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The role of novel inflammation-associated biomarkers in diabetic peripheral neuropathy

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ABSTRACT

Diabetic neuropathy is one of the commonest complications of diabetes mellitus. Its most frequent form is diabetic peripheral neuropathy (DPN). Currently, there is no established and widely used biomarker for diagnosis and clinical staging of DPN. There is accumulating evidence that low-grade systemic inflammation is a key element in its pathogenesis. In this context, several clinical studies have so far identified potential biomarkers of DPN. These studies have enrolled both subjects with type 1 diabetes mellitus (T1DM) and subjects with type 2 diabetes mellitus (T2DM), including children with T1DM and elderly T2DM subjects. They have also evaluated participants with prediabetes. Potential biomarkers include a wide spectrum of cytokines, chemokines and immune receptors, notably interleukins (IL), mostly IL-1, IL-6 or IL-10, as well as mediators of the tumour necrosis factor-α (TNF-α) related pathway. Cell-ratios, such as neurtrophil-to-lymphocyte ratio (NLR), have yielded promising results as well. Other works have focused on adipokines and identified several signalling molecules (adiponectin, neuregulin 4, isthmin-1 and omentin) as promising biomarkers of DPN. Finally, epigenetic biomarkers have been investigated. Further experience is being gathered with the use of biomarkers in specific age groups and in the discrimination between painless and painful DPN. Prospective studies appear promising in monitoring of DPN progression, but experience is rather limited. Finally, certain cut-off values have been proposed for DPN screening, but these need confirmation. Future large-scale studies are now required to validate biomarkers and to investigate their potential clinical utility.

1. Introduction

Diabetic neuropathy is one of the commonest complications of diabetes mellitus (DM), occurring both in type 1 diabetes mellitus (T1DM) and in type 2 diabetes mellitus (T2DM) subjects globally [1]. Its most frequent form is distal symmetrical polyneuropathy (DSPN), also called diabetic peripheral neuropathy (DPN) [2]. Of note, up to 50 % of subjects with DSPN may not present symptoms [3]. Currently, there is no established and widely used biomarker for its diagnosis and staging [3,4].

Low-grade systemic inflammation appears to play a role in the pathogenesis of DSPN [5]. Specific inflammatory pathways emerge as promising, including the pathways associated with the tumour necrosis factor-α (TNF-α) or certain interleukins (IL) [5]. It has been suggested that the interplay between these effectors may provide key elements both in the prevention of diabetes-related complications or even identify novel therapeutic targets [5,6].

Therefore, the aim of this review was to outline current research on inflammatory-associated biomarkers in subjects with DPN.

2. Search strategy

We searched Scopus, PubMed, MEDLINE, and Google Scholar for articles from January 01, 2014 until September 29, 2024, using combinations of the following key words: “diabetic neuropathy”, “polyneuropathy” “diabetic peripheral neuropathy”, “Distal symmetrical polyneuropathy”, “type 1 diabetes mellitus”, “type 2 diabetes mellitus”, “inflammation”. All types of articles (clinical trials, meta-analyses, case-control studies, observational studies, cross-sectional studies, prospective/retrospective studies, cohort studies, comparative studies, randomized trials) were included. Articles on autonomic neuropathy were excluded. Only articles in English were considered.

3. Inflammatory-associated makers in biopsy assays

In an observational clinical study, walking-associated symptoms

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were identified as early symptoms in the course of DM, whereas clinical neurophysiology assays and subsequent biopsies could also confirm neuronal dysfunction, such as demyelination, axonal degeneration and perivascular inflammation [7].

A further study based on sural biopsies assessed 30 subjects with chronic idiopathic axonal polyneuropathy (CIAP) subjects, 28 subjects with DPN and 31 healthy individuals [8]. No significant correlation between CIAP and DPN was shown, based on the number of CD68 or CD8 (CD, cluster of differentiation) positive cells per fascicle ($p = 0.4$) [8]. However, the study confirmed the involvement of inflammation in the pathogenesis of DSPN, as evidenced by the infiltration of inflammatory cells in the biopsies [8].

Kan et al. [9] studied sural nerve biopsies of 28 T2DM subjects and 6 healthy controls. Significant macrophage and T-cell infiltration, as well as an increase in $CD40^+$ cells, expression levels of HIF-1α, mitogen-activated protein kinase activated protein kinase 2 (ML2/MAPKAPK2) and phosphatase and tensin homolog (PTEN) were seen. In another biopsy work [10], macrophage density had a discriminatory capacity both for the diagnosis of neuropathy (as it was significantly increased vs. controls, $p < 0.001$) and for its nature. As regards the latter, a significantly ($p < 0.001$) increased macrophage density was seen in the painful DPN group compared with the painless DPN group [10].

The impact of the complement system was also considered. Yell et al. [11] retrospectively assessed 63 nerve biopsies from DM subjects (with correlated 26 muscle biopsies) and 54 nerve biopsies from subjects without DM (with correlated 18 muscle biopsies). They demonstrated microvascular C5b-9 deposition in 87 % of the nerve and 92 % of the muscle biopsies of DM subjects, but only in 34 % of the nerve 50 % of the muscle biopsies of controls. Differences between the two groups were significant only for microvascular C5b-9 reactivity in both biopsy types ($p < 0.0001$ for nerve and $p = 0.002$ for muscle biopsies), pointing to a role of the complement system in the pathophysiology of DPN [11]. All aforementioned studies are summarised in Table 1.

Table 1
Biopsy-based studies involving inflammatory-associated makers.

Authors	Study design	Major outcomes	Conclusions
Thaisetthawatkul et al. (2018) [7]	Observational study	-Limb mobility weakness and abnormal gait were observed early in the course of DM -Electrophysiological assays and subsequent biopsies confirmed both demyelination and axonal degeneration	-Perivascular inflammation could be documented and was improved under immunotherapy
Hube et al. (2017) [8]	Observational study (30 CIAP subjects, 28 DSPN subjects and 31 healthy individuals)	-In sural nerve biopsies, no statistically significant differences could be established between the 2 conditions in the number of CD68 or CD8 positive cells per fascicle ($p = 0.4$)	-The infiltration of inflammatory cells in the biopsies of DSPN confirms the involvement of inflammation in the pathogenesis of the condition
Kan et al. (2018) [9]	28 T2DM subjects and 6 healthy controls	-In sural nerve samples, significant macrophage and T-cell infiltration, as well as an increase in $CD40^+$ cells, expression levels of HIF-1α, ML2/MAPKAPK2 and PTEN could be documented	-Inflammatory infiltrates are strongly linked with nerve degeneration in DPN
Gylfadottir et al. (2021) [10]	60 skin biopsies, 30 with painful DPN and 30 with DPN	-A significantly increased macrophage density could be assessed in the painful DPN group compared with the painless DPN group ($p < 0.001$) and the macrophage density was significantly increased than in the healthy control group ($p < 0.001$)	-The increased macrophage density indicates the involvement of inflammation in the pathogenesis of DPN
Yell et al. (2018) [11]	Retrospective study (63 nerve biopsies from DM subjects with correlated 26 muscle biopsies, 54 nerve biopsies from subjects without DM with correlated 18 muscle biopsies)	−87 % of the nerve biopsies and 92 % of the muscle biopsies from DM subjects exhibited microvascular C5b-9 deposition −34 % of the nerve biopsies and 50 % of the muscle biopsies from the control arm exhibited microvascular C5b-9 reactivity	-C5b-9 deposition was statistically significantly more frequently observed in nerve ($p < 0.0001$) and muscle ($p = 0.002$) biopsies from DM subjects

DM, diabetes mellitus; DPN, diabetic peripheral neuropathy; CIAP, chronic idiopathic axonal polyneuropathy; DSPN, distal symmetric polyneuropathy; CD, cluster of differentiation; HIF-α, hypoxia-inducible factor; ML2/MAPKAPK2, mitogen-activated protein kinase activated protein kinase 2; PTEN, Phosphatase and tensin homolog.

4. Micronutrient deficiency

Gautam et al. [12] assessed 4 micronutrients (zinc; vitamin B12; copper and magnesium) in a cross-sectional study of 130 DM subjects, 28 of whom had DPN. Only Zn ($p = 0.02$) and vitamin B_{12} ($p = 0.008$) were significantly correlated with DPN. Micronutrient deficiency is considered essentially involved in blood vessel inflammation and thereby may be associated with microvascular diabetes-related complications, including peripheral DPN [12].

5. Cytokines and other inflammatory markers

Several inflammatory biomarkers have repeatedly been found significantly elevated among subjects with DPN. An overview of the studies is provided in Table 2. Duksal et al. [13] found significantly increased TNF-α and significantly decreased IL-10 levels among DM subjects with neuropathy compared with DM subjects without neuropathy ($p < 0.001$) [13].

Another study included 217 DM subjects classified into 3 neuropathy groups (sensory polyneuropathy with hypaesthesia or hyperaesthesia or motor neuropathy), 26 DM subjects without neuropathy and 375 subjects without DM [14]. IL-6 and IL-10 levels were found significantly higher among subjects suffering from neuropathy [14]. Significantly increased IL-6 and IL-10 levels and significantly decreased neutrophil-to-lymphocyte ratio (NLR) ($p < 0.05$) were found in 30 subjects with painful DPN, as compared with 10 healthy individuals [17]. Circulating levels of vascular cell adhesion molecule (VCAM), intercellular cell adhesion molecule (ICAM) and E-selectin were also observed significantly increased among subjects with neuropathy in the same study, whereas decreased levels of nerve growth factor (NGF) were found among subjects with DM [17].

Bäckryd et al. [15] conducted 2 cohorts exploration-replication study of data from 180 participants from Pain in Neuropathy study in each cohort. By use of an inflammation panel assessing 92 inflammation-related proteins, 14 inflammatory biomarkers were associated with neuropathy and particularly with painful neuropathy. The 3 major proteins associated with DPN in both cohorts were HGF (hepatocyte growth factor), CSF1 (colony stimulating factor 1) and CD40 [15].

Genetic studies have provided further evidence on the role of

Table 2
Studies involving cytokines and further inflammatory markers.

Authors	Study design	Major outcomes	Conclusions
Duksal et al. (2016) [13]	Observational study (50 subjects with prediabetes, 50 DM subjects and 44 individuals in the control arm)	-Significantly lower sensory nerve action potential amplitude and nerve conduction velocity were observed for both dorsal sural and medial plantar among DM subjects ($p < 0.001$) -Significantly higher TNF-α and statistically significantly lower IL-10 levels were observed among subjects with DPN compared to subjects without DPN ($p < 0.001$)	-TNF-α and IL-10 emerge as major biomarkers in DPN and show the potential role of inflammation in the pathogenesis of DPN
Carbajal-Ramírez et al. (2017) [14]	Cross-sectional study (217 DM subjects classified in 3 DPN groups [sensory polyDPN with hypoesthesia or hyperesthesia or motor DPN], 26 DM subjects without DPN, 375 subjects without DM)	-Decreased levels of NGF were observed among subjects with DM -IL-6 and IL-10 were found significantly higher among subjects suffering from DPN -The circulating levels of several adhesion molecules (VCAM, ICAM and E-selectin) were also observed significantly increased among subjects with DPN	-DM subjects with DPN exhibit substantial changes in inflammatory markers and cell adhesion molecules
Bäckryd et al. (2022) [15]	2 cohorts exploration-replication study (180 participants from Pain in DPN study in each cohort)	-By using an inflammation panel (simultaneous measurement of 92 inflammation-related proteins), 14 inflammatory biomarkers were associated with DPN and particularly with painful DPN -The top 3 proteins in both cohorts were HGF, CSF1 and CD40	-Low-grade systemic inflammation is associated with DPN severity and pain among subjects with distal symmetrical DPN
Wang et al. (2024) [16]	Two-sample Mendelian Randomization study assessing 41 inflammatory cytokines	-IFN-γ (OR = 1.31 [95 %CI: 1.06–1.63]; $p = 0.014$) and Interferon γ-induced protein 10 (CXCL10) (OR = 1.18 [95 %CI: 1.01–1.36]; $p = 0.031$) were significantly associated with an increased risk for DPN development -Elevated levels of IL-9 (OR = 0.86 [95 %CI: 0.75–1.00]; $p = 0.048$) (OR = 0.86 [95 %CI: 0.75–1.00]; $p = 0.048$) and stem cell factor (OR = 0.83[95 %CI: 0.73–0.94]; $p = 0.003$) were found to act in a protective way	−4 upstream inflammatory cytokines were found directly involved in DPN
Akintoye et al. (2018) [17]	Comparative study (30 subjects with painful DPN and 10 healthy individuals)	-The pain threshold was observed significantly diminished among subjects with peripheral DPN ($p < 0.05$) -IL-6 and IL-10 levels were also found statistically significantly increased and NLR significantly decreased ($p < 0.05$)	-Ongoing inflammation in peripheral DPN impairs pain perception
Ocak et al. (2022) [18]	Comparative study (54 subjects with peripheral DPN and 53 healthy individuals)	-The variant rs2119882 was found to have a protective role for DPN ($p = 0.022$) -rs13140012 was linked to a 5-fold increased risk for neuroparthy ($p = 0.034$)	-Melatonin, through its anti-inflammatory action affects DPN occurrence
Liao et al. (2023) [19]	Cross-sectional study (120 T2DM subjects and 60 controls)	-Serum ISM1 levels were found significantly increased in T2DM subjects ($p < 0.001$) -After binary logistic regression, serum ISM1 emerged as a risk factor for T2DM ($p = 0.001$) -Lower ISM1 levels were observed in T2DM subjects with peripheral DPN, without however reaching statistical significance ($p > 0.05$)	-ISM1 could not be linked to DSPN
Karahmet et al. (2021) [20]	Comparative study (90 DM subjects and 30 healthy individuals)	-IL-6 levels were significantly higher among healthy individuals ($p = 0.0001$) -A significant correlation could be established between IL-6 and the youngest DM subjects with the shortest diabetes duration (<10 years) ($p = 0.0001$), but not to subjects with increased diabetes duration	-IL-6 levels are indicative of inflammatory response and the study confirms the increased inflammatory response capacity of younger DM subjects, which is exacerbated upon disease progression
Herder et al. (2017) [21]	Comparative study (133 subjects with DSPN, 397 without DSPN; 57 subjects with DSPN assessed for disease progression with a mean follow-up period of 6.5 years)	-Increased hs-CRP, IL-6, TNF-α, IL-1 receptor antagonist, siCAM-1 and lower adiponectin levels were significantly associated with DSPN (for all $p < 0.05$) -IL-18 ($p = 0.992$) and omentin ($p = 0.706$) levels were not correlated to DSPN -After adjustment for acknowledged DSPN risk factors, both IL-6 (OR 1.31 [95 % CI 1.00–1.71]) and TNF-α (OR 1.31 [95 % CI 1.03–1.67])were also regarded as biomarkers for DSPN -sICAM-1 and IL-1RA could also be considered as biomarkers in a clinical risk model	-Inflammation is key in the pathogenesis of DSPN and thus inflammatory pathways should be considered for possible therapeutic applications
Schamarek et al. (2016) [22]	Observational study (352 T2DM subjects and 161 T1DM subjects with a recent DM diagnosis)	-Increased serum IL-6 levels could be associated with DSPN occurrence (model 1, $p = 0.028$; model 2, $p = 0.058$; model 3, $p = 0.039$) and diminished NCV (model 1, $p = 0.001$; model 2, $p = 0.005$; model 3, $p = 0.006$) for T2DM subjects	-The involvement of subclinical inflammation in the DSPN pathogenesis is confirmed through the IL-6 assessment and can be further correlated to electrophysiological outcomes

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Table 2 (*continued*)

Authors	Study design	Major outcomes	Conclusions
		-Increased HMW-adiponectin (model 1, $p = 0.021$; model 2, $p = 0.005$; model 3, $p = 0.007$), total adiponectin (model 1, $p = 0.016$; model 2, $p = 0.006$; model 3, $p = 0.005$) and their ratio (model 1, $p = 0.077$; model 2, $p = 0.045$; model 3, $p = 0.032$) were also overall correlated to DSPN and,in the 3rd model to decreased motor and sensory NCV ($p = 0.048$ for total adiponectin and $p = 0.037$ for HMW adiponectin) for T2DM subjects -No statistically significant correlations could be established for CRP, IL-18, sICAM-1 and E-selectin ($p > 0.05$) -For T1DM subjects, only HMW adiponectin (model 1, $p = 0.004$; model 2, $p = 0.001$; model 3, $p = 0.001$) and total adiponectin (model 1, $p = 0.004$; model 2, $p = 0.001$; model 3, $p = 0.001$) were significantly correlated to a motor NCV reduction	
Herder et al. (2015) [23]	Observational study (47 T2DM subjects with sensorimotor polyDPN and 168 T2DM subjects without sensorimotor polyDPN with an age range between 61 and 82 years)	-Serum omentin levels were found negatively significantly correlated to polyDPN ($p = 0.043$) -Omentin levels were further found significantly correlated to adiponectin ($p < 0.001$) and TNF-α ($p < 0.001$)	-Reduced levels of omentin, an adipokine with anti-inflammatory properties are observed among older T2DM subjects and thus indicate active subclinical inflammation
Zheng et al. (2020) [24]	Prospective cohort study (315 T2DM subjects without DPN with an average follow-up period of 5.06 years)	−63 out of 106 selected subjects developed DPN after 5.06 years -Plasma levels of TNF-α, IL-6 and ICAM -1 were significantly higher in the subjects with DPN ($p < 0.05$) -After adjustment for known DPN factors, TNF-α and ICAM-1 emerged also significantly elevated in subjects with DPN ($p < 0.05$)	-Increased levels of proinflammatory factors may predict precisely DPN incidence
Kallestrup et al. (2015) [25]	Case-control study (22 T2DM subjects, 8 out of which with DPN and 12 control subjects)	-Soluble CD163 levels were found significantly increased both in the CSF and serum of T2DM subjects ($p < 0.01$) -Nerve conduction studies associated significantly increased CD163 levels in the CSF to diminished peripheral nerve function ($p = 0.0497$) - Higher CD163 were observed both in the CSF and serum of T2DM subjects with peripheral DPN, without however reaching statistical significance ($p = 0.06$)	-Inflammation plays a major role in peripheral neural impairment among T2DM subjects
Albeltagy et al. (2019) [26]	Cross-sectional study (60 T2DM subjects and 30 healthy individuals)	-PRGN levels were found significantly increased in T2DM subjects ($p < 0.001$) -PRGN levels were found significantly increased in T2DM subjects with DPN compared to those without ($p < 0.001$)	-PRGN, a recently established marker for inflammation in T2DM, could serve as an index for DPN
Kocak et al. (2020) [27]	Observational study (50 T2DM subjects with microvascular complications and 29 T2DM subjects without microvascular complications)	- Significantly lower Nrg4 levels were obtained for T2DM subjects with microvascular complications ($p < 0.001$) -An one unit decrease in Nrg4 levels corresponded to an almost twofold increase in microvascular complications presence (1.9 times increase), according to logistic regression analysis - The cut-off for the clinical implementation of the index was assessed at 1.56 ng/ml with sensitivity at 82.1 % and specificity at 64 %	-Nrg4, a novel adipokine also responsible for chronic inflammation reduction, emerges as a marker for diabetes-related microvascular complications
Bourgonje et al. (2023) [28]	Longitudinal cohort study (145 T2DM subjects without microvascular complications at baseline with a mean follow up period of 3.2 years)	-GlycA levels could be significantly correlated to microvascular complications ($p = 0.048$) (also after adjustments for confounding factors) and to hs-CRP levels ($p = 0.001$) -hs-CRP levels could not be correlated to microvacular complication incidence ($p = 0.792$)	-GlycA, a novel inflammatory glycoprotein, which has been associated with recent T2DM onset and may serve as a biomarker for microvascular complications
Abdulrhaman et al. (2024) [29]	Case-control study (140 DM subjects)	-TNF-α and TGF-β levels were found significantly decreased among DM subjects with peripheral DPN -For TNF-α, sensitivity was assessed at 95.7 %, specificity at 61.4 % and area under the curve at 0.870 - For TGF-β, sensitivity was assessed at 91.4 %, specificity at 67.1 % curve at 0.891	-Both indices could serve as biomarkers for the development of diabetic peripheral DPN
Mussa et al. (2021) [30]	Single-center cross-sectional study (102 T2DM subjects)	-MCP-1 levels were found significantly increased in T2DM subjects with peripheral DPN ($p = 0.002$ or $p = 0.007$ after adjustment) -IL-8 levels were found significantly increased in T2DM subjects with peripheral DPN ($p = 0.008$) -TGF-β levels were found decreased inT2DM	-MCP-1 emerges as a crucial biomarker for T2DM subjects with peripheral DPN and IL-8, as well as TGF-β levels may predict the MCP-1 increase

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Table 2 (*continued*)

Authors	Study design	Major outcomes	Conclusions
		subjects with peripheral DPN, without reaching significance ($p = 0.06$)	
Zhu et al. (2017) [31]	Comparative study (18 T2DM subjects, 20 T2DM subjects with DPN and 19 healthy individuals)	-Increased expression of TLR4, MyD88, phosphorylated IκB, TNF-α and IL-6 in the subjects with DPN ($p < 0.01$ or $p < 0.05$) -Significantly decreased caveolin-1 levels and IκB levels were found in the subjects with DPN ($p < 0.01$) -TNF-α and IL-6 were significantly positively associated with TLR4 expression and negatively with caveolin-1 in subjects with DPN - TLR4 levels were negatively associated with caveolin-1 in subjects with peripheral DPN	-Diminished caveolin-1 expression in monocytes exacerbates TLR-4 pathways in subjects with DPN
Zeng et al. (2018) [32]	Observational study (55 subjects with prediabetes, 55 T2DM subjects, 48 subjects in the control arm)	-TNF-α levels emerged significant increased in DM subjects compared to controls ($p < 0.001$) and in subjects with prediabetes compared to DM subjects ($p < 0.001$), but not in subjects with prediabetes compared to controls ($p = 0.056$) -IL-10 emerged statistically significant decreased in DM subjects compared to controls ($p < 0.001$), in subjects with prediabetes compared to controls ($p < 0.001$) and in subjects with prediabetes compared to DM subjects ($p < 0.001$) -A significant overall increase in TNF-α levels and a decrease in IL10 levels was documented among subjects with DPN compared to subjects without DPN (both $p < 0.001$)	-The elevation of pro-inflammatory cytokines and the decrease in anti-inflammatory cytokines, even during prediabetes, indicates the direct involvement of inflammation in the pathogenesis of the condition
Yu et al. (2017) [33]	Observational clinical and experimental study (154 T2DM subjects with matched controls- 40 streptozocin induced diabetes rats)	-lncRNA NONRATT021972 levels were found increased among T2DM subjects ($p < 0.05$) -Logistic regression analysis indicated that lncRNA NONRATT021972 exacerbated neuropathic pain -TNF-α levels were significantly increased among T2DM subjects ($p < 0.05$)and increased TNF-α levels were significantly correlated to higher lncRNA NONRATT021972 levels ($p < 0.05$) - lncRNA NONRATT021972 siRNA administration improved significantly both glucose levels and TNF-α levels in STZ-induced diabetic rats ($p < 0.05$) and alleviated the neuropathic pain observed	- lncRNA NONRATT021972 emerges as a novel biomarker in T2DM and promotes its action through TNF-α signaling pathways
Ristikj-Stomnaroska et al. (2019) [34]	Comparative study (50 subjects with DPN with an age range between 30 and 80 and 30 healthy individuals with an age range between 18 and 45 years)	-Significantly increased TNF-α levels were observed in subjects with DPN ($p < 0.0001$) -Average levels of TNF-α could be also correlated to DNS score ($p = 0.005$)	-Inflammatory mechanisms play a major role in the pathogenesis of DPN

DM, diabetes mellitus; DPN, diabetic peripheral neuropathy; TNF, tumor necrosis factor; IL, interleukin, VCAM, vascular cell adhesion molecule; ICAM, intercellular cell adhesion molecule; HGF, hepatocyte growth factor; CSF1, colony stimulating factor 1; CD, cluster of differentiation; IFN, interferon; CXCL10, interferon γ-induced protein 10; OR, odds ration; CI, confidence interval; NLR, neutrophil to lymphocyte ratio; ISM-1, isthmin 1; siCAM-1, soluble intercellular adhesion molecule; hs-CRP, high sensitive C-reactive protein; DSPN, distal symmetric polyDPN; IL-1RA,interleukin 1 receptor antagonist; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; HMW, high molecular weight; NCV, nerve conduction velocity; CRP, C-reactive protein; CSF, cerebrospinal fluid; CI, confidence interval; PRGN, progranulin; Nrg4, neuregulin 4; MCP-1, monocyte chemoattractant protein 1; TLR, toll-like receptor; MyD88, Myeloid differentiation primary response 88; lncRNA, long non-coding RNA; siRNA, small-interfering RNA; STZ, streptozocin; DNS, DPN Symptom; NGF, nervous growth factor.

inflammatory cytokines. Wang et al. [16] conducted a two-sample Mendelian randomization study assessing 41 inflammatory cytokines. IFN-γ (Interferon γ) (odds ratio [OR]: 1.31, 95 % confidence interval [CI]: 1.06–1.63; $p = 0.014$) and Interferon γ-induced protein 10 (CXCL10) (OR: 1.18, 95 % CI: 1.01–1.36, $p = 0.031$) were significantly correlated with increased risk of DPN development [16]. On the contrary, elevated levels of IL-9 (OR: 0.86, 95 % CI: 0.75–1.00, $p = 0.048$) and stem cell factor (OR: 0.83, 95 % CI: 0.73–0.94, $p = 0.003$) were found to act in a protective way [16].

Ocak et al. [18] revealed that certain melatonin variants have a particular influence on neuropathy development and speculated that this impact is mediated through the anti-inflammatory properties of the hormone [18]. The variant rs2119882 was protective for neuropathy development ($p = 0.022$), while rs13140012 was linked with a 5-fold increased risk of neuropathy ($p = 0.034$) [18].

Karahmet et al. [20] focused on IL-6 in a study of 90 DM subjects and 30 healthy individuals. Among DM subjects, increased IL-6 levels were associated with younger age and shorter diabetes duration (<10 years) ($p = 0.0001$) and a further correlation between this particular study group and the prevalence of DPN was also established ($p = 0.0001$) [20]. These findings point to the role of IL-6 as an inflammatory response marker among younger study participants [20].

The importance of CD163 was considered in a case-control study evaluating 22 T2DM subjects (8 of whom had neuropathy) and 12 controls [25]. Soluble CD163 levels were significantly increased both in cerebrospinal fluid (CSF) and in serum of T2DM subjects ($p < 0.01$). Significantly increased CD163 levels in CSF were linked with electrophysiological nerve parameters ($p = 0.0497$) [25]. Insignificantly higher CD163 were observed both in CSF and serum of T2DM subjects with DPN [25].

Schamarek et al. [22] included recently diagnosed 352 T2DM subjects and 161 T1DM subjects. They used multiple models to attenuate the effect of confounding factors. Increased serum IL-6 levels were correlated with DSPN prevalence (model 1, $p = 0.028$; model 2, $p = 0.058$; model 3, $p = 0.039$) and diminished nerve conduction velocity (NCV) (model 1, $p = 0.001$; model 2, $p = 0.005$; model 3, $p = 0.006$) for T2DM subjects [22]. In the case of HMW-adiponectin, increased levels (model 1, $p = 0.021$; model 2, $p = 0.005$; model 3, $p = 0.007$), total adiponectin (model 1, $p = 0.016$; model 2, $p = 0.006$; model 3, $p = 0.005$) and their ratio (model 1, $p = 0.077$; model 2, $p = 0.045$; model 3,

p = 0.032) were also correlated with DSPN. CRP, IL-18, sICAM-1 and E-selectin had no significant correlation. Among T1DM subjects, only HMW adiponectin (model 1, p = 0.004; model 2, p = 0.001; model 3, p = 0.001) and total adiponectin (model 1, p = 0.004; model 2, p = 0.001; model 3, p = 0.001) were significantly correlated with motor NCV reduction [22].

In the KORA F4/FF4 Study [21], increased hs-CRP, IL-6, TNF-α, IL-1RA, sICAM-1 (soluble intercellular adhesion molecule) and lower adiponectin levels were strongly associated with DSPN occurrence ($p < 0.05$). After adjustment for acknowledged DSPN risk factors, both IL-6 (OR: 1.31, 95 % CI: 1.00–1.71) and TNF-α (OR: 1.31, 95 % CI: 1.03–1.67) were correlated with DSPN [21]. For IL-18 (p = 0.992) and omentin (p = 0.706) levels, no statistical significance could be established [21]. Despite these findings, a previous study initiated by the same research team concluded that the levels of this particular adipokine yielded reliable results among older subjects with T2DM suffering from DPN [23].

Among elderly subjects with T2DM, Herder et al. [23] showed that significantly decreased omentin levels were observed in subjects with polyneuropathy(p = 0.043) and that serum omentin levels were significantly associated with adiponectin levels ($p < 0.001$) and TNF-α levels ($p < 0.001$) [23]. Omentin appears to exert its function through the inflammatory NF-κB, Akt and AMPK-related pathways [35].

Beyond omentin, further adipokines have been considered as potential biomarkers for DPN [21,23]. Neuregulin 4 (Nrg4), a brown-tissue derived adipokine with anti-inflammatory properties associated with DM, obesity, non-alcoholic fatty liver and cardiovascular disease has been assessed as a biomarker for DPN [36–38]. Yan et al. [39] showed significantly decreased Nrg4 levels among T2DM subjects and a further significant decrease among T2DM subjects with DPN ($p < 0.01$). For screening purposes, a cut-off value of 1.58 ng/mL yielded 90.91 % sensitivity, 54.55 % specificity and area under the curve 0.716 were observed by the researchers [39].

Kocak et al. [27] included 50 T2DM subjects with microvascular complications and 29 T2DM subjects without microvascular complications. The former exhibited significantly diminished Nrg4 levels ($p < 0.001$). In logistic regression analysis, 1 unit decrease in Nrg4 levels corresponded to an almost twofold increase in microvascular complications occurrence (1.9 times increase) [40]. For screening purposes, a 1.56 ng/ml cut-off value of Nrg4 yielded 82.1 % sensitivity and 64 % specificity [27].

Moreover, non-significantly reduced levels of isthmin-1 (ISM1), a novel adipokine with immune-regulating properties in promoting the immune cell apoptosis, have been found in T2DM subjects with neuropathy compared with those without this complication [19,41].

A major prospective study was conducted by Zheng et al. [24] in 2020 in order to evaluate possible changes in the level of inflammatory biomarkers and their impact on DPN development and progression. In a course of a 5.06 years follow-up period, 63 out of 106 selected subjects developed neuropathy [24]. Their plasma levels of TNF-α, IL-6 and ICAM -1 were assessed and were significantly elevated in the subjects with neuropathy ($p < 0.05$) [42]. After adjusting for recognised neuropathy risk factors, TNF-α and ICAM-1 levels ($p < 0.05$) were significantly associated with DPN incidence [24].

6. TNF-α and TGF-β inflammatory pathways

In a case-control study, Abdulrhaman et al. [29] demonstrated significantly decreased TNF-α and TGF-β levels among DM subjects with DPN. For screening purposes, TNF-α yielded 95.7 % sensitivity, 61.4 % specificity and area under the curve 0.870; TGF-β yielded at 91.4 % sensitivity, 67.1 % specificity and area under the curve 0.891 [29].

Conversely, in a cross-sectional study of 102 T2DM subjects, Mussa et al. [30] found insignificantly decreased TGF-β levels in T2DM subjects with DPN (p = 0.06) [30]. However, MCP-1 (monocyte chemoattractant protein 1) levels (p = 0.002) and IL-8 levels (p = 0.008) were significantly increased in T2DM subjects with DPN [30].

Ristikj-Stomnaroska et al. [34] included 50 subjects with DPN aged 30–80 years and 30 healthy individuals aged 18–45 years. TNF-α levels were significantly increased in subjects with neuropathy ($p < 0.0001$). Average levels of TNF-α were associated with clinical severity of neuropathy (p = 0.005) [34].

Zhu et al. [31] evaluated 18 T2DM subjects without neuropathy, 20 T2DM subjects with neuropathy and 19 healthy individuals. Subjects with neuropathy exhibited increased TNF-α and IL-6 levels, decreased caveolin-1 levels and IκB levels, as well as increased expression of TLR4, MyD88, phosphorylated IκB ($p < 0.01$ or $p < 0.05$) [31]. Caveolin-1, an integral membrane protein found in membrane caveolae, is involved in insulin secretion and signalling [43]. As this particular has been linked to insulin resistance, a potential role in diabetic complications has been suggested [43]. TNF-α and IL-6 were also significantly positively correlated with TLR4 expression and negatively with caveolin-1 in subjects with neuropathy [31].

Apart from cytokines, researchers considered further inflammatory-associated effectors. Bourgonje et al. [28] studied the novel biomarker GlycA, a pro-inflammatory glycoprotein. This showed a significant correlation with microvascular complications (p = 0.048) and with hs-CRP levels (p = 0.001) [28]. Finally, progranulin (PRGN), a recent inflammatory marker was assessed in a cross-sectional study (60 T2DM subjects and 30 healthy individuals) [26]. It was significantly elevated in T2DM subjects ($p < 0.001$) [26]. PRGN levels were found also significantly increased in T2DM subjects with neuropathy compared to those without ($p < 0.001$) [26].

7. Inflammatory markers in T1DM subjects with DPN

Several studies attempted to unravel suitable biomarkers for the screening of DPN among subjects with T1DM (Table 3). Okdahl et al. [44] evaluated cytokines (IL-1α, IL-4, IL-12p70, IL-13, IL-17A and TNF-α), chemokines (MCP-1) and adhesion molecules (E-selectin) among 50 T1DM subjects with DPN, 50 T1DM subjects without DPN and 21 healthy individuals. A significant correlation was found for all these factors (with the exception of MCP-1) in subjects with DPN (for all $p < 0.01$) [44].

In a cross-sectional study including 694 T1DM subjects, two soluble tumor necrosis factor receptors sTNFRI (p = 0.00001) and sTNFRII (p = 0.0027), sIL2Rα (soluble interleukin 2 receptor) (p = 0.0023), IGFBP6 (insulin growth factor binding protein 6) (p = 0.0032) and CRP (p = 0.0046) were significantly associated with DPN after adjustment for confounding factors [45]. In addition, significantly increased levels of sTNFRI ($p < 1.5x10^{-15}$), sTNFRII ($p < 1.5x10^{-15}$), IGFBP6 ($p < 7.1x10^{-8}$), IGFBP2 ($p < 5.7x10^{-6}$) and MMP2 (metalloproteinase 2) ($p < 9.4x10^{-5}$) were associated with increased risk of DPN [45].

In a cross-sectional study of 56 adolescents with T1DM and 23 healthy individuals, TNF-α levels were significantly increased among adolescents with DM and large-fibre neuropathy (p = 0.03) [49]. Furthermore, they were significantly negatively associated with nerve conduction velocity of the tibial nerve (p = 0.04) [49].

Chemokines may also serve as biomarkers for DPN in T1DM [46]. Baldimtsi et al. [46] conducted a cross-sectional study based on a long-term longitudinal cohort study with 52 participants (11 of whom had neuropathy) and examined the potential utility of CXCL8 (chemokine (C-X-C motif) ligand), CXCL9 and CXCL10. Only increased CXCL9 levels were associated with neuropathy (p = 0.019) [46]. However, the 2 other chemokines assessed could be correlated with neuropathic symptoms: CXCL10 levels were significantly associated with decreased sural maximal conduction velocity ($p < 0.001$) and increased sural sensory nerve action potential (p = 0.034), while CXCL8 levels were significantly negatively associated with cold perception threshold (p = 0.032) [46].

Ashjari et al. [51] evaluated the Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)/miR-1-3p/CXCR4. MALAT1 (p =

0.03) and CXCR4 ($p = 0.023$) expression levels were increased, whereas miR-1-3p expression levels were decreased ($p = 0.023$) in 20 T2DM subjects with neuropathy, as compared with healthy individuals [51]. MALAT1 expression levels were also associated with CXCR4 expression levels ($p < 0.0001$) [51].

In T1DM subjects, chitotriosidase levels indicative of active inflammation, were significantly associated with the presence DPN ($p < 0.001$) [50]. Chitotridase has been proposed as a potential biomarker for diabetic complications, primarily, but not exclusively for cardiovascular complications [40]. Finally, Hansen et al. [47] reported that a twofold increase in PRO-C6 (pro-peptide of type VI collagen) levels was associated with increased risk of DSPN.

8. Inflammatory markers in T2DM subjects with DPN

The potential clinical significance of inflammatory-related biomarkers for the evaluation of DPN in T2DM subjects has drawn the attention of multiple research teams. An overview of the studies is provided in Table 4.

Gökçay Canpolat et al. [52] included 180 T2DM subjects and assessed major inflammatory biomarkers, such as CRP and monocyte to high-density lipoprotein ratio (MHR). Significantly increased serum CRP levels were found among subjects with DPN ($p = 0.008$) and were an independent prognostic predictor for the presence of DPN ($p = 0.026$) [52]. However, there was no correlation between MHR, which is in general considered to be indicative of active inflammatory status, and DPN prevalence ($p = 0.447$) [52].

Another study including 25 T2DM subjects with neuropathy and 25 T2DM subjects without neuropathy showed the major role of the nuclear factor kappa B (NF-κB) transcription factor [53]. This was significantly higher among DM subjects with neuropathy. It was also significantly associated with total neuropathy score (TNS) ($p < 0.001$) [53]. After adjustment for potential confounding factors, TNS was an independent determinant of NF-κB levels ($p < 0.001$) [53].

In a monumental study, Ziegler et al. [42] compared the involvement of several inflammatory markers in 3 groups: 304 T2DM subjects with DSPN, 158 T2DM subjects without DSPN and 354 subjects with polyneuropathy and normal glucose tolerance. Overall, 17 inflammatory markers were significantly lower in subjects with T2DM and DSPN: the cytokines Oncostatin M, TNFSF10 (tumor necrosis factor superfamliy 10), TRAIL (TNF-related apoptosis-inducing ligand), TNFSF12 (TWEAK), TNFSF14 (LIGHT); the chemokines CCL4 (CC chemokine ligand 4), MIP-1β (macrophage inflammatory protein 1β), CCL8 (MCP-2, monocyte chemoattractant protein 2), CCL28 (MEC, mucosa-associated epithelial chemokine), CXCL1 (MGSA-α, melanoma growth stimulating activity α), CXCL11 (I-TAC, Interferon-inducible T-cell alpha chemoattractant); the growth factors HGF (hepatocyte growth factor), TGF-α (tansforming growth factor α), LAP-TGFβ1 (latency-associated peptide tansforming growth factor β1), Neurotrophin-3; receptors: TNFRSF5 (tumor necrosis factor receptor superfamily 5) (CD40), DNER (Delta and Notch-like epidermal growth factor-related receptor); and AXIN1, MMP1 (metalloproteinase 1) [34]. Nevertheless, these inflammatory markers could not show any discriminatory potential between painless and painful DSPN [42].

Visceral fat area (VFA) measured by a human body composition analyser has been linked with DPN in T2DM subjects in a retrospective study by Sun et al. [54]. They included overall 488 T2DM subjects, 207 of whom had DPN. VFA levels were associated with DPN ($p < 0.05$) and could be further identified as a risk factor for the prevalence of DPN ($p < 0.05$) [54].

9. Inflammatory markers in prediabetes

Zeng et al. [55] included 55 subjects with prediabetes, 55 T2DM subjects and 48 controls. TNF-α levels were significantly increased in DM subjects compared with controls ($p < 0.001$) and in subjects with prediabetes compared with DM subjects ($p < 0.001$), but not in subjects with prediabetes compared with controls ($p = 0.056$) [55]. In contrast to previous studies, IL-10 levels were significantly decreased in DM subjects compared with controls ($p < 0.001$), in subjects with prediabetes compared with controls ($p < 0.001$) and in subjects with prediabetes compared with DM subjects ($p < 0.001$) [55]. An increase in TNF-α levels and a decrease in IL-10 levels was documented among subjects with neuropathy compared with those without neuropathy (both $p < 0.001$) [55].

10. Cell ratios in DPN

In a retrospective study, Liu et al. [32] were the first to report increased neutrophil-to-lymphocyte ratio (NLR) in association with DPN ($p < 0.05$). NLR was also significantly associated with vibration perception threshold ($p < 0.05$) and nerve conduction velocity ($p < 0.05$) [32]. A retrospective study by Fawwad et al. [56] featuring 5620 T2DM subjects further confirmed the utility of NLR as a general index of at least one microvascular complication prevalence ($p < 0.0001$).

The significance of NLR as an inflammatory biomarker for DPN was confirmed in a systematic review and meta-analysis by Rezaei Shahrabi et al. [57] ($p < 0.001$). The geographical distribution was also addressed in the study: increased NLR was observed in India ($p = 0.006$) and East Asia ($p < 0.001$), but not in studies conducted in Turkey ($p = 0.104$) or Egypt ($p = 0.165$) among subjects with DPN [57]. The overall sensitivity and sensitivity of NLR as an index were assessed at 0.67 (95 % CI = 0.49–0.81) and at 0.70 (95 % CI, 0.56–0.81), respectively [57]. The positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio (DOR) of NLR were found at 2.30 (95 % CI: 1.71–3.09), 0.45 (95 % CI: 0.30–0.67), and 5.06 (95 % CI: 3.16–8.12), respectively [57].

A further small study also confirmed the clinical significance of multiple indices: NLR, CRP, sedimentation rate, platelet-to-lymphocyte ratio (PLR) and mean platelet volume (MPV) were statistically significantly associated with DPN. In addition, the study associated the NLR to the neuropathic symptoms, as evidenced by DN4 (Douleur Neuropathique en 4 Questions) score [58]. The DN4 questionnaire is considered a validated tool for DPN screening and the score is calculated based on a combination of subjective (interview of the patient) and objective (physical examination) findings regarding neuropathic pain [59].

In a recent retrospective study of over 700 T2DM subjects, AlShareef et al. [60] confirmed significantly increased NLR levels ($p = 0.011$) and lymphocyte count ($p = 0.028$) among T2DM subjects in general. The research team managed to associate HbA_{1c} with PLT (platelets) ($p = 0.037$) and PLT/MCH (mean corpuscular haemoglobin) ratio ($p = 0.004$) and negatively with MCV (mean corpuscular volume) ($p < 0.001$) and MCH ($p < 0.001$) among other indices [60]. Nevertheless, the NLR could not be significantly correlated to DPN in this particular study ($p = 0.814$) [60].

A retrospective cross-sectional study by Li et al. [61], including more than 1000 T2DM subjects showed however no correlation with DPN for 3 indices (Systemic immune-inflammation index (SII) (calculated as platelet count X neutrophil/lymphocyte count) ($p = 0.299$), NLR ($p = 0.827$) and PLR ($p = 0.938$). Nevertheless, a regression analysis for 181 subjects with a diagnosis of DPN unravelled a significant association between DPN prevalence and NLR ($p = 0.016$) [61].

Conversely, in a cross-sectional study of 1460 T2DM subjects by Li et al. [62], systemic SII was significantly positively linked with DPN ($p < 0.01$). Elevated SII was significantly associated with higher vibration perception threshold ($p < 0.01$) [62]. T2DM subjects in the highest SII quartile exhibited a significantly increased risk for neuropathy development compared with those in the lowest quartile, even after adjustment for confounding factors ($p < 0.05$) [53]. A SII cut-off of 617.67 yielded 45.3 % sensitivity and 73 % specificity [62].

Wang et al. [63] introduced a new ratio-based biomarker, the white blood cell to mean platelet volume ratio (WMR). In a cross-sectional study of 2515 T2DM subjects, WMR was significantly associated with

Table 3
Studies assessing inflammatory-associated biomarkers among T1DM subjects.

Authors	Study design	Major outcomes	Conclusions
Purohit et al. (2021) [45]	Cross-sectional study (694 T1DM subjects)	-For 15 out of 22 inflammatory markers studied, the crude ratios established a significant link to diabetic neuropathy -After adjustment for confounding factors, the levels of sTNFRI ($p = 0.00001$), sTNFRII ($p = 0.0027$), sIL2Rα ($p = 0.0023$), IGFBP6 ($p = 0.0032$) and CRP ($p = 0.0046$) were significantly associated with peripheral neuropathy -Significantly increased levels of sTNFRI ($p < 1.5x10^{-15}$), sTNFRII ($p < 1.5x10^{-15}$), IGFBP6 ($p < 7.1x10^{-8}$), IGFBP2 ($p < 5.7x10^{-6}$) and MMP2 ($p < 9.4x10^{-5}$) were correlated to increased risk for diabetic neuropathy	-Increased levels of these inflammatory markers indicate potential inflammatory pathways in the pathogenesis of diabetic neuropathy in T1DM subjects
Baldimtsi et al. (2023) [46]	Cross-sectional study based on long-term longitudinal cohort study (52 T1DM subjects, 11 out of which with neuropathy)	-Significantly increased CXCL9 levels were found in subjects with neuropathy ($p = 0.019$) -CXCL10 levels were significantly associated with decreased sural maximal conduction velocity ($p < 0.001$) and increased sural sensory nerve action potential ($p = 0.034$) -CXCL8 levels were negatively significantly associated with cold perception threshold ($p = 0.032$)	-Several chemokines, associated with Th1 and Th17 related pathways are linked to peripheral nerve impaired function and related parameters in early-onset T1DM subjects
Hansen et al. (2023) [47]	Cross-sectional study (300 T1DM subjects)	-Twofold PRO-C6 levels were associated with increased odds ratio for DPN (>1)	-Certain collagen markers are associated with DPN
Elbarbary et al. (2018) [48]	Observational study (60 T1DM subjects under 18 years of age and with a minimum diabetes duration of 5 years)	−40 out of 60 (66.7 %) T1DM subjects suffered from peripheral neuropathy -Nerve conduction studies confirmed the diagnosis for 30 T1DM subjects -Neopterin levels were found significantly increased among subjects with peripheral neuropathy compared with subjects without neuropathy ($p < 0.01$) -Neopterin levels were correlated with significantly with hs-CRP levels ($p = 0.012$) among other commonly assessed indices -Nerve conduction studies indicated a statistical significant correlation between neopterin levels and the assessed parameters (latency, amplitude and velocity) for the left tibial (mostly $p < 0.001$) and the right common peroneal nerve ($p < 0.001$) -The cut-off for the clinical implementation of the index was assessed at 32 nmol/L with sensitivity at 100 %, specificity at 96.7 % and area under the curve at 0.989	-Neopterin, a biomarker indicative of inflammation and elevated with increased T-cell and macrophage activity, emerges a significant tool for peripheral neuropathy assessment in pediatric patients
Rasmussen et al. (2023) [49]	Cross-sectional study (56 adolescents with T1DM and 23 healthy individuals)	-Significantly increased IFN-γ, TNF-α, IL-10 and suPAR levels were observed among DM subjects compared with the individuals in the control arm ($p < 0.05$) -TNF-α levels emerged substantially increased among adolescents with DM and large-fiber neuropathy ($p = 0.03$) -The nerve conduction velocity in nervus tibialis emerged significantly decreased in relation to increased TNF-α levels ($p = 0.04$) -Gastric motility index was associated with TNF-α ($p = 0.03$) and IL-6 levels ($p = 0.02$) -The area under the curve for the markers was assessed between 0.47 and 0.67	-Low-grade inflammation, assessed through inflammatory biomarkers, is particularly observed among adolescents with DM and large fiber neuropathy

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Table 3 (*continued*)

Authors	Study design	Major outcomes	Conclusions
Okdahl et al. (2020) [44]	Cross-sectional study (50 T1DM subjects with peripheral neuropathy, 50 T1DM subjects without peripheral neuropathy and 21 healthy individuals)	-The assessed inflammatory markers (cytokines: IL-1α, IL-4, IL-12p70, IL-13, IL-17A and TNF-α, chemokine MCP-1 and the adhesion molecule E-selectin) were observed statistically significantly increased among T1DM subjects with peripheral neuropathy compared with subjects without (for all $p < 0.01$ apart from MCP-1 $p < 0.15$)	-Systemic low-grade inflammation is involved in the pathogenesis of DPN, as denoted by the increased inflammatory markers in T1DM subjects
Cutaş et al. (2021) [50]	Observational study (82 T1DM subjects, 48 out of which with neuropathy)	-Increased chitotriosidase levels were significantly linked to diabetic neuropathy ($p = 0.000$) -No statistically significant correlation could be established between neopterin levels and peripheral neuropathy ($p = 0.645$)	-Chitotriosidase, as a marker for inflammatory status may identify subjects with neuropathy

T1DM, type 1 diabetes mellitus; sTNFR, soluble tumor necrosis factor receptor; sIL2R, soluble interleukin 2 receptor; IGFBP, insulin growth factor binding protein; CRP, C-reactive protein; MMP, metalloproteinase; PRO-C6, pro-peptide of type VI collagen; DPN, diabetic peripheral neuropathy; IFN, interferon; TNF, tumor necrosis factor; IL, interleukin; suPAR, soluble urokinase plasminogen activator receptor; MCP, monocyte chemoattractant protein; hs-CRP; high sensitive C-reactive protein; DM, diabetes mellitus; CXCL, chemokine (C-X-C motif) ligand.

DPN ($p < 0.05$) (9). A WMR cut-off of 0.5395 yielded 65.4 % sensitivity, 41.8 % specificity and area under the curve 0.540 [63]. Table 5 summarises studies assessing cell-ratios.

11. Common blood test markers and their potential use as DPN markers

Established clinical markers, indicative of inflammation may serve as biomarkers for DPN. Aktas [65] has proposed a new index, the C-reactive protein to albumin ratio (CAR) index. The index levels were found at 2.19 % and 0.56 % for subjects with DPN and without DPN, respectively [65]. The subsequent analysis confirmed the significance of CAR as a biomarker for DPN, as significantly elevated CAR levels were observed in subjects with DPN ($p < 0.001$) and CAR emerged as an index of DPN risk ($p < 0.001$) [65]. A CAR cut-off of 1.02 % yielded 78 % sensitivity, 73 % specificity and area under the curve 0.84 [65].

Calprotectin, another commonly used inflammatory biomarker, was evaluated in a study including 29 T2DM with neuropathy, 30 T2DM subjects without neuropathy and 40 healthy individuals [66]. Calprotectin ($p < 0.01$ and $p = 0.017$, respectively) and hs-CRP ($p < 0.001$ and $p = 0.001$, respectively) levels were significantly increased in T2DM subjects with neuropathy and without neuropathy, as compared with controls [66]. In T2DM, subjects with neuropathy had higher serum calprotectin ($p = 0.021$) and hs-CRP ($p < 0.001$) than those without this

Table 4
Studies assessing inflammatory-based markers among T2DM subjects.

Authors	Study design	Major outcomes	Conclusions
Gökçay Canpolat et al. (2019) [52]	Observational study (180 T2DM subjects)	-Serum CRP levels were found significantly increased among subjects with peripheral neuropathy ($p = 0.008$) - MHR was not correlated to DPN ($p = 0.447$) -Serum CRP levels may be considered as an independent prognostic predictor for the presence of DPN ($p = 0.026$)	-Although MHR is indicative of active inflammation, no correlation could be established to DPN
Priyadarsini et al. (2024) [53]	Comparative study (25 T2DM subjects with neuropathy and 25 T2DM subjects without neuropathy)	-Serum NF-κB levels emerged higher among DM subjects with neuropathy - NF-κB levels could be significantly associated with TNS ($p < 0.001$) -After adjustment for confounding factors, the TNS could serve as an independent determinant of NF-κB levels ($p < 0.001$)	-The transcription factor NF-κB levels emerges as a major diagnostic biomarker, as inflammation is linked to DPN progression
Ashjari et al. (2022) [51]	20 T2DM subjects with neuropathy and 20 T2DM subjects	-MALAT1 ($p = 0.03$)and CXCR4 ($p = 0.023$) expression levels were found increased, whereas miR-1-3p expression levels were found decreased ($p = 0.023$) - MALAT1 expression levels were associated with CXCR4 expression levels($p < 0.0001$)	-The MALAT1/miR-1-3p/CXCR4 inflammatory pathway is involved in the DPN pathogenesis
Ziegler et al. (2019) [42]	Cross-sectional study (304 T2DM subjects with DSPN, 158 T2DM subjects without DSPN and 354 subjects with polyneuropathy and normal glucose tolerance)	-From the 18 inflammatory markers assessed (cytokines: Oncostatin M, TNFSF10 (TRAIL), TNFSF12 (TWEAK), TNFSF14 (LIGHT); chemokines: CCL4 (MIP-1β), CCL8 (MCP-2), CCL20 (MIP-3α), CCL28 (MEC), CXCL1 (MGSA-α), CXCL11 (I-TAC); growth factors: HGF, TGF-α, LAP-TGFβ1, Neurotrophin-3; receptors: TNFRSF5 (CD40),	-The observed changes in the inflammatory markers indicate the significant impact of inflammation on peripheral neuropathy, without however any discriminatory capacity between painful and painless neuropathy

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Table 4 (*continued*)

Authors	Study design	Major outcomes	Conclusions
		DNER; miscellaneous: AXIN1, MMP1), all apart from CCL20 were significantly decreased among subjects with T2DM and DSPN compared with the other groups ($p < 0.05$) -Other cytokines and inflammatory markers assessed did not yield differences between the T2DM subjects with and without neuropathy -No significant differences in biomarkers could be observed between painless and painful DSPN	
Sun et al. (2024) [54]	Retrospective study (488 T2DM subjects, 207 out of which with neuropathy)	-VFA levels were associated with peripheral neuropathy in T2DM subjects ($p < 0.05$) -VFA levels were identified as a risk factor for the prevalence of peripheral neuropathy ($p < 0.05$)	-VFA levels are associated with inflammation among other conditions and is further linked to peripheral neuropathy

T2DM, type 2 diabetes mellitus; DPN, diabetic peripheral neuropathy; CRP, C-reactive protein; MHR, monocyte to high-density lipoprotein ratio; CRP, C-reactive protein; NF-κB, nuclear factor kappa B; TNS, total neuropathy score; TNF, tumor necrosis factor; IL, interleukin; T1DM, type 1 diabetes mellitus; DM, diabetes mellitus; MCP, monocyte chemoattractant protein; DSPN, distal symmetric polyneuropathy; TNFSF, tumor necrosis factor superfamliy; TRAIL, TNF-related apoptosis-inducing ligand; CCL,CC chemokine ligand; MIP, macrophage inflammatory protein; MEC, mucosa-associated epithelial chemokine; MGSA-α, melanoma growth stimulating activity α, CXCL, chemokine (C-X-C motif) ligand; I-TAC, Interferon-inducible T-cell alpha chemoattractant; HGF, hepatocyte growth factor; TGF, tansforming growth factor; LAP, latency-associated peptide; TNFRSF, tumor necrosis factor receptor superfamily DNER, Delta and Notch-like epidermal growth factor-related receptor; MMP, metalloproteinase; VFA, visceral fat area; CD, cluster of differentiation; CXCL, chemokine (C-X-C motif); MALAT1, metastasis-associated lung adenocarcinoma transcript 1.

complication [66].

Total bilirubin (TBIL) was evaluated in a cross-sectional study of 1342 T2DM subjects [67]. TBIL was significantly decreased in T2DM subjects with DPN ($p < 0.01$ or $p < 0.05$) [67]. TBIL was negatively associated with VPT ($p < 0.01$ or $p < 0.05$) [67]. After adjustment for confounding factors, TBIL emerged as an independent risk factor for DPN: subjects in the lowest quartiles exhibited a significantly increased risk of neuropathy, compared with those in the highest quartiles ($p < 0.01$) [67]. A TBIL cut-off of 10.75 μmol/L yielded 54.6 % sensitivity and 62.9 % specificity [67].

Demirtas et al. [68] proposed lymphocyte count as an additional index for DPN. They included 307 DM subjects (104 subjects with DPN). Lymphocyte count was lower in subjects with compared with those without neuropathy ($p = 0.046$) [68]. El-Samahy et al. [69] showed that particularly the lymphocyte cells expressing the markers $CD4^{+}CD28^{null}$ were strongly associated with DPN ($p < 0.05$).

Furthermore, urinary secretory phospholipase 2 (sPLA2) was assessed in a prospective study of 90 DSPN subjects [70]: sPLA2 levels were significantly higher in subjects with at least one impairment in nerve conduction velocity ($p < 0.01$) [70]. Accordingly, sPLA2 might help towards identification of a subgroup of DSPN subjects with demyelination, but further experience is required [70].

12. Inflammatory markers in children with DPN

In a study including 100 T1DM children (of whom 12 had neuropathy) and 100 healthy children, significantly increased NLR ($p < 0.001$) and significantly decreased PLR ($p = 0.005$) were observed among children with vs. those without microvascular complications [64]. In regression analysis, both indices were significantly associated with the presence of microvascular complications (NLR, $p = 0.013$; PLR, $p = 0.004$) [64].

Elbarbary et al. [48] studied neopterin in a study including 60 T1DM subjects (of whom 40 had DPN) under 18 years of age and with a minimum diabetes duration of 5 years. Significantly increased neopterin levels were noted in subjects with DPN compared to subjects without neuropathy ($p < 0.01$) [48]. Nerve conduction studies showed a significant correlation between increasing neopterin levels and electrophysiological impairment in the left tibial (mostly $p < 0.001$) and in the right common peroneal nerve ($p < 0.001$) [19]. A neopterin cut-off of 32 nmol/L yielded 100 % sensitivity, 96.7 % specificity and area under the curve 0.989 [48].

13. The perspective of epigenetics

The effect of epigenetics on the pathophysiology of DPN is being increasingly considered. A combined clinical and basic research study by Yu et al. [33] assessed the importance of a long non-coding RNA, lncRNA NONRATT021972 in humans (154 T2DM subjects and 154 matched controls) and in 40 streptozocin induced diabetic rats. lncRNA NONRATT021972 levels were significantly ($p < 0.05$) increased among T2DM subjects compared with controls. In logistic regression analysis, lncRNA NONRATT021972 aggravated neuropathic pain [33]. In addition, TNF-α levels were significantly ($p < 0.05$) increased among T2DM subjects. Increased TNF-α levels were significantly associated with higher lncRNA NONRATT021972 levels ($p < 0.05$) [33]. The latter indicated interplay between the 2 effectors [30]. In streptozotocin-induced diabetic rats, lncRNA NONRATT021972 siRNA administration resulted in a significant reduction of TNF-α levels and of neuropathic pain [33].

14. Discussion

This review has summarised original studies over the last decade on novel inflammatory-associated diagnostic approaches and biomarkers in DPN. Multiple studies have provided evidence that low-grade systemic inflammation is crucial in the initiation and progression of DPN. Persistent inflammation is documented by the increased levels of established inflammatory markers (e.g. CRP or hs-CRP, sedimentation rate) and appears to be mediated by many effectors [21,45,52,58]. The latter cover a wide range: from widely known inflammatory proteins, like interleukins and/or chemokines, to adipokines, less known proteins unravelled by genetic studies or even epigenetic effectors.

The 4 major and repeatedly studied cytokines were IL-1, IL-6, IL-10 and TNF-α. However, results have been conflicting. Indeed, some studies found increased levels of these cytokines in association with DPN, while others linked decreased levels with this condition [13,14,49]. Such discrepancies could be documented in the assessment of cell ratios as well: while most studies have supported NLR as a reliable biomarker [32,56–58], two studies were negative [60,61]. Large-scale studies could identify those subpopulations with DPN and reliable NLR levels and validate further the association of NLR to neuropathic symptoms.

Moreover, several chemokines (such as CXCR4, CXCL9, CXCL10, CXCL8 and MCP-1) have been studied. Again, there has been no consensus, given that results have not been consistent. For example, Mussa et al. [30] showed that MCP-1 levels correlated to DPN, while Okdahl et al. [44] showed the exact opposite. Of note, some chemokines could be correlated to certain clinical neurophysiological parameters according to Baldimitsi et al. [46]: CXCL10 could be associated with nerve conduction velocity, whereas CXCL8 was linked with cold perception.

Other parameters studied include adipokines, such as adiponectin (in

Table 5
Studies involving cell-ratios.

Authors	Study design	Major outcomes	Conclusions
Li et al. (2024) [61]	Retrospective cross-sectional study (1058 T2DM subjects)	-SII ($p = 0.299$), NLR ($p = 0.827$) and PLR ($p = 0.938$) were not significantly correlated to DPN -The regression analysis for 181 subjects with DPN showed an important correlation particularly for NLR ($p = 0.016$)	-The NLR emerges as a significant index for DPN
Liu et al. (2017) [32]	Retrospective study (T2DM subjects divided into tertiles according to NLR)	-The rate of subjects with DPN ($p < 0.05$), the vibration perception threshold ($p < 0.05$) and the nerve conduction velocity ($p < 0.05$) were significantly correlated to the NLR	-NLR, a major index of chronic inflammation, indicates the stage of DPN
Rezaei Shahrabi et al. (2023) [57]	Systematic review and meta-analysis	-The meta-analysis confirmed the importance of NLR as an index for peripheral DPN ($p < 0.001$) -Increased NLR was observed in India ($p = 0.006$) and East Asia ($p < 0.001$), but not in studies conducted in Turkey ($p = 0.104$) or Egypt ($p = 0.165$) among subjects with peripheral DPN - The overall sensitivity and sensitivity of NLR as an index was found at 0.67 (95 % CI = 0.49–0.81), at 0.70 (95 % CI, 0.56–0.81), respectively - The positive likelihood ratio, negative likelihood ratio, DOR of NLR were assessed at 2.30 (95 % CI = 1.71–3.09), 0.45 (95 % CI = 0.30–0.67), and 5.06 (95 % CI = 3.16–8.12), respectively.	-NLR emerges as major inflammatory index of DPN and shows the major impact of inflammation in the development of the condition
Mustafa et al. (2023) [58]	Comparative study (44 healthy subjects, 46 DM subjects without polyneuropathy, 44 subjects with DPN confirmed through electroneuromyography)	-NLR, CRP, sedimentation rate, PLR and MPV were statistically significantly associated with DPN -NLR could be also linked to neuropathic pain according to the DN4 questionnaire	-The inflammatory markers could be effectively used in clinical settings for the diagnosis DPN and might indicate the important role of inflammation in the pathogenesis
Wang et al. (2024) [63]	Cross-sectional study (2515 T2DM subjects)	-WMR was found significantly correlated to DPN ($p < 0.05$) -The cut-off for the clinical implementation of the index was assessed at 0.5395 with sensitivity at 65.4 %, specificity at 41.8 % and area under the curve at 0.540	-WMR, as a promising inflammation marker, could be associated with DPN
Li et al. (2023) [62]	Cross-sectional study (1460 T2DM subjects)	-SII was significantly positively linked to DPN ($p < 0.01$) -An increased SII was significantly associated with higher vibration perception threshold ($p < 0.01$) -T2DM subjects, with an assessed SII in the highest quartile, were confronted with a significantly increased risk for neuropathy development compared with those in the lowest quartile, even after adjustment for confounding factors ($p < 0.05$) - The cut-off for the clinical application of the index was assessed at 617.67 with sensitivity at 45.3 % and specificity at 73 %	-SII, a novel index for inflammation already associated with T2DM and vascular complication, is of utility for neuropathy as well
Salah et al. (2022) [64]	Comparative study (100 T1DM children, 12 out of which suffering from neuropathy and 100 healthy children)	-A significantly increased NLR ($p < 0.001$) and a significantly decreased PLR ($p = 0.005$) were observed among children with microvascular complications compared with children without -Both indices (NLR, $p = 0.013$; PLR, $p = 0.004$) were significantly correlated to microvascular complications, according to regression analysis	-Chronic inflammation markers exhibit prognostic value among children with DM in the development of microvascular complications
Aktas (2024) [65]	Observational study	-CAR was assessed at 2.19 % and 0.56 % for subjects with DPN and without DPN, respectively -The CAR was thus statistically significantly correlated to DPN ($p < 0.001$) and furthermore increased CAR levels emerged as an independent biomarker for DPN risk ($p < 0.001$) - The cut-off for the clinical implementation of the index was assessed at 1.02 % with sensitivity at 78 %, specificity at 73 % and area under the curve at 0.84	-CAR emerges as an important biomarker for DPN, as the condition is characterized by low-grade inflammation
Fawwad et al. (2018) [56]	Retrospective study (5620 T2DM subjects)	-NLR was associated in a significant way with the presence of at least one microvascular complication ($p < 0.0001$)	-The importance of NLR as a biomarker for microvascular complication and indicates the pathophysiological implication of inflammation

CAR, C-reactive protein to albumin ratio; DPN, diabetic peripheral neuropathy; T2DM, type 2 diabetes mellitus; SII, systemic immune-inflammation index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MPV, mean platelet volume; DOR, diagnostic odds ratio; DM, diabetes mellitus; CRP, C-reactive protein; DN4, Douleur Neuropathique en 4 Questions; WMR, white blood cell to mean platelet volume ratio; CI, confidence interval; T1DM, type 1 diabetes mellitus.

various forms: HMW, total or their combined ratio), omentin, Nrg4, ISM1 [19,21–23,39]. These could serve as potential biomarkers and confirm the crucial role of visceral fat in promoting the endocrine and inflammatory crosstalk in DPN [23,39,19]. As there are indications of a diminished VFA among subjects with DPN, this interplay and the impact on adipokine function need to be further elucidated. Further studies need to determine which adipokines yield reliable result among subjects with DPN [54].

The strengths of this review include the comprehensive overview of current research on inflammatory-associated biomarkers in DPN and the wide spectrum of subjects assessed (T1DM and T2DM subjects of a wide age spectrum, from children to elderly, and also those with prediabetes) [23,55,48]. However, there are limitations as well. The first relates to the heterogeneous design of studies with remarkable differences in study populations, ranging from only 22 to more than 5000 participants [20, 56]. Furthermore, recommended cut-off values for each inflammatory parameter as a biomarker are based on a single study. Accordingly, further experience with larger works is needed to confirm findings.

Currently, emerging practical implications may be outlined as follows. Some biomarkers could serve as biomarkers in specific age groups. For example, decreased omentin levels were shown to provide reliable results relating to DNP prevalence among elderly T2DM subjects [23]. Another potential benefit is discriminatory capacity between painless and painful DPN: macrophage density was decreased among subjects with painful DPN [10]. In addition, prospective studies appear promising in monitoring of DPN progression, but experience is rather limited [24]. Finally, certain cut-off values have been proposed [39,27,62,63], but these need confirmation.

In conclusion, low-grade systemic inflammation plays a major role in the pathophysiology of DPN. In this context, several potential biomarkers have been proposed. These include a wide spectrum of cytokines, chemokines and immune receptors (IL-1, IL-6, IL-10, TNF-α). Other studies have focused on adipokine research or epigenetic biomarkers. Future large-scale studies are now required to validate these biomarkers and to investigate their potential clinical utility.

Conflicts of interest: Theodoros Panou has nothing to disclose. **Evanthia Gouveri** has attended conferences sponsored by Berlin-Chemie, Sanofi, AstraZeneca, Novo Nordisk, Lilly and Boehringer Ingelheim; received speaker honoraria by Boehringer-Ingelheim, Sanofi-Aventis and Menarini. **Dimitrios Papazoglou** declares associations: with Menarini, Novo Nordisk, Astra-Zeneca, Boehringer Ingelheim and Sanofi-Aventis. **Nikolaos Papanas** has been an advisory board member of Astra-Zeneca, Bayer, Boehringer Ingelheim, Menarini, MSD, Novo Nordisk, Pfizer, Takeda and TrigoCare International; has participated in sponsored studies by Astra-Zeneca, Eli-Lilly, GSK, MSD, Novo Nordisk, Novartis and Sanofi-Aventis; has received honoraria as a speaker for Astra-Zeneca, Bayer, Boehringer Ingelheim, Eli-Lilly, Elpen, Menarini, MSD, Mylan, Novo Nordisk, Pfizer, Sanofi-Aventis and Vianex; and has attended conferences sponsored by TrigoCare International, Astra-Zeneca, Boehringer Ingelheim, Eli-Lilly, Galenica, Menarini, Novo Nordisk, Pfizer and Sanofi-Aventis.

CRediT authorship contribution statement

Theodoros Panou: Writing – review & editing, Writing – original draft, Investigation, Data curation, Conceptualization. **Evanthia Gouveri:** Writing – review & editing, Writing – original draft, Supervision, Data curation, Conceptualization. **Dimitrios Papazoglou:** Writing – review & editing, Writing – original draft. **Nikolaos Papanas:** Writing – review & editing, Validation, Supervision, Conceptualization.

Abbreviations

DM	diabetes mellitus
CIAP	chronic idiopathic axonal polyneuropathy
DSPN	distal symmetrical polyneuropathy
DPN	diabetic peripheral neuropathy
CD	cluster of differentiation
HIF-α	hypoxia-inducible factor
MAPK	mitogen-activated protein kinase
PTEN	Phosphatase and tensin homolog
TNF	tumour necrosis factor
IL	interleukin
VCAM	vascular cell adhesion molecule
ICAM	intercellular cell adhesion molecule
HGF	hepatocyte growth factor
CSF1	colony stimulating factor 1
IFN	interferon
CXCL10	interferon γ-induced protein 10
OR	odds ration
CI	confidence interval
NLR	neutrophil to lymphocyte ratio
ISM1	isthmin 1
siCAM-1	soluble intercellular adhesion molecule
hs-CRP	high sensitive C-reactive protein
IL-1RA	interleukin 1 receptor antagonist
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
HMW	high molecular weight
NCV	nerve conduction velocity
CRP	C-reactive protein
CSF	cerebrospinal fluid
CI	confidence interval
PRGN	progranulin
Nrg4	neuregulin 4
MCP-1	monocyte chemoattractant protein 1
TLR	toll-like receptor
MyD88	Myeloid differentiation primary response 88
lncRNA	long non-coding RNA
siRNA	small-interfering RNA
STZ	streptozocin
DNS	Diabetic Neuropathy Symptom
NGF	nerve growth factor
sTNFR	soluble tumor necrosis factor receptor
sIL2R	soluble interleukin 2 receptor
IGFBP	insulin growth factor binding protein
MMP	metalloproteinase
PRO-C6	pro-peptide of type VI collagen
suPAR	soluble urokinase plasminogen activator receptor
MCP	monocyte chemoattractant protein
CXCL	chemokine (C-X-C motif) ligand
MHR	monocyte to high-density lipoprotein ratio
NFκB	nuclear factor kappa B
TNS	total neuropathy score
TNFSF	tumour necrosis factor superfamliy
TRAIL	TNF-related apoptosis-inducing ligand
CCL	CC chemokine ligand
MIP	macrophage inflammatory protein
MEC	mucosa-associated epithelial chemokine
MGSA-α	melanoma growth stimulating activity α
CXCLI-TAC	interferon-inducible T-cell alpha chemoattractant
TGF	tansforming growth factor
LAP	latency-associated peptide
TNFRSF	tumour necrosis factor receptor superfamily
DNER	Delta and Notch-like epidermal growth factor-related receptor
VFA	visceral fat area
MALAT1	metastasis-associated lung adenocarcinoma transcript 1
CAR	C-reactive protein-to-albumin ratio
SII	systemic immune-inflammation index
PLR	platelet-to-lymphocyte ratio
DOR	diagnostic odds ratio

DN4 Douleur Neuropathique en 4 Questions
WMR white blood cell-to-mean platelet volume ratio

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