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Adiponectin, markers of subclinical inflammation and nerve conduction
in individuals with recently diagnosed type 1 and type 2 diabetes

Short title: Inflammation, nerve conduction and DSPN

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Abstract

Objective: Subclinical inflammation has been implicated in the development of diabetic sensorimotor polyneuropathy (DSPN), but studies using electrophysiological assessment as outcomes are scarce. Therefore, we aimed to investigate associations of biomarkers reflecting different aspects of subclinical inflammation with motor and sensory nerve conduction velocity (NCV) in individuals with diabetes.

Design and Methods: Motor and sensory NCV was assessed in individuals with recently diagnosed type 2 ($n=352$) or type 1 diabetes ($n=161$) from the baseline cohort of the observational German Diabetes Study. NCV sum scores were calculated for median, ulnar and peroneal motor as well as median, ulnar and sural sensory nerves. Associations between inflammation-related biomarkers, DSPN and NCV sum scores were estimated using multiple regression models.

Results: In type 2 diabetes, high serum interleukin (IL)-6 was associated with the presence of DSPN and reduced motor NCV. Moreover, higher levels of high-molecular weight (HMW) adiponectin, total adiponectin and their ratio were associated with prevalent DSPN and both diminished motor and sensory NCV, whereas no consistent associations were observed for C-reactive protein, IL-18, soluble intercellular adhesion molecule-1 and E-selectin. In type 1 diabetes, only HMW and total adiponectin showed positive associations with motor NCV.

Conclusions: Our results point to a link between IL-6 and both DSPN and slowed motor NCV in recently diagnosed type 2 diabetes. The reverse associations between adiponectin and NCV in type 1 and type 2 diabetes are intriguing, and further studies should explore whether they may reflect differences in the pathogenesis of DSPN in both diabetes types.
Introduction

Inflammatory processes have been implicated in the pathogenesis of experimental diabetic neuropathy (1). Subclinical inflammation, i.e. the form of low-grade inflammation that is characterised by elevated systemic levels of mainly proinflammatory immune mediators in the absence of clinical symptoms which is commonly found in patients with cardiometabolic diseases, has also been observed in diabetes patients with polyneuropathy. Several clinical studies demonstrated positive associations between systemic levels of proinflammatory cytokines and symptoms or signs of diabetic sensorimotor polyneuropathy (DSPN) in type 2 diabetes patients (2-8) and in the older general population [9]. Overall, observational findings are most consistent for interleukin (IL)-6 (4, 7, 9), but there is also some evidence for associations of high-sensitivity C-reactive protein (hsCRP), proinflammatory cytokines and soluble cell adhesion molecules with diabetic neuropathy (2-6, 8).

In contrast, data regarding associations of adiponectin with DSPN are conflicting (4, 9-12). Adiponectin is an adipocyte-derived protein with multiple paracrine and endocrine activities. These include local and systemic anti-inflammatory, insulin-sensitising and proangiogenic effects so that a protective function in the context of diabetic polyneuropathy is conceivable (13-15).

Only few studies investigated the association between biomarkers of subclinical inflammation and DSPN in type 1 diabetes. One study observed increased plasma levels of soluble tumour necrosis factor (TNF) receptors in patients with DSPN compared to patients without the condition, but no differences for hsCRP, IL-6 or adiponectin (16). Another study reported that plasma sialic acid, a marker of the acute-phase response, was positively associated with diabetic neuropathy in men, but not independently of other risk factors (17).

However, the interpretation of the aforementioned studies is complicated by the fact that the definition of DSPN differed between studies. Definitions were based on varying combinations
of subjective (neuropathic symptoms and signs) and objective (nerve conduction) measurements, therefore also reflecting different aspects of the pathophysiology of DSPN. Nerve conduction studies are important, because they give objective, non-invasive and highly reliable measures (18, 19). Abnormalities in nerve conduction appear to be among the first indications of DSPN in both type 1 and type 2 diabetes (20, 21). They are used to diagnose subclinical DSPN (22) and are of particular interest at early stages of diabetes as predictors of symptomatic DSPN, foot ulceration, amputation and mortality (23-25). In addition, abnormal nerve conduction results are required to confirm the diagnosis of DSPN (22).

So far, data on the relationship between inflammation-related biomarkers and nerve conduction velocity (NCV) are scarce and mostly based on small study samples of patients with type 2 diabetes (2, 3, 6-8, 26). Interestingly, one large population-based study indicated that circulating levels of the soluble IL-6 receptor (sIL-6R) may be inversely associated with peroneal motor NCV (MNCV) (27).

The aim of this study was to test the hypothesis that serum levels of biomarkers reflecting different aspects of subclinical inflammation (acute-phase protein, proinflammatory cytokines, adiponectin, soluble adhesion molecules) are associated with DSPN based on objective electrophysiological assessment and with individual and summated motor and sensory NCV in patients with recently diagnosed type 1 and type 2 diabetes.

Materials and Methods

Study population

The German Diabetes Study (GDS) is an ongoing prospective observational study, which evaluates the natural history of recent-onset diabetes and its sequelae (ClinicalTrials.gov identifier NCT01055093) (21, 28). The study is being conducted according to the declaration of Helsinki and was approved by the ethics committee of Heinrich Heine University, Düsseldorf, Germany. All participants provided written informed consent.
Inclusion criteria for entry into the GDS are type 1 or type 2 diabetes, time since diabetes diagnosis ≤1 year and age of 18-69 years at the baseline examination. Diabetes was initially diagnosed by a general practitioner according to the guidelines of the American Diabetes Association (29). The concordance with these criteria was validated before inclusion into the study by the study centre staff. Exclusion criteria are secondary diabetes, current pregnancy, acute infections, cancer, evidence of congestive heart failure, kidney diseases, liver diseases, symptomatic peripheral arterial disease, psychiatric or addictive disorders, immunosuppressive therapy or participation in pharmacological intervention studies. The experimental design including a structured interview, anthropometry and measurement of HbA1c and lipids has been reported in detail before (28).

This cross-sectional analysis was based on consecutive participants who entered the study between its start in September 2005 and December 2011 (n=513).

**Neurological examination and definition of DSPN**

Neurological examination was performed using the Neuropathy Disability Score (NDS) and the Neuropathy Symptom Score (NSS). Peripheral nerve function tests were performed as described before (21). Briefly, MNCV was determined in the median, ulnar and peroneal nerves, and sensory nerve conduction velocity (SNCV) as well as sensory nerve action potentials (SNAPs) were measured in the median, ulnar and sural nerves at a skin temperature of 33-34°C with surface electrodes (Nicolet VikingQuest; Natus Medical, San Carlos, CA, USA).

Neuropathy stages were defined according to modified Toronto Consensus criteria (22). The definition of DSPN comprised subclinical DSPN (stage 1a: NDS≤2, NSS≤2, peroneal MNCV<2.5th percentile and sural SNCV<2.5th percentile and/or sural SNAP<2.5th percentile), confirmed asymptomatic DSPN (stage 1b: NDS≥3, NSS≤2, peroneal MNCV<2.5th percentile and sural SNCV<2.5th percentile and/or sural SNAP<2.5th percentile) and confirmed...
symptomatic DSPN (stage 2a: NSS≥3, peroneal MNCV<2.5\textsuperscript{th} percentile and sural SNCV<2.5\textsuperscript{th} percentile and/or sural SNAP<2.5\textsuperscript{th} percentile).

Only symptoms and signs were included in the clinical neuropathy scores that were considered by the experienced investigator to be due to distal sensorimotor polyneuropathy, but not other neurological diseases. Vitamin B6 or B12 deficiency as potential other causes of polyneuropathy cannot be completely ruled out, since their concentrations were not measured, but individuals with clinical symptoms or signs suspicious of manifest vitamin B6 or B12 deficiency were excluded from this study.

**Measurement of biomarkers of subclinical inflammation**

Serum concentrations of hsCRP, IL-6, IL-18, soluble intercellular adhesion molecule-1 (sICAM-1) and soluble E-selectin (sE-selectin) were measured as described before (28). Detailed information on biospecimen type, pre-analytical processes and assay used for the quantification of total and high-molecular-weight (HMW) adiponectin is provided in Supplementary Table 1.

**Statistical analysis**

Analyses were stratified by diabetes type because there is evidence that risk factors of DSPN differ between type 1 and type 2 diabetes (30). Data are presented as mean±SD, median (25\textsuperscript{th}; 75\textsuperscript{th} percentiles) or percentages (%). Differences between diabetes types were tested using Student’s t\textsuperscript{-}test, Mann-Whitney test or \( \chi^2 \)-test. Variables without normal distribution (triglycerides, all biomarkers of subclinical inflammation) were log-transformed before they entered regression models.

Associations between inflammation-related biomarkers and DSPN were assessed using multivariable logistic regression models with increasing complexity. Model 1 adjusted for age and sex. Model 2 additionally adjusted for time since diagnosis of diabetes, HbA1c, waist
circumference, height, total cholesterol and hypertension. Model 3 adjusted for variables in
model 2 and current smoking, physical activity, use of lipid-lowering medication, use of non-
steroidal anti-inflammatory drugs and history of myocardial infarction and/or stroke. The
latter variable was not used in the subgroup with type 1 diabetes, because only one individual
was affected.

Associations between inflammation-related biomarkers and NCV as continuous variables
were assessed using multivariable linear regression using the same covariables as in the
logistic regression models. For the main analysis, MNCV and SNCV sum scores were
calculated as the sums of individual z-scores of MNCV in the median, ulnar and peroneal
nerves, and SNCV in the median, ulnar and sural nerves, respectively. In both cases, the sum
scores combine NCVs of three different nerves giving equal weight to each nerve and
allowing a more comprehensive assessment of nerve function in an individual with low sum
scores reflecting a more severe impairment of peripheral nerve function. In addition, the same
analyses were performed for NCV and SNAPs in the individual nerves, which constitute the
sum scores.

All statistical analyses were carried out using SPSS version 22 (IBM, Ehningen, Germany). A
$P$ value of $<0.05$ was considered to indicate statistically significant differences or
associations.

**Results**

**Study population**

Table 1 provides an overview of the study sample which included 352 individuals with type 2
diabetes and 161 individuals with type 1 diabetes. The subgroup with type 2 diabetes was
characterised by a higher proportion of men, higher age, higher body mass index and waist
circumference, shorter height, better glycaemic control, higher lipid levels and blood pressure,
less physical activity and higher prevalence of myocardial infarction and/or stroke compared
to the subgroup of type 1 diabetes. Systemic levels of hsCRP, IL-6, IL-18 and soluble
adhesion molecules were higher, total and HMW adiponectin levels lower in type 2 diabetes
compared to type 1 diabetes. The prevalence of DSPN was higher among individuals with
type 2 diabetes, which was mirrored by lower NCV.

**Association between biomarkers of subclinical inflammation and DSPN in type 2 and
type 1 diabetes**

Among individuals with type 2 diabetes, IL-6, total adiponectin and HMW adiponectin were
positively associated with the presence of DSPN in age- and sex-adjusted analyses (Table 2,
model 1). These associations remained significant in the fully adjusted model (Table 2, model
3). In contrast, no associations were observed for hsCRP, IL-18, sE-selectin and sICAM-1.
None of the measured biomarkers of subclinical inflammation displayed significant
associations with DSPN among individuals with type 1 diabetes.

**Association between biomarkers of subclinical inflammation and NCV in type 2 diabetes**

In line with the aforementioned findings regarding DSPN, total adiponectin, HMW
adiponectin and their ratio were inversely associated with sum scores of both MNCV and
SNCV in the fully adjusted models (Table 3). In addition, IL-6 levels were inversely
associated with motor NCV, and hsCRP levels were inversely associated with motor NCV in
model 1, but the latter association failed to reach statistical significance after further
adjustment (Table 3). In the fully adjusted model, IL-18 was positively associated with
sensory NCV.

The associations of total and HMW adiponectin with MNCV were mainly driven by peroneal
NCV (Supplementary Table 2), whereas their association with SNCV was similar for median,
ulnar and sural SNCV (Supplementary Table 3). In addition, IL-6 levels were inversely
associated with median MNCV, and sICAM-1 levels were positively associated with median SNCV (Supplementary Tables 2, 3).

There was also evidence for inverse associations of total and HMW adiponectin with median and sural SNAPs ($P$ between 0.024 and 0.084), whereas IL-6 was inversely associated with ulnar SNAP ($P=0.007$) in the fully adjusted models (data not shown).

**Association between biomarkers of subclinical inflammation and NCV in type 1 diabetes**

In type 1 diabetes, hsCRP, IL-6 and sICAM-1 levels were inversely associated with motor NCV. However, statistical significance was lost after further adjustment. In contrast, adjustment strengthened the positive associations between total and HMW adiponectin, which reached statistical significance in the full model. No associations were observed after full adjustment for sensory NCV (Table 4).

The associations of total and HMW adiponectin with motor NCV were strongest for ulnar and peroneal nerves. Some inverse associations between hsCRP, IL-6 and sICAM-1 were observed in median and ulnar nerves, but not in the full model (Supplementary Table 4). Inverse associations between HMW adiponectin and the ratio of HMW to total adiponectin with ulnar SNCV were the only significant associations with sensory NCV after full adjustment (Supplementary Table 5).

Neither total nor HMW adiponectin levels were associated with median, ulnar or sural SNAPs (data not shown).

**Discussion**

This study identified associations between multiple biomarkers of subclinical inflammation and NCV in patients with recently diagnosed type 2 or type 1 diabetes by three main findings:

(i) In individuals with type 2 diabetes, high serum IL-6 was associated with the presence of DSPN and reduced motor NCV, whereas no consistent associations were observed for
hsCRP, IL-18, sICAM-1 and E-selectin. (ii) Higher levels of HMW and total adiponectin were consistently associated with the presence of DSPN and both reduced motor and sensory NCV in individuals with type 2 diabetes. (iii) By contrast, in participants with type 1 diabetes, associations between high HMW and total adiponectin and higher motor NCV were found.

**Subclinical inflammation, DSPN and NCV in type 2 diabetes**

This study extends the current literature as it represents a comprehensive analysis of associations between biomarkers reflecting different aspects of subclinical inflammation and NCV in a fairly large study sample of patients with recently diagnosed diabetes. Another novel aspect of the study is the calculation of sum scores in the main analysis rather than analysing single nerves. This approach was chosen following the recommendation to use composite nerve conduction test scores to identify early nerve dysfunction in diabetes (24). Different composite scores have been validated by other studies investigating associations between NCV and future DSPN (24, 25) as well as associations between inflammation and NCV (8).

Our first main finding regarding associations of higher serum IL-6 with reduced MNCV, but not with SNCV, suggests a differential risk conferred by IL-6 for NCV slowing between motor and sensory nerves. These results are of particular interest in the context of data from InCHIANTI, a population-based study in Italy, which reported associations of higher IL-6 and sIL-6R levels with reduced peroneal MNCV (27). Furthermore, an association of higher IL-6 with reduced sural and peroneal NAPs was observed in a small study (7). Collectively, these studies underline the notion that the IL-6 system may represent a determinant of motor nerve function and integrity.

In contrast, we did not find consistent associations between hsCRP and DSPN or NCV. Data regarding the relationship of hsCRP with DSPN have been less consistent (4, 5, 9) than the association between IL-6 and DSPN. Overall, these data are reminiscent of the role of
inflammation in the development of cardiovascular disease (CVD). IL-6 is one of the main inducers of CRP, and even if hsCRP is used frequently as risk marker for CVD, there is considerably more evidence for a causal role of the IL-6 system in the development of CVD (31), which itself represents a risk factor for DSPN.

Our second main finding of robust associations between higher total adiponectin, higher HMW adiponectin and higher values of their ratio (HMW/total) on the one hand and the presence of DSPN and reduced NCV on the other hand may appear counterintuitive, because adiponectin shows consistent associations with lower risk of diabetes in humans and because of its antiatherogenic properties in preclinical studies (13, 15). Our observation may appear particularly surprising given that it has been hypothesised that HMW adiponectin and a higher HMW/total adiponectin ratio may be even more strongly associated with favourable cardiometabolic health than total adiponectin (32).

We are not aware of studies that have demonstrated an independent inverse association between circulating adiponectin (irrespective of its isoforms) and DSPN. Whereas no associations were found in some populations (4, 9, 10), others also observed increased levels of total adiponectin in DSPN (11, 12). However, our study extends these data because we (i) included measurements of HMW adiponectin, (ii) performed more extensive adjustment to rule out false-positive findings due to confounding and (iii) provide novel data on the associations between adiponectin and both MNCV and SNCV. It is interesting to note that the association with MNCV was strongest for the peroneal nerve, which is often used as a surrogate endpoint in clinical studies and to monitor progression of DSPN.

Since the literature on adiponectin and DSPN is scarce, one may compare the present study with studies investigating associations between adiponectin and other microvascular outcomes. Indeed, higher levels of total adiponectin have been found in patients with type 2 diabetes and retinopathy compared to those without retinopathy (10-12). In addition, inverse or no associations of total adiponectin have been reported with respect to cardiovascular risk
in the general population, whereas positive associations were found in patients with type 2 diabetes and/or micro- and macrovascular disease (33, 34). HMW adiponectin levels were inversely associated with cardiac autonomic imbalance in type 2 diabetes in one study (35), while a second study reported a positive association between total adiponectin and cardiac autonomic neuropathy (36), underlining the need for further investigations.

From a mechanistic perspective, we hypothesised that proinflammatory immune mediators would be associated with reduced NCV reflecting impaired integrity and degree of myelination of large fibres (18). It is biologically plausible that elevated circulating levels of IL-6, which has various proinflammatory properties, may cause structural and functional deficits of nerve fibres by triggering intracellular signaling downstream of the IL-6R/gp130 complex or by indirect effects through activation of macrophages and other cell types.

In contrast, adiponectin has anti-inflammatory properties (13), and currently there are no data supporting a direct detrimental impact of adiponectin on nerve function. It has been suggested that adiponectin could be upregulated by metabolic and/or inflammatory insults, which are causal for the development of adverse cardiometabolic outcomes so that adiponectin may be interpreted as indirect risk marker, not as genuine risk factor (37). With respect to cardiovascular risk, adiponectin expression and release is increased by atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) (38). In order to rule out confounding by CVD, we adjusted for the history of myocardial infarction and/or stroke and for multiple cardiovascular risk factors. However, even if the mechanism linking adiponectin and DSPN is not clear yet, our data strongly suggest that although adiponectin may serve as protective factor for incident diabetes, the time around the manifestation of type 2 diabetes may be characterised by metabolic and/or proinflammatory perturbations that reverse the direction of the association between adiponectin levels and risk of micro- and macrovascular complications.
This study indicates that there are both similarities and differences in associations between biomarkers of subclinical inflammation and NCV between type 1 and type 2 diabetes. In both diabetes types we found inverse associations between high hsCRP and IL-6 on the one hand and reduced motor NCV on the other hand in our initial models. Effect estimates in the final models were similar, but adjustment for potential confounders attenuated the associations in type 1 diabetes to non-significance, which most likely reflects reduced statistical power in this subgroup. The lack of associations between IL-6 and sensory NCV as well as the absence of associations between soluble adhesion molecules and NCV in the final models were also comparable between both diabetes types.

Clear differences were observed for adiponectin, which was inversely associated with both MNCV and SNCV in type 2 diabetes, whereas a positive association was found with MNCV in type 1 diabetes. It is well known that patients with type 1 diabetes have increased levels of total and HMW adiponectin in the circulation, whereas decreased levels are found in type 2 diabetes (39, 40). The mechanism behind this upregulation and its physiological relevance are currently only poorly understood. Although adiponectin levels in type 1 diabetes are also positively associated with insulin sensitivity, insulin sensitivity is lower at any given adiponectin level compared to non-diabetic controls (41). Prospective studies demonstrated that higher adiponectin levels in type 1 diabetes are linked to an elevated risk of progression of nephropathy and increased cardiovascular and all-cause mortality (42, 43). The difference in adiponectin between both diabetes types may be due to the interplay of insulin and adiponectin in a way that adiponectin levels are increased in type 1 diabetes due to the lack of endogenous insulin production, whereas they are decreased in response to hyperinsulinaemia in type 2 diabetes (44, 45). Alternative explanations implicate increased adiponectin levels as reflection of underlying CVD or impaired renal function (45), but these mechanisms would
apply to both diabetes types and are unlikely to play a role in our cohort of patients with recently diagnosed diabetes.

Adiponectin levels are also determined by genetic variants within the gene encoding adiponectin and in other loci, and these effects may be modified by dietary components (46). Although one small study indicated that polymorphisms within the adiponectin gene may be associated with polyneuropathy in type 2 diabetes (47), there is currently insufficient evidence for the hypothesis that different gene variants that have an impact on adiponectin levels could explain the differences in adiponectin levels and their associations with diabetic complications between type 1 and type 2 diabetes.

It is currently not possible to infer whether the upregulation of adiponectin in type 1 diabetes reflects a protective mechanism to maintain motor nerve function or whether this association is confounded. Our data support the hypothesis that the pathogenesis of DSPN may differ between type 1 and type 2 diabetes and involve at least in part different sets of risk factors with a more prominent role of metabolic risk factors and subclinical inflammation in type 2 diabetes compared to type 1 diabetes (30).

Strengths and limitations

The comparably short known duration of disease represents a strength of the study, because it allowed to analyse associations between inflammatory markers and DSPN before the onset of potentially confounding diabetes-related complications. Detailed nerve conduction studies for assessing large-fibre function were carried out rigorously using gold-standard methods, validated criteria and reference values. Our statistical analysis included sum scores for MNCV and SNCV rather than NCV of single nerves and adjusted for multiple confounders.

The limitations include the cross-sectional design precluding the assessment of temporal relationships between the upregulation of inflammation-related biomarkers and changes in NCV. We could not assess the direct impact of glucose-lowering treatment on inflammation-
related biomarkers, because blood samples from before the onset of therapy were not available. The statistical power differed between both diabetes types as a consequence of the study design (inclusion of consecutive study participants with skewed enrolment regarding diabetes types), which entails the risk of type II errors in the smaller subsample of individuals with type 1 diabetes. Finally, study population of adult patients with short known diabetes duration and rather good glycaemic control renders our data not generalisable to diabetes patients with longer disease duration and/or worse glycaemic control.

Conclusions

This study demonstrates that increased serum IL-6 is associated with reduced NCV in type 2 diabetes and corroborates the hypothesis that the IL-6 system may contribute to peripheral large nerve fibre dysfunction and DSPN. Circulating total and HMW adiponectin are also associated with NCV in type 2 and type 1 diabetes, but in opposite directions. The association between high adiponectin and reduced NCV is consistent with positive associations between adiponectin and retinopathy or cardiovascular outcomes in type 2 diabetes. Our data support the notion that the pathomechanisms leading to DSPN may only partially overlap between type 1 and type 2 diabetes.

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Author contribution statement

I Schamarek designed the study, performed the statistical analysis, interpreted the data,
contributed to discussion and critically reviewed the manuscript. C Herder designed the study,
researched data, contributed to data analysis, interpreted the data and wrote the manuscript. B
Nowotny researched data and critically reviewed the manuscript. M Carstensen-Kirberg
researched data, contributed to discussion and critically reviewed the manuscript. K
Straßburger contributed to data analysis, contributed to discussion and critically reviewed the
manuscript. P Nowotny, A Strom and S Püttgen researched data and critically reviewed the
manuscript. K Müßig and J Szendroedi researched data, contributed to discussion and
critically reviewed the manuscript. M Roden designed the study, contributed to discussion,
critically reviewed and edited the manuscript. D Ziegler designed the study, researched data,
interpreted the data, contributed to discussion, critically reviewed and edited the manuscript.
All authors approved of the final version of the manuscript.

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Table 1 Patient characteristics stratified by diabetes type.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type 2 diabetes (n=352)</th>
<th>Type 1 diabetes (n=161)</th>
<th>(P)</th>
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</thead>
<tbody>
<tr>
<td>Sex (% male)</td>
<td>66.2</td>
<td>60.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52.6 ± 10.6</td>
<td>35.9 ± 12.5</td>
<td>&lt;0.001</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>31.7 ± 6.1</td>
<td>24.9 ± 4.3</td>
<td>&lt;0.001</td>
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<tr>
<td>Waist circumference (cm)</td>
<td>106 ± 14</td>
<td>87 ± 14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172 ± 9</td>
<td>176 ± 10</td>
<td>0.001</td>
</tr>
<tr>
<td>Time since diagnosis of diabetes (days)</td>
<td>181 ± 96</td>
<td>195 ± 100</td>
<td>0.125</td>
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<tr>
<td>HbA1c (%)</td>
<td>6.53 ± 1.09</td>
<td>6.91 ± 1.70</td>
<td>0.008</td>
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<tr>
<td>HbA1c (mmol/mol)</td>
<td>48 ± 12</td>
<td>52 ± 19</td>
<td>0.008</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.2 ± 1.1</td>
<td>4.7 ± 0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting triglycerides (mmol/l)</td>
<td>1.4 (1.0; 2.1)</td>
<td>0.8 (0.6; 1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>142 ± 18</td>
<td>131 ± 15</td>
<td>&lt;0.001</td>
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<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85 ± 11</td>
<td>78 ± 10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)(^a)</td>
<td>60.1</td>
<td>16.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>24.6</td>
<td>25.6</td>
<td>0.82</td>
</tr>
<tr>
<td>Physically inactive (%)(^b)</td>
<td>39.9</td>
<td>23.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of myocardial infarction and/or stroke (%)</td>
<td>5.1</td>
<td>0.6</td>
<td>0.010</td>
</tr>
<tr>
<td>Lipid-lowering medication (%)</td>
<td>23.6</td>
<td>2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive medication</td>
<td>52.1</td>
<td>8.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------</td>
<td>-----</td>
<td>--------</td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drugs (%)</td>
<td>4.5</td>
<td>1.9</td>
<td>0.961</td>
</tr>
<tr>
<td>Biomarkers of subclinical inflammation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsCRP (mg/l)</td>
<td>3.0 (1.6; 5.6)</td>
<td>1.1 (0.6; 2.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>1.94 (1.32; 2.65)</td>
<td>0.88 (0.65; 1.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IL-18 (pg/ml)</td>
<td>287 (227; 384)</td>
<td>260 (183; 322)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total adiponectin (ng/ml)</td>
<td>4008 (2983; 5355)</td>
<td>6101 (4112; 8095)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HMW adiponectin (ng/ml)</td>
<td>1636 (995; 2440)</td>
<td>2751 (1557; 4280)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HMW/total adiponectin</td>
<td>0.40 (0.33; 0.48)</td>
<td>0.45 (0.36; 0.54)</td>
<td>0.003</td>
</tr>
<tr>
<td>sE-selectin (ng/ml)</td>
<td>244 (205; 288)</td>
<td>217 (182; 253)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sICAM-1 (ng/ml)</td>
<td>40.9 (30.7; 55.2)</td>
<td>34.5 (24.8; 44.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DSPN (%)</td>
<td>25.6</td>
<td>19.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NDS</td>
<td>1.7 ± 2.2</td>
<td>0.6 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NSS</td>
<td>1.2 ± 2.4</td>
<td>0.5 ± 1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Motor nerve conduction velocity (MNCV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median MNCV (m/s)</td>
<td>53.4 ± 3.2</td>
<td>55.5 ± 3.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ulnar MNCV (m/s)</td>
<td>55.8 ± 5.7</td>
<td>56.7 ± 5.3</td>
<td>0.097</td>
</tr>
<tr>
<td>Peroneal MNCV (m/s)</td>
<td>44.7 ± 5.1</td>
<td>46.1 ± 4.0</td>
<td>0.002</td>
</tr>
<tr>
<td>Sensory nerve conduction velocity (SNCV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median SNCV (m/s)</td>
<td>51.7 ± 6.8</td>
<td>55.3 ± 6.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ulnar SNCV (m/s)</td>
<td>53.3 ± 5.8</td>
<td>54.1 ± 4.4</td>
<td>0.100</td>
</tr>
</tbody>
</table>
Sural SNCV (m/s) | 44.6 ± 5.8 | 45.6 ± 5.0 | 0.066

Data are given as mean ± SD, median (25th; 75th percentile) or %.

\(^a\)Hypertension is defined as blood pressure ≥140/90 mmHg or use of antihypertensive medication. \(^b\)Physical inactivity is defined as absence of regular physical training at the time of the examination.

The maximum number of missing data is 28 for T2D and 7 for T1D.
Table 2: Association between biomarkers of subclinical inflammation and presence of DSPN.

<table>
<thead>
<tr>
<th>Diabetes type</th>
<th>Immune mediator</th>
<th>Model 1</th>
<th></th>
<th></th>
<th></th>
<th>Model 2</th>
<th></th>
<th></th>
<th></th>
<th>Model 3</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>β</td>
<td>P</td>
<td>β</td>
<td>P</td>
<td>β</td>
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<td>β</td>
<td>P</td>
<td>β</td>
<td>P</td>
<td>β</td>
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<tr>
<td>Type 2 diabetes</td>
<td>hsCRP</td>
<td>0.207</td>
<td>0.136</td>
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<td>0.261</td>
<td>0.175</td>
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<tr>
<td></td>
<td>IL-6</td>
<td>0.513</td>
<td>0.028</td>
<td>0.486</td>
<td>0.058</td>
<td>0.575</td>
<td>0.039</td>
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<tr>
<td></td>
<td>IL-18</td>
<td>-0.282</td>
<td>0.352</td>
<td>-0.515</td>
<td>0.114</td>
<td>-0.484</td>
<td>0.152</td>
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<tr>
<td></td>
<td>Total adiponectin</td>
<td>0.784</td>
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<td>0.949</td>
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<tr>
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<td>HMW adiponectin</td>
<td>0.478</td>
<td>0.021</td>
<td>0.579</td>
<td>0.005</td>
<td>0.615</td>
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<td>HMW/total adiponectin</td>
<td>0.812</td>
<td>0.077</td>
<td>0.974</td>
<td>0.045</td>
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<tr>
<td></td>
<td>sE-selectin</td>
<td>0.241</td>
<td>0.416</td>
<td>0.008</td>
<td>0.980</td>
<td>0.005</td>
<td>0.988</td>
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<td></td>
<td>sICAM-1</td>
<td>0.417</td>
<td>0.329</td>
<td>0.151</td>
<td>0.734</td>
<td>0.149</td>
<td>0.760</td>
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<tr>
<td>Type 1 diabetes</td>
<td>hsCRP</td>
<td>0.197</td>
<td>0.327</td>
<td>0.249</td>
<td>0.301</td>
<td>0.244</td>
<td>0.337</td>
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</tr>
<tr>
<td></td>
<td>IL-6</td>
<td>0.201</td>
<td>0.573</td>
<td>0.155</td>
<td>0.707</td>
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<td>0.796</td>
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<td>IL-18</td>
<td>0.025</td>
<td>0.953</td>
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<td>0.994</td>
<td>-0.032</td>
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<tr>
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<td>Total adiponectin</td>
<td>-0.477</td>
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<td>-0.692</td>
<td>0.166</td>
<td>-0.883</td>
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<tr>
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<td>HMW/total adiponectin</td>
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<td>0.323</td>
<td>-0.838</td>
<td>0.248</td>
<td>-1.086</td>
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<td>0.385</td>
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</tr>
</tbody>
</table>
The table gives regression coefficients ($\beta$) and corresponding $P$ values from logistic regression models. Immune mediators entered the models as log-transformed levels in the units given in Table 1.

Model 1: adjusted for age and sex.

Model 2: model 1 + time since diagnosis of diabetes, HbA1c, waist circumference, height, total cholesterol, hypertension.

Model 3: model 2 + current smoking, physical activity, use of lipid-lowering medication, use of NSAIDs, history of myocardial infarction and/or stroke (the latter variable for type 2 diabetes only).
Table 4 Association between biomarkers of subclinical inflammation and sum scores for nerve conduction velocity (NCV) in patients with type 1 diabetes.

<table>
<thead>
<tr>
<th>Nerve type</th>
<th>Immune mediator</th>
<th>Model 1</th>
<th></th>
<th>Model 2</th>
<th></th>
<th>Model 3</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β</td>
<td>P</td>
<td>β</td>
<td>P</td>
<td>β</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>Motor NCV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsCRP</td>
<td>-0.176</td>
<td>0.027</td>
<td>-0.162</td>
<td>0.073</td>
<td>-0.107</td>
<td>0.238</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>-0.233</td>
<td>0.003</td>
<td>-0.209</td>
<td>0.017</td>
<td>-0.120</td>
<td>0.199</td>
<td></td>
</tr>
<tr>
<td>IL-18</td>
<td>-0.014</td>
<td>0.859</td>
<td>0.005</td>
<td>0.954</td>
<td>0.017</td>
<td>0.830</td>
<td></td>
</tr>
<tr>
<td>Total adiponectin</td>
<td>0.112</td>
<td>0.188</td>
<td>0.143</td>
<td>0.113</td>
<td>0.211</td>
<td>0.017</td>
<td></td>
</tr>
<tr>
<td>HMW adiponectin</td>
<td>0.113</td>
<td>0.198</td>
<td>0.133</td>
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<td>0.208</td>
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<td>0.314</td>
<td>0.154</td>
<td>0.072</td>
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</tr>
<tr>
<td>sE-selectin</td>
<td>-0.012</td>
<td>0.878</td>
<td>0.043</td>
<td>0.606</td>
<td>0.088</td>
<td>0.298</td>
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</tr>
<tr>
<td>sICAM-1</td>
<td>-0.179</td>
<td>0.020</td>
<td>-0.180</td>
<td>0.023</td>
<td>-0.117</td>
<td>0.195</td>
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</tr>
<tr>
<td>Sensory NCV</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
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<td>0.152</td>
<td>-0.141</td>
<td>0.139</td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>0.035</td>
<td>0.650</td>
<td>0.015</td>
<td>0.866</td>
<td>-0.001</td>
<td>0.991</td>
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</tr>
<tr>
<td>IL-18</td>
<td>0.028</td>
<td>0.721</td>
<td>0.005</td>
<td>0.951</td>
<td>0.010</td>
<td>0.900</td>
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<tr>
<td>Total adiponectin</td>
<td>-0.078</td>
<td>0.353</td>
<td>0.055</td>
<td>0.541</td>
<td>-0.045</td>
<td>0.631</td>
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</tr>
<tr>
<td>HMW adiponectin</td>
<td>-0.132</td>
<td>0.126</td>
<td>-0.111</td>
<td>0.221</td>
<td>-0.101</td>
<td>0.280</td>
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<tr>
<td>HMW/total adiponectin</td>
<td>-0.187</td>
<td>0.028</td>
<td>-0.165</td>
<td>0.055</td>
<td>-0.160</td>
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<tr>
<td>sE-selectin</td>
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<td>0.850</td>
<td>-0.024</td>
<td>0.771</td>
<td>-0.008</td>
<td>0.928</td>
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<td>-0.116</td>
<td>0.150</td>
<td>-0.146</td>
<td>0.118</td>
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</tbody>
</table>
The table gives regression coefficients (β) and corresponding $P$ values from linear regression models. Immune mediators entered the models as log-transformed levels in the units given in Table 1.

Model 1: adjusted for age and sex.

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Table 4 Association between biomarkers of subclinical inflammation and sum scores for nerve conduction velocity (NCV) in patients with type 1 diabetes.

<table>
<thead>
<tr>
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<th></th>
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<th></th>
<th>Model 3</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>β</td>
<td>P</td>
<td>β</td>
<td>P</td>
<td>β</td>
<td>P</td>
</tr>
<tr>
<td>Motor NCV</td>
<td>hsCRP</td>
<td>-0.176</td>
<td>0.027</td>
<td>-0.162</td>
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<td>0.188</td>
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<td>0.113</td>
<td>0.211</td>
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<td>-0.055</td>
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<td>-0.045</td>
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<td>0.126</td>
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<td>-0.078</td>
<td>0.313</td>
<td>-0.116</td>
<td>0.150</td>
<td>-0.146</td>
<td>0.118</td>
</tr>
</tbody>
</table>
The table gives regression coefficients (β) and corresponding P values from linear regression models. Immune mediators entered the models as log-transformed levels in the units given in Table 1.

Model 1: adjusted for age and sex.

Model 2: model 1 + time since diagnosis of diabetes, HbA1c, waist circumference, height, total cholesterol, hypertension.

Model 3: model 2 + current smoking, physical activity, use of lipid-lowering medication and use of NSAIDs.