52 ± 0.02* 1.59 ± 0.04* H: Non-diabetic healthy controls 1.47 ± 0.03* 1.52 ± 0.03* | Sciatic Tibial A vs. C and D; p < 0.01 B vs. C and D; p < 0.01 E vs. G and H; p < 0.05 F vs. H; p < 0.05 A vs. C and D; p < 0.01 B vs. C and D; p < 0.01 E vs. C and D; p < 0.05 A vs. C and D; p < 0.01 B vs. C and D; p < 0.01 E vs. G and H; p < 0.05 F vs. H; p < 0.05 All comparisons N.S. |
| References       | Magnetic field strength (T) | Nerve/Segment | Results                                                                                                                                 |
|------------------|-----------------------------|---------------|----------------------------------------------------------------------------------------------------------------------------------------|
| Wang et al. (2018) | 3                           | Tibial nerve (ankle) | **T<sub>2</sub> relaxometry, ms (0.4 x 0.4 x 2.0 mm<sup>3</sup>)**<br>**Measurement (spatial resolution)**<br>A: DM with DPN (22)<br>B: DM without DPN (20)<br>C: Non-diabetic healthy control<br>**Mean ± standard error (‘’ indicates that values have been converted from the original standard deviation to standard error)**<br>A: 55.1 ± 4.1<br>B: 48.9 ± 3.1<br>C: 45.6 ± 1.9<br>**P-value**<br>All comparisons p < 0.001<br>**Other Correlations:**<br>T<sub>2</sub> relaxometry vs. HbA1c r = −0.58, p < 0.0001<br>Other Correlations: Total serum cholesterol vs. lipid equivalent lesion (LEL) load r = −0.41, p < 0.001<br>LDL cholesterol vs. LEL load r = −0.33, p = 0.003<br>Total serum cholesterol vs. maximum lesion length (MLL) r = −0.44, p < 0.001<br>LDL cholesterol vs. MLL r = 0.38, p = 0.001<br>Total serum cholesterol vs. mean cross-sectional area (MCA) r = −0.38, p < 0.001<br>LDL cholesterol vs. MCA r = 0.33, p = 0.002 |
| Jende et al. (2018) | 3                           | Sciatic nerve (thigh) | **T<sub>2</sub>-weighted imaging (0.5 x 0.3 x 4.0 mm<sup>3</sup>)**<br>**Measurement (spatial resolution)**<br>A: All neuropathy (T1DM and T2DM)<br>B: All no neuropathy (T1DM and T2DM)<br>C: T1DM with neuropathy<br>D: T2DM with neuropathy<br>E: T1DM without neuropathy<br>F: T2DM without neuropathy<br>**T<sub>2</sub>-weighted hypointensities (mm<sup>3</sup>)**<br>A: 23.41 ± 2.69<br>B: 11.43 ± 1.74<br>C: 19.74 ± 5.57<br>D: 27.54 ± 3.53<br>E: 7.52 ± 0.97<br>F: 16.83 ± 3.16<br>**P-value**<br>A vs. B: p = 0.002<br>C vs. D: p = 0.046<br>E vs. F: p = 0.027<br>**Other Correlations:**<br>T<sub>2</sub>-weighted hyperintense lesions vs. tibial compound motor action potential r = 0.51, p = 0.00002<br>T<sub>2</sub>-weighted hyperintense lesions vs. peroneal nerve conduction r = 0.52, p < 0.0001<br>T<sub>2</sub>-weighted hyperintense lesions vs. NDS T<sub>2</sub>-weighted hyperintense lesions vs. HbA1c r = 0.23, p = 0.014<br>T<sub>2</sub>-weighted hypointense lesions vs. NDS r = 0.28, p = 0.002<br>T<sub>2</sub>-weighted hypointense lesions vs. serum triglycerides r = 0.34, p = 0.0003<br>T<sub>2</sub>-weighted hypointense lesions vs. HDL r = −0.48, p < 0.0001<br>Other N.S. |
TABLE 2 | Continued

| References          | Magnetic field strength (T) | Nerve/Segment                      | Measurement (spatial resolution) | Mean ± standard error (* indicates that values have been converted from the original standard deviation to standard error) | P-value                        |
|---------------------|-----------------------------|------------------------------------|----------------------------------|-----------------------------------------------------------------------------------------------------------------|--------------------------------|
| Jende et al. (2020a) | 3                           | Tibial nerve (thigh)               | **T2-weighted MRI (0.3 x 0.3 x 4.0 mm³)** | Lesions as % of nerve volume A: Painful DPN 15.15 ± 1.61 A vs. B: p = 0.3  
B: Non-painful DPN 10.35 ± 1.66 A vs. C: p < 0.01  
C: Diabetes without DPN 8.26 ± 1.72 B vs. C: N.S.  
D: Painful DPN 63.62 mm ± 3.01 D vs. E: p = 0.0  
E: Non-painful DPN 51.35 mm ± 4.58 3 D vs. F: p < 0.01  
F: Diabetes without DPN 41.20 mm ± 4.75 E vs. F: p = 0.048  
Cross-sectional area (mm²)† G: Painful DPN 136.4 mm² ± 4.58 All comparisons N.S.  
H: Non-painful DPN 144.2 mm² ± 5.80  
I: Diabetes without DPN 134.9 mm² ± 6.07 |
| Groener et al. (2020)| 3                           | Sciatic nerve bifurcation           | **T2-weighted MRI (0.5 x 0.3 x 4.0 mm³)** | **T2-weighted hyperintense lesions/healthy nerve (%)** 8.07 (1–49)  
T2DM with DPN 6.13 (0–14)  
T2DM without DPN 4.75 (0–12)  
Non-diabetic healthy control |
| Other correlations/ regressions: |                     |                                    | Hyperintense nerve lesion load vs. NDS r = 0.37, p < 0.05  
Hyperintense nerve lesion load vs. NSS r = 0.41, p < 0.05  
Hyperintense nerve lesion load vs. tibial nerve conduction velocity r = −0.23, p < 0.05  
Mean nerve cross-sectional area vs. SC level r = −0.32, p < 0.05  
Mean nerve cross-sectional area vs. LDL-C level r = −0.31, p < 0.05 |

(Continued)
| References              | Magnetic field strength (T) | Nerve/Segment                  | Measurement (spatial resolution) | Results                      | P-value                        |
|-------------------------|-----------------------------|--------------------------------|---------------------------------|------------------------------|--------------------------------|
|                         |                             |                                | Mean ± standard error (* indicates that values have been converted from the original standard deviation to standard error) |                              |                                |
| Edward et al. (2020)    | 1.5                         | Median nerve (forearm)          | Diffusion tensor imaging (resolution not specified) | Proximal median 0.49 ± 0.05  | Proximal: N.S                  |
|                         |                             |                                |                                 | Distal median 0.42 ± 0.04    | Distal: p = 0.016              |
|                         |                             |                                | Fractional anisotropy (FA)      |                              |                                |
|                         |                             |                                | T2DM with DPN                   |                              |                                |
|                         |                             |                                | Non-diabetic healthy controls   | 0.51 ± 0.10                  |                                |
|                         |                             |                                | Apparent diffusion coefficient (ADC; × 10³ mm²/s) T2DM with DPN | 0.46 ± 0.05                  |                                |
|                         |                             |                                | Non-diabetic healthy controls   | 1.196 ± 0.199                | Proximal: p = 0.027            |
|                         |                             |                                |                                 | 1.379 ± 0.209                | Distal: p < 0.001              |
|                         |                             |                                |                                 | 1.070 ± 0.112                |                                |
|                         |                             |                                |                                 | 1.149 ± 0.064                |                                |
|                         |                             |                                | Other correlations:             |                              |                                |
|                         |                             |                                | Distal median FA vs. distal radial conduction velocity | r = 0.299, p = 0.02           |
|                         |                             |                                | Distal median FA vs. sensory amplitude | r = 0.257, p = 0.048         |
|                         |                             |                                | Median FA vs. proximal radial conduction velocity | r = −0.267, p = 0.039        |
|                         |                             |                                | Distal median ADC vs. sensory amplitude | r = −0.278, p = 0.032        |
|                         |                             |                                | Distal median FA vs. neuropathy disability score | r = −0.518, p = 0.003        |
|                         |                             |                                | Distal median ADC vs. neuropathy disability score | r = 0.482, p = 0.007         |
| Jende et al. (2020b)    | 3                           | Tibial nerve (thigh)            | Diffusion tensor imaging (1.3 x 1.3 x 4.0 mm³) |                              |                                |
|                         |                             |                                | Fractional anisotropy (FA)      |                              |                                |
|                         |                             |                                | T2DM with DPN                   | 0.473 ± 0.056                | ANOVA p < 0.001 (no pairwise comparisons) |
|                         |                             |                                | T2DM without DPN                | 0.531 ± 0.038                |                                |
|                         |                             |                                | Non-diabetic healthy controls   | 0.549 ± 0.052                |                                |
|                         |                             |                                | Other correlations:             |                              |                                |
|                         |                             |                                | Tibial FA vs. neuropathy symptoms score (NSS) | r = −0.36, p = 0.009         |
|                         |                             |                                | Tibial FA vs. neuropathy disability score (NDS) | r = −0.52, p < 0.001         |
|                         |                             |                                | Tibial FA vs. tibial nerve conduction velocity* | r = 0.37, p = 0.011          |
|                         |                             |                                | Tibial FA vs. tibial amplitudes² | r = 0.57, p < 0.001          |
|                         |                             |                                | Tibial FA vs. tibial distal motor latencies* | r = −0.32, p = 0.029         |
|                         |                             |                                | Tibial FA vs. high-sensitivity Troponin T (partial correlation accounting for age and cystatin C levels) | r = −0.31, p = 0.030         |
|                         |                             |                                | o All T2DM subjects             |                                |
|                         |                             |                                | o T2DM with neuropathy²         | r = −0.61, p = 0.001         |
|                         |                             |                                | Similar data shown for Tibial FA vs. common peroneal electrophysiology (data not shown here) |                                |

(Continued)
| References                  | Magnetic field strength (T) | Nerve/Segment                  | Results                                                                 |
|----------------------------|----------------------------|--------------------------------|-------------------------------------------------------------------------|
|                            |                            |                                | Measurement (spatial resolution) Mean ± standard error (* indicates that values have been converted from the original standard deviation to standard error) |
|                            |                            |                                | P-value                                                                 |
| Vaeggemose et al. (2020)   | 3                          | Sciatic nerve (thigh) T1b nerve (calf) | Multi-echo turbo spin echo sequence (0.3 x 0.3 x 3.0 mm³)             | Sciatric                                | Tibial                                 |
|                            |                            |                                | T2 relaxometry time (ms) | A: T2DM with DPN 90 ± 5.7* 78 ± 7.6* |                                | Tibial ANOVA p = 0.02 |
|                            |                            |                                |                            | B: T2DM without DPN 84 ± 2.5* 62 ± 3.2 |                                | Sciatric ANOVA N.S. |
|                            |                            |                                |                            | C: Non-diabetic healthy controls 81 ± 1.8* 61 ± 2.7*                   |                                | All comparisons N.S. |
|                            |                            |                                |                            | D: T2DM with DPN 432 ± 25.9* 485 ± 37.3* |                                | Sciatic and tibial: |
|                            |                            |                                |                            | E: T2DM without DPN 380 ± 10.8* 548 ± 44.6* |                                | H vs. I p < 0.01 |
|                            |                            |                                |                            | F: Non-diabetic healthy controls 370 ± 18.3* 517 ± 24.8* |                                | J vs. K p < 0.001 |
|                            |                            |                                | Diffusion tensor imaging (1.36 x 1.36 x 3.0 mm³) Mean diffusivity (MD; x 10⁻³ mm²/s) |                                |                                | J vs. L p < 0.05 |
|                            |                            |                                |                            | G: T2DM with DPN | − 0.37 ± 0.02* | − 0.30 ± 0.02* | Sciatic and tibial: |
|                            |                            |                                |                            | H: T2DM without DPN | 0.51 ± 0.02* | − 0.45 * 0.02* | M vs. O p < 0.01 |
|                            |                            |                                |                            | I: Non-diabetic healthy controls | − 0.48 ± 0.01* | − 0.42 * 0.01* | P vs. Q p < 0.001 |
|                            |                            |                                |                            | J: T2DM with DPN | − 1.75 ± 0.07 | − 1.76 ± 0.08* | P vs. R p < 0.01 |
|                            |                            |                                |                            | K: T2DM without DPN | 1.47 ± 0.03* | − 1.48 ± 0.06* | Q vs. R p < 0.005 |
|                            |                            |                                |                            | L: Non-diabetic healthy controls | − 1.58 ± 0.04* | − 1.56 ± 0.04* | Sciatic only |
|                            |                            |                                |                            | M: T2DM with DPN | − 2.42 ± 0.06* | − 2.32 ± 0.07* | Sciatic and tibial: |
|                            |                            |                                |                            | N: T2DM without DPN | − 2.31 ± 0.04* | − 2.19 ± 0.06* | Sciatic and tibial: |
|                            |                            |                                |                            | O: Non-diabetic healthy controls | − 2.21 ± 0.04* | − 2.11 ± 0.03* | M vs. O p < 0.01 |
|                            |                            |                                |                            | P: T2DM with DPN | 1.41 ± 0.07* | − 1.48 ± 0.09* | Sciatic and tibial: |
|                            |                            |                                |                            | Q: T2DM without DPN | 1.05 ± 0.03* | − 1.13 ± 0.07* | P vs. R p < 0.01 |
|                            |                            |                                |                            | R: Non-diabetic healthy controls | 1.27 ± 0.04* | − 1.29 ± 0.04* | Sciatic and tibial: |

For ease of comparison we have also converted any data expressed as standard deviation to standard error, by dividing the standard deviation by square root of N. These data are marked with an * so that readers can refer back to original data if required.
content, despite clearly worsening nerve conduction studies. This led the authors to hypothesise a bell-shaped distribution, with early diabetic neuropathy being associated with an oedematous phase, which “burns out” as the disease progresses.

These studies used a mixed population of T1DM and T2DM (most of which are insulin-dependent), but the proportion of T1DM and T2DM in each group is not clear, which limits interpretation given differences in MRI signature between T1DM and T2DM shown in some later studies. These early studies also did not control for pertinent confounding variables, and demonstrated statistically significant group differences in age, gender, disease duration and cardiovascular risk factors.

It should be noted that the increased water content demonstrated here was reversed with the use of an aldose reductase inhibitor (ARI) (Griffey et al., 1988). As discussed in the introduction, despite the biochemical rationale for why these agents might be effective in DPN, meta-analyses have failed to show any clinically meaningful benefit (Chalk et al., 2007). Therefore, whilst it is possible that use of these agents would have an effect on fluid compartments of nerve tissue, and therefore measures of water content on MRI, it does draw into question the clinical relevance of this imaging biomarker given the lack of clinical efficacy of ARIs.

More recently, however, Felisaz et al. (2017) have used a 3-point Dixon (IDEAL) sequence to obtain ultra-high resolution images of the tibial nerve at the ankle, with the fat-only images best visualising the interfascicular epineurium, and the water-only images (and T1-weighted turbo spin echo, TSE) giving the best contrast of nerve fascicles. This approach allowed imaging at a very high resolution (0.11 × 0.17 × 2 mm³), and segmentation of the nerve fascicles from the surrounding epineurium. The authors were able to demonstrate increased nerve volume and fascicle volume, but also a decreased nerve-to-fascicle ratio in DPN compared with healthy controls, suggestive of expansion of the epineurial connective tissue as well as fascicular enlargement in these patients.

**T1 Relaxometry**

Shibata et al. (1998) studied 92 patients with non-insulin-dependent diabetes mellitus compared with 19 non-diabetic healthy controls using T1 relaxometry (i.e., direct measurement of the longitudinal relaxation time T1). They found higher T1 in DPN (831 ± 495 ms) compared with healthy controls (472 ± 258 ms), which the authors proposed was due to nerve oedema. The authors also reported significant positive correlations for T1 with glycaemic measures and heart rate variability (as a measure of autonomic function), and negative correlations with nerve conduction. Furthermore, they found that in a smaller group of 16 patients, T1 was reduced by nearly 50% after treatment with Epalrestat, an aldose reductase inhibitor (1,056 ± 530 ms pre-treatment; 573 ± 335 ms post-treatment), although the duration of treatment is not clear from the manuscript. Whilst measures of nerve conduction were carried out as part of this study, it is not clear from the methods how many of the patients with diabetes had a clinical diagnosis of DPN, and so it is not clear to what extent these changes represent neuropathic changes per se, or changes related to diabetes and confounding variables such as BMI. Also as was discussed above, the changes shown in this study were dramatically improved with ARI treatment, which is not thought to be effective for treating DPN.

As described above, Felisaz et al. (2017) also used a T1-weighted TSE sequence in addition to Dixon imaging to provide ultra-high resolution at 3T of 0.11 × 0.17 mm² in plane with 2 mm slice thickness, allowing separation of the nerve into fascicular and epineurial components, with findings discussed in the previous section.

**T2-Weighted and Proton Density-Weighted MRI**

T2-weighted imaging-based and T2 relaxometry are the most commonly used methods for nerve imaging in the literature to date. This has been reported in a number of different ways, the most common using T2-weighted voxel intensities, with normalisation of signal intensity to some internal (adjacent muscle) or external (healthy control nerve signal intensity) control, and then using arbitrary cut offs to define “hyperintense” or “hypointense” lesions. Pham et al. (2011) was the earliest study to demonstrate proximal T2 lesions in DPN, initially simply imaging patients with T1DM and T2DM with and without DPN, and had expert neuroradiologists review the T2-weighted images and code them as having visually apparent lesions or not. They reported that 3/10 of the patients with T2DM and DPN, and 1/2 of the patients with T1DM and DPN had observable lesions, but none of the diabetic patients without DPN (15) or healthy controls (25). They then calculated contrast ratios of T2-weighted signal intensity in nerve vs. adjacent muscle and showed increased signal intensity in those patients with visually observable lesions, compared with patients with diabetes but no DPN, or healthy controls. The latter is somewhat of an odd statistical comparison, as these subjects have by definition been chosen as having visually higher T2-weighted signal in segments of the nerve compared with their “control group” and it is not clear how this finding relates to the overall population of patients with DPN as assessed by clinical (rather than radiological) criteria. However, the same group subsequently published a paper with more objective metrics, where they normalised T2-weighted voxel intensity to age- and sex-matched healthy controls and used a cut off of >1.5x above the average normalised signal intensity to define (hyperintense) lesions. They show both proximally and distally increasing lesion burden from diabetes with no DPN (proximal 21 ± 5.5; distal 8 ± 2.9), to mild-moderate DPN (proximal 35 ± 4.0; distal 12 ± 1.8), to severe DPN (proximal 57 ± 18.4; distal 22 ± 8.1), with significantly more lesions apparent proximally compared with distally. However, the latter statistic does not seem to have been adjusted for nerve cross-sectional area, which would be expected to decrease with more distal location.

These studies only consider hyperintense lesions, but lesions with low T2-weighted signal intensity are also possible. Jende et al. (2018) took a large cohort of T1DM and T2DM with (64) and without DPN (36). They manually segmented the sciatic nerve in the thigh and defined “hyperintense” lesions as those with signal intensity 25% above adjacent muscle tissue,
FIGURE 1 | PRISMA chart. Adapted from Page et al. (2021). For more information, visit: http://www.prisma-statement.org/.
and "hypointense" as 25% below muscle tissue. Patients with DPN had significantly more hyperintense and hypointense lesions compared with those without DPN, and when splitting the DPN group according to diabetes type, there were significant more hyperintense lesions in T1DM and more hypointense lesions in T2DM. Given that hyperintense lesion load correlated with HbA1c, whereas hypointense lesion load correlated with triglycerides and HDL cholesterol, the authors propose that hyperintense lesions are due to complications of hyperglycaemia (such as production of advanced glycation end products, AGEPs), whereas hypointense lesions reflect nerve lipid deposition. Note that the $T_2$ sequence employed here uses fat suppression, so areas of nerve with lipid deposition would be suppressed causing hypointensities. The fact that areas of low $T_2$ signal correspond to high $T_1$ signal is also supportive of the hypothesis that lipid deposition is the cause of $T_2$ hypointensities in this study. Increased hyperintense and hypointense lesions in DPN compared with diabetic controls have now been replicated in a number of follow up studies (Jende et al., 2019, 2020b). These data also suggest that taking an average signal intensity as a measure of nerve pathology is fundamentally flawed if there are varying contributions of lesions with high or low signal, as a nerve with equal contributions of both may average to a normal range signal intensity.

Numerous associations have been made between lesions on $T_2$-weighted imaging and other important outcomes in DPN, including electrophysiological measures (Jende et al., 2018, 2020b; Groener et al., 2020), NDS and NSS scores (Jende et al., 2018, 2020b), quantitative sensory testing (Groener et al., 2020) and glycaemic/lipid measures (Jende et al., 2018, 2019). Jende et al. (2019) also followed up their finding of an association of $T_2$-weighted hypointense lesions with dyslipidaemia in a follow up study focusing on T2DM only. Somewhat in contrast to their previous findings in...
a mixed sample of patients with diabetes, they demonstrated a
negative correlation between hypointense lesion load and total
\((r = -0.41)\), HDL \((r = -0.30)\) and LDL cholesterol \((r = -0.33)\),
suggesting that excessive lowering of cholesterol with statin use
might actually promote DPN. This is in line with evidence that
statins may limit the supply of cholesterol required for nerve
repair (Gaist et al., 2002; Novak et al., 2015) and demonstrates the
value of MRI biomarkers in informing pathogenesis. However,
caution should be taken in interpreting this cross-sectional study,
especially in light of the clear benefit of cholesterol lowering for
macrovacular complications in diabetes (Hebert et al., 1997). Longitudinal and randomised control designs would be of benefit
to better understand this relationship.

**T2 Relaxometry**

Signal intensity in T2-weighted images is largely determined by the
transverse relaxation time \((T2)\) of the tissue and its proton
density, and some studies have calculated these more direct
measures to study pathology in DPN. Vaeggemose et al. (2017a)
calculated \(T2\) in patients with T1DM, and whilst they did not
report significant group differences, there was a trend to longer
\(T2\) for DPN in the sciatic nerve \((DPN 86 \pm 5.1\text{ ms}; control 79 \pm
3.2\text{ ms})\) and distal tibial nerve \((DPN 65 \pm 4.7\text{ ms}; control 58 \pm
3.8\text{ ms})\). The same group have reported this metric in two follow
up papers (Vaeggemose et al., 2017b, 2020), and most recently
Vaeggemose et al. (2017b) reported statistically longer \(T2\) in the
distal tibial nerve for DPN \((78 \pm 7.6\text{ ms})\) compared with diabetes
without DPN \((62 \pm 3.2\text{ ms})\) and healthy controls \((61 \pm 2.8\text{ ms})\),
with a non-significant trend in the same direction for the sciatic
nerve. It should be noted that the sample sizes in the studies by
Vaeggemose et al. are relatively modest with around 10 subjects
per group. Wang et al. (2018) used a similar technique in a mixed
group of T1DM and T2DM with a larger sample size and showed
progressively longer \(T2\) in healthy controls \((45.6 \pm 1.9\text{ ms})\)
compared to diabetic patients without DPN \((48.9 \pm 3.1\text{ ms})\) and
those with DPN \((55.1 \pm 4.1\text{ ms})\), with no relationship between \(T2\)
and HbA1c. In contrast to these findings, Pham et al. (2015) used
logistic regression to investigate whether there was a significant
difference between patients with DPN of different severities and
healthy controls and found a significant effect of proton density
\((severe\ DPN \ 360 \pm 22.9;\ controls \ 288 \pm 13.4)\), but no effect of
\(T2\) relaxation. They also showed small but significant correlations
between proton density and scores on the neuropathy disability score
\((NDS)\) and neuropathy symptom score \((NSS)\). The authors propose that the findings discussed above relating to elevated signal in \(T2\)-weighted imaging actually relate to changes in proton
density rather than \(T2\) itself, and that this suggests a change to the
macromolecular environment through, for example, production of
AGEPs, rather than due to tissue oedema. However, this is not
born out by other studies which have failed to show an effect of
proton density (Vaeggemose et al., 2017a,b; Vaeggemose et al.,
2020), although the smaller sample size of these studies should
be taken into consideration.

**Diffusion Tensor Imaging**

Diffusion tensor imaging provides various metrics that can
reflect aspects of nerve integrity, including fractional anisotropy
\((FA)\), apparent diffusion coefficient/mean diffusivity \((ADC/MD)\),
radial diffusivity \((RD)\) and axial diffusivity \((AD)\). FA is a
measure of the directionality of proton diffusion, with 0
representing isotropic diffusion and values closer to 1 indicating
a strongly preferred direction of diffusion. Due to water diffusing
preferentially along the axis of axons, nerves demonstrate higher
FA values, and a reduction indicates loss of nerve structural
integrity. Studies have consistently shown a reduction in FA in
patients with DPN compared with both healthy controls and
diabetic patients without DPN, for the sciatic nerve (Vaeggemose
et al., 2017a,b; Vaeggemose et al., 2020), tibial nerve (Vaeggemose
et al., 2017a,b; Wu et al., 2017; Vaeggemose et al., 2020; Jende
et al., 2020a), and common peroneal nerve (Wu et al., 2017),
which has been demonstrated at the thigh and ankle level.
Edward et al. (2020) also demonstrated reduced FA in the distal
median nerve in the wrist. ADC or MD is a measure of the
average diffusivity of protons across all directions, with higher
values in nerves suggesting some degree of axonal disruption
(Tievsky et al., 1999). In line with the decreased FA values, the
above studies also demonstrate increased MD values in each of
the nerves (Vaeggemose et al., 2017a,b, 2020; Wu et al., 2017;
Edward et al., 2020; Jende et al., 2020a). Importantly there seems
to be clear evidence of increased MD and decreased FA in DPN
compared with diabetes without DPN as well as healthy controls
(Vaeggemose et al., 2017a,b; Jende et al., 2020a), and worsening
of values in line with severity of DPN (Vaeggemose et al., 2017b).
Therefore, these changes seem to reflect neuropathic changes
per se, rather than changes related to diabetes.

Other important metrics can also be extracted from the
diffusion tensor. AD represents the maximum diffusivity of
protons along any axis \((i.e.,\ along\ the\ nerve\ axon)\), whereas
RD is a measure of diffusivity perpendicular to this. Early
work suggested that AD is sensitive to axonal loss and RD
to demyelination, but it is now thought to be more complex
than this, with RD also affected by demyelination, axon loss
or reduced axonal density. One study to date has investigated
these parameters in DPN, showing generally higher AD, RD
and MD in DPN compared with diabetes without DPN, and
higher for diabetes without DPN compared with healthy controls
(Vaeggemose et al., 2020). However, the authors were less
consistently able to show a significant difference between DPN
and healthy controls, in part due to the increased variance in
these measures in the DPN group and may be a reflection of the
relatively small sample size in the diabetes groups \(10\ per\ group\).

**Nerve Cross-Sectional Area**

Cross sectional area studied has most commonly been studied in
the sciatic nerve and its branches at the level of the thigh. Note
that some studies report true cross-sectional areas (Shibata et al.,
1998; Vaeggemose et al., 2017a,b, 2020), whilst others report slice
volume \((cross-sectional\ area\ \times\ slice\ thickness)\) (Pham et al., 2015;
Jende et al., 2019, 2020b). The slice volumes discussed below have
been converted to areas by dividing by slice thickness in order to
allow for comparison between studies.

Two studies by Vaeggemose et al. (2017a,b) reported CSA
for the sciatic nerve \((encompassing\ both\ tibial\ and\ peroneal\ components)\) at the level of the distal thigh. In an earlier
study (Vaeggemose et al., 2017a) there was a higher CSA for T1DM with (29 ± 2.2 mm²) and without DPN (29 ± 2.8 mm²) compared with non-diabetic healthy controls (26 ± 1.6 mm²), but this was not statistically significant. However, the sample size was only 10 per group in this study so may not have been powered for this comparison. The authors repeated this metric in a larger sample (Vaeggemose et al., 2017b) and showed statistically higher CSA in all diabetic patients (28 ± 2.4 mm² for severe DPN, 26 ± 1.4 mm² in mild DPN, and 27 ± 1.6 mm² in T1DM without DPN) compared with healthy controls (21 ± 1.1 mm²). Jende et al. (2019) also scanned the sciatic nerve at the distal thigh, but restricted analysis to the tibial component. They did not include a healthy control group but showed an increased CSA for patients with T2DM with DPN (37.1 ± 1.3 mm²) compared with those without DPN (30.6 ± 0.9 mm²). In a follow up study, the same group compared a mixed population of T1DM and T2DM with painful neuropathy (34.1 ± 1.1 mm²), painless neuropathy (36.1 ± 1.5 mm²) and no neuropathy (33.7 ± 1.51 mm²), demonstrating no statistically significant group differences (Jende et al., 2020b). However, the authors did demonstrate a negative correlation between CSA and conduction velocities of the tibial and common peroneal nerves, suggesting a relationship between CSA and nerve function, but not painful symptoms.

Pham et al. (2015) scanned the tibial and peroneal nerves of both the thigh and lower leg, and report average cross-sectional areas across the whole length of the nerve in DPN. They showed a significant group difference with ANOVA for both the tibial and common peroneal nerves. Whilst they did not report pairwise comparisons, for the tibial nerve there seems to be a stepwise increase in CSA compared to healthy controls (15.1 ± 0.4 mm²) for diabetes without DPN (17.3 ± 0.9 mm²), mild-moderate DPN (17.9 ± 0.8 mm²) and most prominently, severe DPN (21.3 ± 1.7 mm²). However, for the common peroneal nerve there only seems to be an increase from healthy controls (6.7 ± 0.3 mm²) for the severe DPN group (8.3 ± 0.9 mm²).

Finally, of studies investigating the tibial nerve CSA in the lower leg, Vaeggemose et al. (2017b) showed a higher CSA for patients with moderate DPN (9 ± 1.1 mm²) compared with both T1DM without DPN (6 ± 1.4 mm²) and healthy controls (7 ± 0.4 mm²), but this was not replicated in another study by the same group (Vaeggemose et al., 2017a). Felisaz et al. (2017) investigated distal tibial nerve structure in diabetic neuropathy using ultra-high resolution MRMRI and showed higher CSA in mild DPN (12.6 ± 1.3 mm²) and moderate-severe DPN (13.0 ± 0.9 mm²) compared with non-diabetic healthy controls (10.2 ± 0.5 mm²). Interestingly, this study obtained sufficient resolution to segment out the fascicles from surrounding epineurium and found a decreased fascicle-to-nerve ratio, most noticeable for severe DPN, suggestive of some expansion of the interfascicular epineurium as well as enlargement of the fascicles themselves. Only one study has reported sural nerve CSA in diabetes (Griffey et al., 1988), and there was no significant difference between groups noted. However, this study was published over 20 years ago using a 1.5T system, so was likely limited by available signal-to-noise ratio.

Taken together, there seems to be reasonable evidence that diabetes (type 1 and type 2) increases the cross-sectional area of nerves (whether or not neuropathy is present), but there is insufficient evidence to suggest that nerve CSA is higher in patients with DPN compared with diabetic patients without DPN, or that it tracks with severity of DPN or painful neuropathy. The values reported here for CSA of the lower extremity nerves are largely in line with the ultrasound literature with regards to healthy controls (Lee and Dauphinee, 2005; Cartwright et al., 2008; Seok et al., 2014), save for the Vaeggemose study which seem much lower (26 mm²) than values reported for the sciatic nerve at the thigh in healthy individuals (42–52 mm²). The data are also broadly in line with the ultrasound literature on DPN which shows that nerves are larger in diabetes compared with non-diabetic nerves and are larger in those with less well-controlled disease, including in those with DPN (Riazi et al., 2012; Breiner et al., 2017).

**DISCUSSION**

There is increasing interest in using MRI as a non-invasive biomarker in various neuropathies, including DPN. In this review we use systematic search tools to summarise this emerging field, with discussing biomarkers using T1-weighted, T2-weighted, proton density-weighted, relaxometry and diffusion tensor imaging. We also highlight the lack of research in HIV neuropathy. We will now discuss caveats and challenges in this field, and potential for future developments.

**Confounding Variables and Control Groups**

Choosing which confounding variables to control for with peripheral nerve imaging is difficult, as there is scarcity of evidence for how MRI metrics change with age and other demographic factors for peripheral nerve imaging compared with more commonly used imaging modalities like brain imaging. However, one study from Bendszus et al. used MR neuropathy in 60 healthy volunteers to examine the relationship with various demographic variables. For nerve CSA they found a trend towards increasing size with age, which was more pronounced at the sciatic nerve in the thigh (Kronlage et al., 2019). This finding is in agreement with some previous ultrasonographic studies showing increasing size with age (Cartwright et al., 2008). They also found a positive correlation between cross-sectional area and weight, height and BMI (Kronlage et al., 2019). T2 was not found to be associated with any demographic variable in this study, and proton density was strongly negatively correlated with weight and BMI. Proton density also had a negative correlation with age in the sciatic nerve at the thigh, possibly secondary to fatty infiltration.

In this study, gender was only moderately associated with nerve CSA, but this relationship disappeared when accounting for bodyweight. In a second study, the same group investigated demographic influences in diffusion tensor parameters (Kronlage et al., 2018), showing an age-related decrease in FA, caused
by a reduction in axial, and an increase in radial diffusivity. FA was also negatively correlated with height, weight and BMI, and there was no association with gender for any metric after accounting for bodyweight. Whilst these studies on normal controls do not seem to show evidence for an effect of gender, one MR neurography study in DPN showed that male sex was associated with higher $T_2$-weighted lesion volume in subjects with diabetic neuropathy (Groener et al., 2020). Age has also been associated with changes in other MR parameters including magnetisation transfer ratio (Kollmer et al., 2018).

Finally, in studies comparing multiple diabetes groups (e.g., with or without DPN), disease duration is an important variable to consider, as whilst various MRI measures become deranged in diabetic neuropathy per se, some studies show a difference between healthy controls and patients with diabetes without clinically apparent neuropathy (Eaton et al., 1996; Pham et al., 2011; Wang et al., 2018; Vaeggemose et al., 2020). At present it is unclear whether these changes represent subclinical neuropathic changes—and studies demonstrating an association between MR values and nerve conduction in patients with diabetes but no DPN would support this hypothesis—or incidental changes in nerve water content related to diabetes that have no effect on nerve function. Given this uncertainty, controlling for disease duration between DPN and non-DPN groups of diabetic patients would be prudent.

On a related point, the choice of control group differs between studies in the literature. Some studies compare patients with DPN to healthy controls (Shibata et al., 1998; Felisaz et al., 2017; Wu et al., 2017; Vaeggemose et al., 2020), others compare DPN to diabetes without neuropathy (Jende et al., 2018, 2019, 2020b) and other studies have both control groups (Griffey et al., 1988; Eaton et al., 1996; Pham et al., 2011, 2015; Vaeggemose et al., 2017a,b, 2020; Wang et al., 2018; Edward et al., 2020; Groener et al., 2020; Jende et al., 2020b). Including both control groups would be preferable, as this allows to distinguish changes related to diabetes and those directly related to neuropathy. However, MRI studies are expensive and resource-intensive, and sample sizes can be around 30–40 per group in well-powered studies. Therefore, of the two potential control groups, patients with diabetes without neuropathy may be the preferable choice, as these will control for confounds related to the underlying diabetic pathology including cardiovascular risk factors.

Accounting for confounding variables can be achieved in a number of ways. Firstly, groups can be “matched” for pertinent variables, most commonly done for age and gender. Alternatively, a variable can be controlled for statistically by using multiple regression or partial correlation methods. It is worth remembering for the latter approach that adding additional independent variables into a model risks compromising statistical power. Therefore, improved accounting for confounding variables by group-matching will preserve power and require smaller sample sizes.

Sample Size and Power Calculations

Our risk of bias assessment has shown that sample size estimations and power calculations are consistently absent from studies in this this field. This is likely linked to the small number of studies having been published on this subject, with only 18 studies meeting the criteria of this review to date, most of which have been published in the past 5 years. Therefore, much of the work thus far has been relatively exploratory, and it would have been difficult until recently to estimate effect sizes. Also, analysis approaches differ substantially between studies which may impact differentially on sample size requirements and experimental power. However, there are probably sufficient data now using $T_2$-weighted MRI, DTI, and measures of nerve cross sectional area to be able to make more informed decisions regarding expected effect sizes in the future. For example, with the approach taken by Jende et al. in analysis $T_2$-weighted hyperintense and hypointense lesions, group sizes of around 40 seem to be required (Cohen’s $d = 0.62$). Effect size for nerve CSA calculated from Jende et al. (2019) is slightly higher (Cohen’s $d = 0.71$), suggesting a minimum sample size of 30 per group. However, it is noteworthy that results are inconsistent between different studies for nerve CSA, with some finding no significant difference (Jende et al., 2020b). DTI studies to date have used around 10 participants per group, which is around the minimal sample size given the effect sizes in these studies (Cohen’s $d = 1.24$). Given that there seems to be trends for some metrics which did not consistently meet statistical significance (axial, radial and mean diffusivity), it may be that these studies were underpowered. Aiming for larger samples of 20–30 subjects per group in future studies may be beneficial.

Anatomy Scanned, Magnetic Field Strength, and Image Resolution

Whilst early studies in this field scanned the sural nerve at the level of the ankle (Griffey et al., 1988; Koechner et al., 1995; Eaton et al., 1996; Shibata et al., 1998), most of the studies published since 2011 have focused on the sciatic nerve and the proximal extent of one of its branches (tibial nerve, common peroneal nerve) (Pham et al., 2011; Wu et al., 2017; Jende et al., 2018, 2019, 2020b; Groener et al., 2020). The sciatic nerve at the level of the thigh is significantly larger compared with more distal nerves, making it more feasible to get sufficient resolution for analysis within the limits of current magnets and pulse sequences. Also, some studies have shown a proximal-distal gradient, with a greater number of lesions at the level of the thigh than in the calf, both for lesion-load on $T_2$-weighted imaging (Pham et al., 2015), and fractional anisotropy measures (Vaeggemose et al., 2017a,b). This gradient seems to add to symptoms in DPN, which seem to have a more distal predominance. However, respective authors note that the multifocal involvement of the fascicles of the thigh would correspond to histopathological findings seen at this location (Dyck et al., 1986). Some studies have also investigated more distal nerves such as distal tibial and common peroneal nerves (Pham et al., 2015; Felisaz et al., 2017;
Vaeggemose et al., 2017a,b, 2020; Wu et al., 2017), the sural nerve (Griffey et al., 1988; Koechner et al., 1995; Eaton et al., 1996; Shibata et al., 1998), and the median nerve in the arm (Edward et al., 2020).

In terms of magnetic field strength, all included studies used a 3 T MRI system, except for the earliest studies in the 1980’s and early ’90s (Griffey et al., 1988; Koechner et al., 1995; Eaton et al., 1996; Shibata et al., 1998) and one more recent diffusion tensor imaging study (Edward et al., 2020). This has allowed excellent spatial resolution and anatomic detail to be obtained for the relatively small structures imaged, with resolutions of around 0.3 × 0.3 mm² to 0.5 mm² in-plane, using 3–4 mm slice thickness for T₂-weighted imaging (Pham et al., 2011, 2015; Vaeggemose et al., 2017a,b, 2020; Wu et al., 2017; Jende et al., 2018, 2019, 2020b). Studies using DTI have typically obtained a resolution of 1.25 × 1.25 mm² to 1.36 × 1.36 mm² in-plane resolution using slice thicknesses of 3–4 mm (Vaeggemose et al., 2017a,b, 2020; Wu et al., 2017; Jende et al., 2020a). One exception to the above is a study by Felisz et al. (2017), who performed Dixon imaging in the distal tibial nerve at 3 T, using a spoiled gradient sequence with IDEAL, and by using a very restricted field of view they were able to push to a resolution of 0.117 × 0.143 × 2 mm³. This impressive resolution is at the limit of what is currently achievable with 3 T systems. The authors were able to segment the nerve into fascicles and epineurium, demonstrating compartment-specific changes in DPN. However, it is worth noting that all of the studies in the field so far have sacrificed resolution in the slice direction (by having greater slice thickness) to provide optimal in-plane resolution. Whilst improving SNR, this will also create partial volume effects in the slice direction, leading to some small lesions potentially being missed.

Methods of Image Segmentation and Analysis

Analysing the MR indices described above generally requires a segmentation of nerve tissue from non-nerve tissue, so that the given index (e.g., signal intensity, T₂, measures of diffusivity) can be calculated. While some of these techniques, such as DTI, use pre-existing software (generally adapted from brain imaging), which use in-built (semi)-automated segmentation, all studies focusing on T₂-weighted MRI use an initial fully manual segmentation (Felisz et al., 2017; Vaeggemose et al., 2017a,b, 2020; Jende et al., 2018, 2019, 2020b; Groener et al., 2020), generally performed by trained neuroradiologists with experience of nerve imaging. Manual segmentation is extremely time consuming and will become more so with the availability of higher resolution imaging. When multiple researchers are performing segmentation, it is also important to show intra- and inter-rater reliability, which is generally not discussed in papers to date. If the expectation is that segmenters should have substantial clinical training in neuroradiology, this is an unnecessary barrier to carrying out nerve imaging research. Therefore, adapting (semi)-automated algorithms from brain imaging research or creating custom algorithms for nerve imaging should be a research priority over the coming years.

Finally, in terms of methods of analysis the greatest variability in the literature comes from T₂-weighted MRI. Whilst it is possible to calculate absolute T₂ and proton density values (Pham et al., 2015; Wu et al., 2017; Vaeggemose et al., 2020), the required sequences are often more time consuming, but can give useful information about the source of T₂-weighted signal intensity and shed light on the underlying pathophysiology. Another approach has been to take T₂-weighted signal intensities and average them over an area of nerve to compare between groups (Pham et al., 2011), or to identify values above a cut of as “hyperintense lesions” (Pham et al., 2015). These approaches are problematic in light of subsequent data from Jende et al. (2018), demonstrating convincingly that there are areas of both hyper- and hypointense lesions, possibly reflecting different pathogenic mechanisms. Therefore, any assessment using T₂-weighted MRI should assess both of these lesion types.

Future Directions

A number of priorities for future directions are apparent from the above review of available literature. The first relates to the fact there are no published studies on HIV neuropathy, despite 18 studies to date having developed MRI biomarkers of DPN. Broadening the scope of research to other forms of neuropathy, including HIV and chemotherapy-induced neuropathy, would allow us to answer questions on how specific these biomarkers are to DPN, or whether they represent nerve damage across a range of aetiologies. There is also significant debate about the pathological underpinnings of the changes apparent in diabetic neuropathy using MRI. Comparing and contrasting MRI signatures of neuropathies of different aetiologies, with different underlying pathological processes, may help to shed light on this issue.

Similarly, longitudinal imaging will also be of great value. By comparing the same patients at multiple timepoints we will be able to track the evolution of MRI changes and relate them to changes in other biomarkers and clinical assessments. This will also be a more powerful way to study if there are objective imaging changes which occur when transitioning from absence to presence of neuropathy, potentially allowing for the development of pre-symptomatic biomarkers which predict the risk of developing clinical neuropathy. Some researchers have already begun to investigate whether MRI can detect specific changes in the nerve that relate to the development of neuropathic pain (Jende et al., 2020b). Longitudinal imaging comparing patients before and after the development of neuropathic pain, or with increasing severities of neuropathic pain, would be a powerful tool in this regard. As discussed above, the single time point design used by previous studies led to difficulties in interpreting causal relationships between blood biomarkers and MRI signatures of neuropathy, for example whether high or low serum lipids confer increased risk of developing neuropathy (Jende et al., 2019). Tracking these relationships over time in cohort studies would help clarify.
In terms of technical aspects, ultra-high field MRI (e.g., 7T) is becoming increasingly available and will allow even greater signal-to-noise, and therefore spatial resolution, than the current body of research discussed above. Feliszaz et al. (2017) have pushed the resolution at 3T to its extreme, achieving a resolution of 0.117 × 0.147 × 2 mm³ using $T_1$-weighted and Dixon imaging. At this level, the authors offer a tantalising glimpse at fascicular resolution nerve imaging with the ability to segment out structures within the nerve. Improving further on this resolution will allow more in-depth understanding of how individual nerve compartments change structurally over the course of DPN. The improved resolution available at 7T will also be able to probe whether the increased proximal density of hyperintense and hypointense lesions shown in previous studies (e.g., Pham et al., 2015) is a true representation of the pathology in DPN, or is simply related to decreased sensitivity for picking up lesions at the smaller, distal extent of nerves when imaging at lower field strength. Finally, whilst there are methods for functional brain imaging to obtain indirect measures of activity of brain tissue, no such techniques exist yet for nerve imaging. There are numerous reasons for this, for example the clear neurovascular coupling which exists in the brain, with spatio-temporal relationships. Similar blood-flow measures are unlikely to be of value in nerve imaging. That is not, however, to say that measures will not be able to be developed which probe the ability of nerves to function, and we refer readers to the paper in this edition by Jende et al. (2021), exploring DTI as a surrogate measure of nerve function.

**PROTOCOL AND REGISTRATION**

The protocol used in this systematic review was published a priori on the University of York/National Institute of Health Research (NIHR) international prospective register of systematic reviews (PROSPERO) at the following link https://www.crd.york.ac.uk/ PROSPERO/display_record.php?RecordID=167322.

In the original published protocol (Evans et al., 2020), we had aimed to search until Jan 16th 2020. However, preparation of this review was delayed by the coronavirus pandemic, and we therefore decided to extend the search to include the most up to date journal articles. Otherwise, the study was carried out as described in the original protocol.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/subsupplementary material, further inquiries can be directed to the corresponding author/s.

**AUTHOR CONTRIBUTIONS**

ME, CW, AR, and DS were involved in overall structure and concept for review. Data collection/extraction and analysis by ME, CW, DH-S, AU, and KS. Manuscript writing by ME. All authors contributed to editing of manuscript.

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Conflict of Interest: AR undertakes consultancy and advisory board work for Imperial College Consultants- in the last 24 months this has included remunerated work for: Abide, Confo, Vertex, Pharmano, Lateral, Novartis, Mundipharma, Orion, Shanghai SIMR Biotech, Asahi Kasei, Toray & Theranexis. AR was the owner of share options in Spinifex Pharmaceuticals from which personal benefit accrued upon the acquisition of Spinifex by Novartis in July 2015 and from which future milestone payments may occur. AR is also named as an inventor on patents: AR, Vandevoorde S., and Lambert D. M Methods using N-2-propenylhexadecanamide and related amides to relieve pain. WO 2005/079771. Okuse K. et al. Methods of treating pain by inhibition of vgf activity EP13702262.0/ WO2013 110945.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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