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Characterization and quantification of alcohol-related polyneuropathy by magnetic resonance neurography

Original research article

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Abstract**Background**

We characterized and quantified peripheral nerve damage in alcohol-dependent patients (ADP) by magnetic resonance neurography (MRN) in correlation with clinical and electrophysiologic findings.

Methods

Thirty-one adult patients with a history of excessive alcohol consumption and age-/sex-matched healthy controls were prospectively examined. After detailed neurologic and electrophysiologic testing, the patient group was subdivided into ADP with alcohol-related

polyneuropathy (ALN) and without ALN (Non-ALN). 3T MRN with anatomical coverage from the proximal thigh down to the tibiotalar joint was performed using dual-echo 2-dimensional relaxometry sequences with spectral fat saturation. Detailed quantification of nerve injury by morphometric (cross-sectional area (CSA)) and microstructural MRN markers (proton-spin density (ρ), T2-relaxation-time (T_{2app})) was conducted in all study participants.

Results

MRN detected nerve damage in ADP with and without ALN. A proximal-to-distal gradient was identified for nerve T2w-signal and T_{2app} in ADP, indicating a proximal predominance of nerve lesions. While all MRN markers differentiated significantly between ADP and controls, microstructural markers were able to additionally differentiate between subgroups: Tibial nerve ρ at thigh level was increased in ALN ($p < 0.0001$) and in Non-ALN ($p = 0.0052$) versus controls, and T_{2app} was higher in ALN versus controls ($p < 0.0001$) and also in ALN versus Non-ALN ($p = 0.0214$). T2w-signal and CSA were only higher in ALN versus controls.

Conclusions

MRN detects and quantifies peripheral nerve damage in ADP in vivo even in the absence of clinically overt ALN. Microstructural markers (T_{2app}, ρ) are most suitable to differentiate between ADP with and without manifest ALN, and may help to elucidate the underlying pathomechanism in ALN.

Abbreviation key:

ADP	alcohol-dependent patients
ALN	alcohol-related polyneuropathy
ATTRv	hereditary transthyretin amyloidosis
CMAP	compound muscle action potentials
CNS	central nervous system
CSA	cross-sectional area
DML	distal motor latencies
MRN	magnetic resonance neurography
MS	multiple sclerosis
NCS	nerve conduction studies
NCV	nerve conduction velocities
NIS-LL	neuropathy impairment score of the lower limb
NDS	neuropathy disability score
NSS	neurological severity score
ρ	proton spin density
PN	peroneal nerve
PNP	polyneuropathy
PNS	peripheral nervous system
SMA	spinal muscular atrophy
SNAP	sensory nerve action potentials
T2 _{app}	T2 relaxation time
TE	echo time
TN	tibial nerve
TNS	total neuropathy score

Introduction

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Alcohol-related polyneuropathy (ALN) is the second most common polyneuropathy (PNP) in the United States and is present in 25-66% of individuals with alcohol dependence (alcohol-dependent patients, ADP).¹ It is characterized by slowly progressive, sensory-dominant symptoms and often incapacitating pain, while motor weakness and autonomic dysfunction occur at later stages.^{2,3} Typically, electrophysiologic and histopathologic findings indicate an axonal neuropathy with predominant small-fiber loss, explaining the painfulness of the disease.⁴ The exact pathophysiology of ALN is still unclear, but a multifactorial genesis including malnutrition, thiamine deficiency, and direct neurotoxic effects of ethanol and its metabolites is discussed.¹

The diagnostic gold-standard in the assessment of PNPs is based on neurologic examinations and nerve-conduction-studies (NCS), however, well-known limitations make detecting early nerve lesions and identifying spatial nerve lesion patterns difficult.^{5,6} Nerve biopsies are limited to functionally less relevant distal nerves and may not be indicated in patients with a typical clinical history. To date, comprehensive data on the exact extent and distribution of peripheral nerve lesions in ALN are not available, making the understanding of the pathomechanism challenging.

High-resolution magnetic-resonance-neurography (MRN) overcomes typical limitations of conventional diagnostics by directly visualizing peripheral nerve lesions *in vivo*.^{5,7-12} With this study, we aim to characterize, localize, and quantify peripheral nerve lesions in ADP with and without ALN by MRN in correlation with clinical scores and electrophysiologic results, and in comparison with healthy controls.

Methods

Study design, neurologic, electrophysiologic, and laboratory assessments

This prospective case-control study was approved by the institutional ethics board (University of Heidelberg; S-037/2018), and written informed consent was obtained from all participants according to the Declaration of Helsinki.

Thirty-one consecutive adult ADP who met the diagnostic criteria for alcohol dependence according to the Diagnostic Statistical Manual of Mental Disorders (DSM-IV; 21 males, 10 females, mean age 51.1±2.1 years, range 27–74 years) were enrolled from May 2018 to January 2020 at the Department of Addictive Behavior and Addiction Medicine of the Central

Institute of Mental Health Mannheim. Exclusion criteria were age <18 years, pregnancy, additional illegal drug consumption as excluded by urine drug screening and patient information, prior treatment with neurotoxic agents, concomitant causes of PNP such as diabetes mellitus, severe hypothyroidism, Vitamin B12 deficiency, malignant or infectious diseases, and contraindications for MRI. 20 age- and sex-matched healthy volunteers (14 males, 6 females, 48.2±2.6 years, range 30–67 years) were recruited upon public announcement by the Department of Neuroradiology of the Heidelberg University Hospital.

A detailed medical history was taken in all patients including specifications on the total duration of alcohol consumption, day of last consumption, quantity of alcohol consumption in gram per day, and tobacco use in pack years (J.M.B.; Table 1). Neurologic examinations included assessments for the Total Neuropathy Score (TNS), the Neuropathy Disability Score (NDS), the Neurological Severity Score (NSS), and the Neuropathy Impairment Score of the Lower Limb (NIS-LL; A.B.). Motor NCS assessed distal motor latencies (DML), compound muscle action potentials (CMAP), nerve conduction velocities (NCV), and F waves of the left and right tibial and peroneal nerve. Sensory nerve action potentials (SNAP) and NCVs were measured for the left and right sural nerve (G.S., M.W., Table 1). Autonomic dysfunction was assessed by testing the palmar and plantar sympathetic skin response (SSR; A.B.).¹³

Blood samples were collected from all patients and levels of cholesterol, vitamins B1, B6, B12, folic acid, and hemoglobin A1c (HbA1c) were measured to exclude nutritional or metabolic causes for the development of a PNP.

MRN protocol

All participants underwent high-resolution MRN in a 3.0 Tesla MR-scanner (Magnetom PRISMA, Siemens-Healthineers, Erlangen, Germany) by using a 15-channel transmit-receive extremity coil (INVIVO, Gainesville, FL, USA) and the following sequence for T2-relaxometry:

Axial dual-echo turbo-spin-echo 2D sequence with spectral fat saturation with four continuous slabs at the left leg: Slab 1: proximal to mid-thigh; slab 2: mid to distal thigh with alignment of the distal edge of this imaging slab on the tibiofemoral joint space; slab 3: lower leg with alignment of the proximal edge with the tibiofemoral joint space; slab 4: ankle with alignment of the distal edge on the tibiotalar joint space.

One additional slab was acquired at the right leg with coverage from mid to distal

thigh (same position as slab 2). Sequence parameters were: Repetition time 5860ms, lower echo time (TE_1) 14ms, higher TE (TE_2) 86ms, field-of-view $170 \times 170 \text{mm}^2$, matrix-size 512×512 , slice thickness 3.5mm, interslice gap 0.35mm, voxel-size $0.3 \times 0.3 \times 3.5 \text{mm}^3$, flip angle 180° , 35 slices, acquisition time per slab 8:25 minutes.

The net acquisition time including survey scans was 44:39 minutes, with a total examination time of approximately 60 minutes per participant due to coil repositioning.

Image post-processing and analyses

MRN images were analyzed with FSL software.¹⁴ Tibial and peroneal fascicles of the left sciatic nerve and their distal continuation as either tibial (TN) or peroneal nerve (PN) with coverage from the proximal thigh down to the distal ankle were manually segmented on 140 axial slices per leg by one neuroradiologist (C.R.) blinded to clinical data. Slice numbering for the TN was from 0 (most proximal slice at the proximal thigh) to 139 (most distal slice at the ankle), while the PN was evaluated from slice positions 0 to 69 (knee level). To exclude side differences, the TN and PN were additionally segmented on 35 axial slices from mid- to distal thigh level on the right side. This region was chosen as previous studies in different neuropathies identified nerve lesions predominantly at thigh level.^{11,15}

Signal quantification

Signal quantification was performed by calculating the apparent T2 relaxation time ($T2_{app}$) and proton spin density (ρ) according to the following two formulas by using data from the relaxometry sequence with TE_1 set at 14 ms and TE_2 set at 86 ms.^{16,17}

$$T2_{app} = \frac{TE_2 - TE_1}{\ln \left(\frac{SI(TE_1)}{SI(TE_2)} \right)}$$

$$\rho = \frac{SI(TE_1)}{\exp \left(\frac{TE_1}{T2_{app}} \right)}$$

Mean values of nerve ρ and $T2_{app}$ were calculated per slice position for each participant. Subsequently, we compared averaged mean TN ρ and $T2_{app}$ values of the thigh (imaging slabs 1 and 2, slice positions 0–69) to respective mean values of the lower leg (imaging slabs 3 and 4; slice positions 70–139) to test for potential location-dependent differences along the

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proximal-to-distal course of the TN. The PN was evaluated from the proximal thigh to the knee (imaging slabs 1 and 2).

In the same way, mean values for nerve T2-weighted-(w)signal, the single most established yet not directly quantifiable MRN marker, were additionally calculated.

Morphometric quantification

Signal-independent, morphometric quantification of nerve caliber was performed by measuring the cross-sectional area (CSA) of the TN on each axial slice. The CSA of the PN was analyzed at the thigh only.

Statistical analyses

Statistical data analyses were performed with GraphPad Prism 8.4.2 (J.K.;J.M.H.). Differences between ADP and controls, left and right distal thigh, as well as thigh and lower leg were evaluated with the Mann-Whitney test. Further subgroup analyses between ADP with ALN, ADP without ALN, and healthy controls were performed by using a one-way ANOVA for *a priori* assumptions. Subsequent post hoc analyses were corrected for multiple comparisons using the Tukey-Kramer test which allows for the possibility of unequal sample sizes. Pearson's correlation coefficients were calculated for correlation analyses. Statistical tests were two-tailed and an alpha level of significance was defined at $p < 0.05$. All results are documented as mean values \pm SEM.

All data used to conduct this study are documented in the "Methods" section. Additional anonymized datasets will be shared by the request from any qualified investigator.

Results

Clinical and electrophysiologic data

According to neurologic and electrophysiologic examination results, 25 of the 31 ADP were diagnosed with ALN, while 6 participants had no signs of a PNP (Non-ALN). Ten ADP with ALN had normal electrophysiologic results, but were classified as having PNP based on clinical findings. Detailed demographic, clinical and electrophysiologic data are shown in table 1. HbA1c, thiamine, and vitamin B12 levels were in physiologic ranges in all ADP (Table 1).

MRN data

Signal quantification: proton spin density (ρ)

ρ of the TN and PN at thigh level was markedly increased in ADP versus controls (Table 2, Figure 1A). At lower leg level, TN ρ was higher in ADP versus controls (Table 2, Figure 1B). ANOVA revealed marked differences in ρ between ALN, Non-ALN, and controls at thigh (TN:F=20.70; PN:F=17.82; $p<0.0001$ respectively) and lower leg level (TN:F=7.566, $p=0.0010$). In detail, ρ at thigh level was higher in ALN versus controls (TN and PN: $p<0.0001$) and higher in Non-ALN versus controls (TN: $p=0.0052$; PN: $p=0.0190$), while we observed no differences between ALN and Non-ALN (Table 2, Figure 1C). At lower leg level, ρ of the TN differentiated well between ALN and controls ($p=0.0008$), but not between Non-ALN and controls ($p=0.12$) or between ALN and Non-ALN (Table 2, Figure 1D). A proximal-to-distal gradient or side differences in TN or PN ρ at mid- to distal thigh level were not identified in ADP or controls ($p>0.05$).

Signal quantification: apparent T_2 -relaxation time (T_{2app})

T_{2app} of the TN and the PN was higher in ADP versus controls at the thigh (Figure 1E), but not at the lower leg (Table 2, Figure 1F). ANOVA revealed marked differences between the three subgroups at the thigh (TN:F=11.02; PN:F=14.53; $p<0.0001$ for both nerves respectively; Figure 1G), but not at the lower leg (TN:F=2.110, $p=0.13$; Figure 1H). Further post hoc comparisons showed that T_{2app} at thigh level was higher in ALN versus controls (TN and PN: $p<0.0001$), and higher in ALN versus Non-ALN (Table 2), but no differences existed between Non-ALN and controls (TN and PN: $p=0.99$). In ADP, T_{2app} of the TN showed a decrease from proximal (thigh) to distal (lower leg; $p=0.0025$), while no such gradient existed in controls ($p=0.08$). Side differences in T_{2app} did not exist in ADP or controls ($p>0.05$).

Semi-quantitative MRN marker: T_2w -signal

Nerve T_2w -signal separated well between ADP and controls at thigh and lower leg level (Table 2, Figure 2A, 2B, Figure 3). One-way ANOVA revealed distinct differences between subgroups at proximal and distal locations (thigh, TN:F=6.329, $p=0.0028$; PN:F=6.667, $p=0.0021$; lower leg, TN:F=3.880, $p=0.0247$). At thigh level, post hoc comparisons revealed a higher T_2w -signal in ALN versus controls (TN: $p=0.0019$; PN: $p=0.0014$). Differences between Non-ALN and controls (TN: $p=0.63$; PN: $p=0.58$) as well as between ALN and Non-

ALN were not observed (Table 2, Figure 2C, Figure 3). At lower leg level, TN T2w-signal was higher in ALN versus controls ($p=0.0183$), but differences were absent between Non-ALN and controls ($p=0.68$), as well as between ALN and Non-ALN (Table 2, Figure 2D). A proximal-to-distal decrease in TN T2w-signal was observed in ADP ($p<0.0001$) but not in controls ($p=0.11$). Side differences were not detected ($p>0.05$). Nerve lesion distribution in ADP was heterogenous and diffuse, with pathologically T2w-hyperintense nerve fascicles being located next to normointense appearing nerve fascicles on nerve cross-sections (Figure 3).

Morphological quantification: nerve cross sectional areas

CSA of the TN and PN at thigh level was markedly higher in ADP than in controls (Figure 4A), while differences between the two groups were not observed at the lower leg (Table 2, Figure 4B). Further subgroup analyses revealed marked CSA differences at thigh level (TN:F=6.852, $p=0.0018$; PN:F=7.915, $p=0.0007$; Figure 4C), but not at the lower leg (TN:F=1.068, $p=0.35$; Figure 4D). Further post hoc comparisons identified an increased CSA at the thigh in ALN compared to controls (TN: $p=0.0012$; PN: $p=0.0005$), while no differences existed between Non-ALN and controls (TN: $p=0.19$; PN: $p=0.20$) as well as between ALN and Non-ALN (Table 2). Side differences were not observed for ADP or controls ($p>0.05$).

Correlation analyses

We found no correlation between age, sex, body weight, body height or BMI of ADP with any of the evaluated MRN makers. The duration of heavy drinking, total lifetime alcohol amount, and time since last alcohol consumption had no measurable influence on MRN parameters. A positive correlation was found between nicotine consumption and proximal TN T2_{app} ($r=0.3452$; $p=0.0106$), while no correlation existed with HbA1c, thiamine, and vitamin B12 levels. Besides positive correlations between the NSS and lower leg TN T2w-signal ($r=0.3555$; $p=0.0174$), ρ ($r=0.3277$; $p=0.0299$), and CSA ($r=0.5084$; $p=0.0004$), we identified no consistent correlations with other neuropathy symptom scores. Left TN F-waves correlated with TN ρ at the thigh ($r=0.3223$; $p=0.0351$) and lower leg ($r=0.3752$; $p=0.0264$), as well as with TN T2w-signal at the lower leg ($r=0.4345$; $p=0.0102$), while F-waves of the right TN correlated with TN ρ ($r=0.3736$; $p=0.0227$) and T2w-signal ($r=0.4379$; $p=0.0077$) at the lower leg. Negative correlations were found between the NCV of the right ($r=-0.1256$; $p=0.0339$)

and left TN ($r=-0.3266$; $p=0.0485$) with the lower leg TN $T2_{app}$, and between CMAPs of the left TN and the TN CSA at the lower leg ($r=-0.3838$; $p=0.0229$).

Discussion

ALN accounts for the second most common PNP, and it is likely that the PNS of ADP is affected long before first PNP symptoms occur.¹ While different pathophysiologic pathways are under debate, the exact pathomechanism of peripheral nerve injury in ADP is still unknown.¹ Reliable biomarkers for early diagnosis as well as ALN monitoring are not yet available, and comprehensive histopathologic data of peripheral nerve lesions in ADP do not exist. However, a better understanding of the pathomechanism together with an earlier diagnosis of ALN would be highly relevant and contribute to improved management of these patients.

Here, we report that high-resolution MRN characterizes and quantifies lower extremity peripheral nerve lesions in ADP with and without ALN. Our results show that all MRN markers differentiate well between ADP and controls. However, only the quantitative microstructural markers ρ and $T2_{app}$ were able to differentiate between subgroups. In detail, while both ρ and $T2_{app}$ were markedly increased in ALN compared to controls, only ρ was higher in Non-ALN versus controls (Figure 1C), and only $T2_{app}$ was higher in ALN versus Non-ALN (Figure 1G). T2w-signal and CSA were also increased in ADP versus controls, but did not distinguish between subgroups (Figure 3 and 4).

From CNS studies, ρ and $T2_{app}$ are known as distinct microstructural markers of nerve tissue integrity.¹⁶⁻¹⁸ After successful implementation in the PNS in patients with ATTRv amyloidosis,¹¹ we validated them in other diffuse neuropathies such as diabetic PNP or light-chain amyloidosis, where they reliably correlated with disease severity.^{15,19} The exact mechanism leading to an alteration of ρ and $T2_{app}$ is still unknown, but most CNS studies concluded that changes in ρ and $T2_{app}$ are induced by changes in the density and macromolecular composition of nerve tissue.¹⁶⁻¹⁸ In PNP, such a variation in macromolecules with a subsequent increase of ρ , might be caused, e.g., by an accumulation of proteins in hereditary or systemic amyloidosis,^{11,19} or by an accumulation of glycosylated end-products in diabetes.^{9,15}

The observed alteration of microstructural MRN markers in ALN has similarly been described in PNPs of other origin. In detail, ρ seems to be most sensitive for an early nerve lesion detection: It was previously found to identify asymptomatic carriers of the variant *transthyretin*-gene in ATTRv-amyloidosis,^{11,12} and is now the only parameter that can distinguish between clinically and electrophysiologically completely asymptomatic Non-ALN patients and healthy controls. A likely explanation for the increased ρ in Non-ALN patients is that nerve lesions, altered in their macromolecular composition, accumulate over time, but remain clinically inapparent until a certain threshold is exceeded. Further evidence that ρ is the most sensitive marker comes from the observed positive correlation between TN ρ and F-waves, as F-waves often show abnormalities long before NCVs are reduced. $T2_{app}$ on the other hand, was only increased in symptomatic ALN, and inversely correlated with NCVs as indicators of more advanced disease stages. This is in line with previous studies where an additional increase of $T2_{app}$ was only identified in manifest PNP, potentially caused by the occurrence of an endoneural edema at more advanced PNP stages.^{11,12,19}

In other non-PNP diseases with PNS involvement, the direction of change in quantitative MRN markers (i.e., an increase or decrease in ρ and/or $T2_{app}$) was also specific and seemingly reflected the underlying pathomorphology. A study conducted by our group in MS patients, found an increased ρ (similar to the results found in PNPs) and a decreased $T2_{app}$ (opposing to the results in PNPs) in lower extremity nerves, excluding an endoneural edema as the predominant pathomechanism of PNS lesions.²⁰ Instead, an inflammatory process leading to an impaired blood-nerve barrier with subsequent leakage of plasma proteins was favored as a potential explanation. Additionally, as a post-mortem study found an increased ρ in demyelinated areas in the CNS of MS patients,²¹ we hypothesized a potential peripheral co-demyelination to be the origin of the observed increase in sciatic nerve ρ .²⁰ Another study conducted in SMA, a motor neuron disease of degenerative etiology, revealed a decreased ρ (opposing to the results in PNPs), and an increased $T2_{app}$ (similar to the results in PNPs) in the PNS of these patients.¹⁰ Again, the observed specific alteration of microstructural markers can be well explained with the decay of lower motor neurons and axonal loss in SMA.¹⁰ However, etiology specific alterations of microstructural markers in different PNP have not yet been reported. Here, ongoing studies evaluating diffusion tensor or magnetization transfer contrast imaging might increase the diagnostic accuracy in the future.

In ALN, the pathomechanism is still not sufficiently understood. Histopathologic and electronmicroscopy studies point towards direct axonal damage by ethanol and its metabolites followed by secondary demyelination of sensory and motor nerve fibers.²² Acetaldehyde, an important metabolite in the degradation of ethanol, binds irreversibly to proteins, creating cytotoxic proteins that adversely affect the function of nerve cells.¹ A subsequent deceleration of the axoplasmic flow in combination with the degradation of axonal enzymes and proteins is hypothesized to be the origin of the secondary demyelination.²² This alcohol induced accumulation of altered proteins together with demyelinating processes at later stages, might explain the observed increase in nerve ρ in the study at hand.

Additional nutritional aspects are discussed in the literature, but results are inconclusive. While thiamine deficiency has known neurotoxic effects,²³ axonal degeneration and PNP occurred in a rat model of alcoholism despite an adequate nutrition status.²⁴ In our study, malnutrition was also a negligible factor as all ADP had a normal BMI, and serum levels of glucose, HbA1C, and important B vitamins were in physiologic ranges. We cannot exclude an existing thiamine deficiency during the patients' time of chronic alcohol intake as all ADP were treated with vitamin B1 supplements for approximately one week starting at the day of their admission, and therewith prior to the conduction of MRN and electrophysiologic examinations. However, a multifactorial genesis of ALN including nutritional and genetic factors is discussed in the literature, potentially explaining that the amount of alcohol did not correlate with clinical or electrophysiologic findings.^{25,26}

One of the problems in diagnosing and treating ALN is the lack of validated clinical symptom scores that represent the severity and functional impairment in ALN. While the NIS-LL is validated for amyloidotic and diabetic PNP, the NDS and NSS for diabetic PNP, and the TNS for neurotoxic PNP under chemotherapy, it is unclear which score is best suitable for ALN. The positive correlation between MRN markers (ρ , T2w-signal, CSA) with the NSS, and the missing correlation with any of the other symptom scores, might point towards a greater importance of using the NSS in ALN.

Previous MRN studies gathered information on the proximal-to-distal distribution of nerve lesions only from evaluations of the semi-quantitative T2w-signal.^{5,11,15,19,20} In the present study, we performed an additional signal quantification from proximal thigh to distal ankle,

showing a clear proximal-to-distal gradient in ADP for nerve T2w-signal, and more importantly, for T2_{app}. Such a gradient was not found in controls, pointing towards a proximal predominance of nerve lesions in ALN, a phenomenon that we previously identified in other PNPs.^{11,15,19} However, group differences in T2w-signal and ρ were also observed at the lower leg, well-reflecting the involvement of the whole lower extremity nerves in ALN.

The cross-sectional study design limits any interpretation regarding the temporal development of ALN so that it remains unclear when first PNS lesions occur in ADP. This would be particularly interesting as some ADP present with polyneuropathic symptoms early after starting their chronic alcohol abuse, while others remain asymptomatic despite a long history of heavy alcohol consumption, similar to a phenomenon described for alcohol-induced brain atrophy.^{27,28} Therefore, longitudinal studies in long-term ADP who are still active drinkers, and in ADP who just started their chronic alcohol abuse, would be desirable. In addition, the majority of our patients were alcohol-dependent since their 30s, so that MRN findings could be potentially different if patients became addicted to alcohol earlier in their life. Another limitation is the small sample size in our Non-ALN group, potentially explaining why i) differences between ALN and Non-ALN were only observable for T2_{app} and ii) results from NCS lacked to reach consistent statistical significance between ALN and Non-ALN.

Our study provides a comprehensive in vivo characterization of peripheral nerve damage in ADP by applying high-resolution MRN and by analyzing different signal-dependent (ρ , T2_{app}) and signal-independent (CSA) quantitative markers in relation to clinical and electrophysiologic findings. While the most established MRN markers, T2w-signal and CSA, can differentiate between ADP and healthy controls, the microstructural markers ρ and T2_{app} are better suited to differentiate between ALN, Non-ALN, and controls. Furthermore, these microstructural markers might contribute to a better understanding of the underlying pathomechanism in ALN as they seemingly reflect the altered protein composition combined with axonal damage and demyelination in ALN.

References

1. Chopra K, Tiwari V. Alcoholic neuropathy: Possible mechanisms and future treatment possibilities. *Br J Clin Pharmacol* 2012;73:348-362.
2. Sobue G, Koike H. Alcoholic neuropathy. *Med J Aust* 1982;2:274-275.

3. Koike H, Sobue G. Alcoholic neuropathy. *Curr Opin Neurol* 2006;19:481-486.
4. Koike H, Mori K, Misu K, et al. Painful alcoholic polyneuropathy with predominant small-fiber loss and normal thiamine status. *Neurology* 2001;56:1727-1732.
5. Thompson PD, Thomas PK. Clinical Patterns of Peripheral Neuropathy. In: Dyck P, Thomas PK, eds. *Peripheral Neuropathy*. 4th ed. Australia: Elsevier, Saunders; 2005:1137-61.
6. Dyck PJ, Oviatt KF, Lambert EH. Intensive evaluation of referred unclassified neuropathies yields improved diagnosis. *Ann Neurol* 1981;10:222-226.
7. Bendszus M, Stoll G. Technology insight: visualizing peripheral nerve injury using MRI. *Nat Clin Pract Neurol* 2005;1:45-53.
8. Pham M, Bäumer P, Meinck HM, et al. Anterior interosseous nerve syndrome: Fascicular motor lesions of median nerve trunk. *Neurology* 2014;82:598-606.
9. Jende JME, Groener JB, Oikonomou D, et al. Diabetic neuropathy differs between type 1 and type 2 diabetes: Insights from magnetic resonance neurography. *Ann Neurol* 2018;83:588-598.
10. Kollmer J, Hilgenfeld T, Ziegler A, et al. Quantitative MR neurography biomarkers in 5q-linked spinal muscular atrophy. *Neurology* 2019;93:e653-e664.
11. Kollmer J, Hund E, Hornung B, et al. In vivo detection of nerve injury in familial amyloid polyneuropathy by magnetic resonance neurography. *Brain* 2015; 138:549-562.
12. Kollmer J, Sahm F, Hegenbart U, et al. Sural nerve injury in familial amyloid polyneuropathy MR neurography vs clinicopathologic tools. *Neurology* 2017;89:475-484.
13. Shahani BT, Halperin JJ, Boulu P, Cohen J. Sympathetic skin response - A method of assessing unmyelinated axon dysfunction in peripheral neuropathies. *J Neurol Neurosurg Psychiatry* 1984;47:536-542.
14. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, et al. Review FSL. *Neuroimage* 2012;62:782-790.
15. Pham M, Oikonomou D, Hornung B, et al. Magnetic resonance neurography detects diabetic neuropathy early and with Proximal Predominance. *Ann Neurol* 2015;78:939-948.
16. Heiland S, Sartor K, Martin E, Bardenheuer HJ, et al. In vivo monitoring of age-related changes in rat brain using quantitative diffusion magnetic resonance imaging and

- magnetic resonance relaxometry. *Neurosci Lett* 2002;334:157-160.
17. Miot E, Hoffschir D, Alapetite C, et al. Experimental MR study of cerebral radiation injury: Quantitative T2 changes over time and histopathologic correlation. *Am J Neuroradiol* 1995;16:79-85.
 18. Walimuni IS, Hasan KM. Atlas-based investigation of human brain tissue microstructural spatial heterogeneity and interplay between transverse relaxation time and radial diffusivity. *Neuroimage* 2011;57:1402-1410.
 19. Kollmer J, Weiler M, Purrucker J, et al. MR neurography biomarkers to characterize peripheral neuropathy in AL amyloidosis. *Neurology* 2018;91:e625-e634.
 20. Jende JME, Hauck GH, Diem R, et al. Peripheral nerve involvement in multiple sclerosis: Demonstration by magnetic resonance neurography. *Ann Neurol* 2017;82:676-685.
 21. Nijeholt GJ, Bergers E, Kamphorst W, et al. Post-mortem high-resolution MRI of the spinal cord in multiple sclerosis: A correlative study with conventional MRI, histopathology and clinical phenotype. *Brain* 2001;124:154-166.
 22. Kucera P, Balaz M, Varsik P, Kurca E. Pathogenesis of alcoholic neuropathy. *Bratisl Lek Listy* 2002;103:26-29.
 23. Victor M, Adams RD. On the etiology of the alcoholic neurologic diseases with special reference to the role of nutrition. *Am J Clin Nutr* 1961;9:379-397.
 24. Mellion ML, Nguyen V, Tong M, Gilchrist J, et al. Experimental model of alcohol-related peripheral neuropathy. *Muscle Nerve* 2013;48:204-211.
 25. Hammoud N, Jimenez-Shahed J. Chronic Neurologic Effects of Alcohol. *Clin Liver Dis* 2019;23:141-155.
 26. Sadowski A, Houck RC. Alcoholic Neuropathy. *StatPearls*. Treasure Island (FL)2021.
 27. García-Valdecasas-Campelo E, González-Reimers E, Santolaria-Fernández F, et al. Brain atrophy in alcoholics: Relationship with alcohol intake; liver disease; nutritional status, and inflammation. *Alcohol Alcohol* 2007;42:533-538.
 28. Nicolás JM, Fernández-Solà J, Robert J, et al. High ethanol intake and malnutrition in alcoholic cerebellar shrinkage. *QJM - Mon J Assoc Physicians* 2000;93:449-456.

Figure legends

Figure 1.

Signal quantification

Mean values of tibial nerve ρ and $T2_{app}$ were plotted at thigh (ρ : A, C; $T2_{app}$: E, G) and lower leg level (ρ : B, D; $T2_{app}$: F, H) for controls and ADP (ρ : A, B; $T2_{app}$: E, F) as well as for controls, Non-ALN and ALN patients (ρ : C, D; $T2_{app}$: G, H). ρ was clearly higher in ADP than in controls and also higher in ALN versus controls in both proximal and distal locations. In addition, ρ differentiated well between Non-ALN and controls when measured in the tibial nerve at the thigh. In contrast, differences in tibial nerve $T2_{app}$ between ADP and controls, and between ALN and controls were only found at the thigh. Here, $T2_{app}$ was also higher in ALN than in Non-ALN patients. Error bars represent SEM. Significant differences are indicated by p-values.

ADP = alcohol-dependent patients; ALN = alcohol related polyneuropathy; Non-ALN = patients without alcohol related polyneuropathy; ρ = proton spin density; $T2_{app}$ = apparent T2-relaxation time.

Figure 2.

T2w-signal

Mean values of T2w signal of the left tibial nerve at thigh (A, C) and lower leg level (B, D) are plotted for controls and ADP (A, B) as well as for the subgroups consisting of controls, Non-ALN and ALN patients (C, D). Tibial nerve T2w signal was clearly increased in ADP compared to controls in both anatomical regions. When evaluating the different subgroups, T2w signal differentiated well between ALN and controls, but not between Non-ALN and controls or between Non-ALN and ALN patients. Error bars represent SEM. Significant differences are indicated by p-values.

ADP = alcohol-dependent patients; ALN = alcohol related polyneuropathy; Non-ALN = patients without alcohol related polyneuropathy.

Figure 3.

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MRN source images

Representative magnetic resonance neurography (MRN) images (axial dual-echo turbo spin echo relaxometry sequences with spectral fat saturation) at left midthigh level are shown at equal slice positions in a healthy control (A.a, A.b), an ADP without polyneuropathy (Non-ALN; B.a, B.b) and an ADP with ALN (C.a., C.b). The first row presents complete cross-sectional images of the respective thigh, while the details in the second row show the tibial and peroneal fascicles within the sciatic nerve as indicated by the white boxes. While only very few T2w hyperintense fascicles are visible in the Non-ALN patient (B.b), a clearly increased T2w signal in multiple sciatic nerve fascicles can be observed in a representative ALN patient (C.b). A.a shows a healthy control with a regular T2w signal of the sciatic nerve, that is similar to the signal of surrounding muscles.

Figure 4.

Morphometric quantification

Mean values of tibial nerve CSA at thigh (A, C) and lower leg level (B, D) are plotted for controls and ADP (A, B) as well as for controls, Non-ALN and ALN patients (C, D). At thigh level, tibial nerve CSA was markedly higher in ADP versus controls, and also in ALN versus controls, while no such differences existed at the lower leg or between other subgroups. Error bars represent SEM. Significant differences are indicated by p-values.

ADP = alcohol-dependent patients; ALN = alcohol related polyneuropathy; Non-ALN = patients without alcohol related polyneuropathy.

Table legends

Table 1.

Demographic, clinical and electrophysiologic data

ADP = alcohol-dependent patients; ALN = alcohol related polyneuropathy; CMAP = compound muscle action potential; DML = distal motor latency; HbA1c = Glycosylated hemoglobin; LPN = left peroneal nerve; LSN = left sural nerve; LTN = left tibial nerve; NDS = Neuropathy Disability Score; NIS-LL = Neuropathy Impairment Score of the Lower Limb; Non-ALN = No signs of alcohol related polyneuropathy; NSS = Neurological Severity Score; NCV = nerve conduction velocity; RPN = right peroneal nerve; RSN = right sural nerve; RTN = right tibial nerve; SNAP = sensory nerve action potential; SSR = Sympathetic skin response; TNS = Total Neuropathy Score

ns = not significant, * = significant, *** = highly significant

Table 2.

Summary of MRN results in ADP, Non-ALN, and ALN

ADP = alcohol-dependent patients; ALN = alcohol related polyneuropathy; CSA = cross sectional area; LL = lower leg; Non-ALN = No signs of alcohol related polyneuropathy; ρ = proton spin density; PN = peroneal nerve; $T2_{app}$ = apparent T2-relaxation time; T2w = T2-weighted; TN = tibial nerve

ns = not significant, * = significant, *** = highly significant

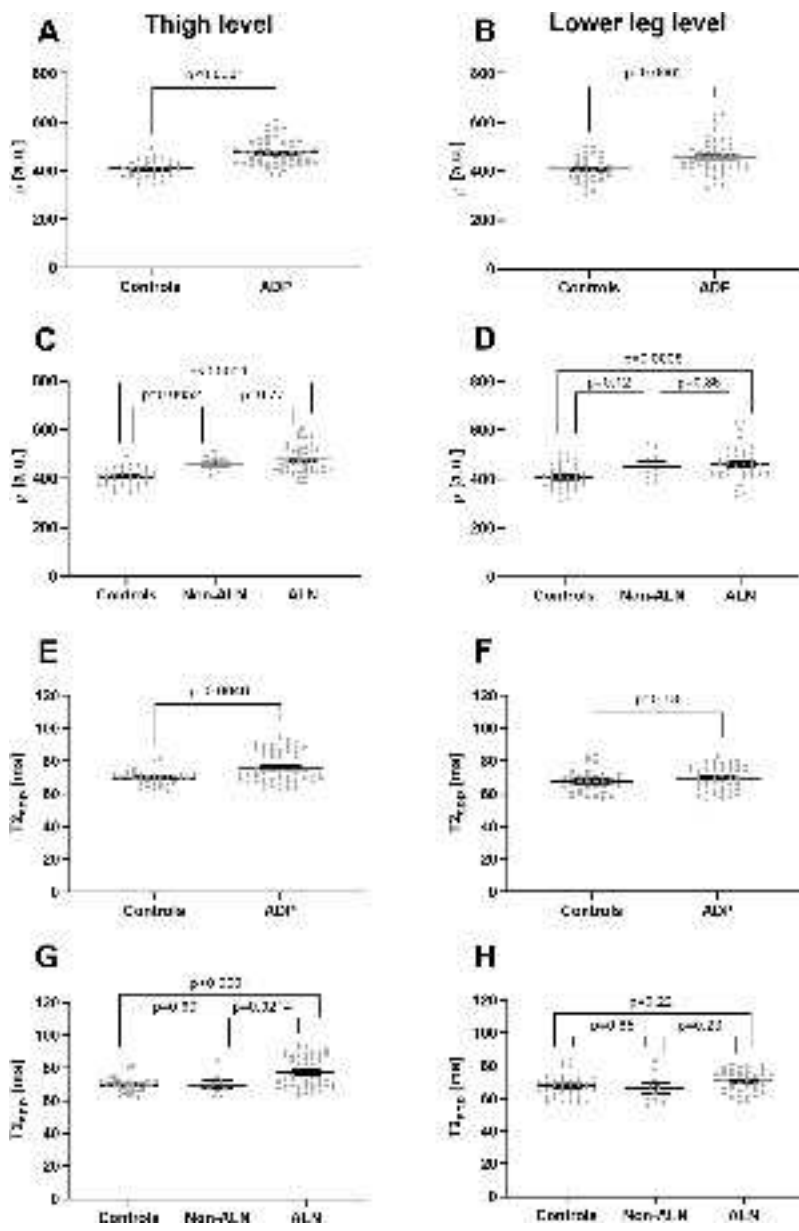
Table 1: Demographic, clinical and electrophysiologic data

Parameter	ADP	ALN	Non-ALN	p value ALN vs. Non-ALN
Age (year)	51.1 ± 2.1	50.8 ± 2.1	52.2 ± 6.8	0.67 (ns)
Sex (M/F)	21 / 10	16 / 9	5 / 1	N/A
Body weight (kg)	84.8 ± 2.9	83.4 ± 3.3	90.7 ± 5.6	0.30 (ns)
Height (cm)	174.0 ± 1.4	174.4 ± 1.7	172.5 ± 1.9	0.45 (ns)
Body mass index (kg/m ²)	27.9 ± 0.9	27.4 ± 1.0	30.3 ± 1.4	0.11 (ns)
Duration of heavy drinking (years)	20.2 ± 2.4	20.3 ± 2.7	19.5 ± 5.6	0.65 (ns)
Last consumption before examination (months, 0 for persistent consumption)	1.5 ± 0.7	1.8 ± 0.9	0.5 ± 0.3	0.64 (ns)
Amount of alcohol (grams per day)	180.6 ± 22.5	173.3 ± 24.5	208.3 ± 58.7	0.55 (ns)
Pack years (0 for non-smoking)	13.2 ± 2.9	16.7 ± 3.3	0.0 ± 0.0	0.0077*
Thiamine (reference value 28 - 85 µg/l)	81.63 ± 3.6	80.46 ± 4.0	86.33 ± 8.3	0.85 (ns)
Vitamin B12 (reference value >150 pmol/l)	364.3 ± 24.0	381.8 ± 21.3	291.5 ± 86.0	0.10 (ns)
HbA1c (reference value <6.5%)	5.4 ± 0.1	5.3 ± 0.1	5.5 ± 0.2	0.52 (ns)
TNS (range 0 to 40)	9.0 ± 1.3	10.4 ± 1.4	0.5 ± 0.5	0.0003***
NDS (range 0 to 8)	3.4 ± 0.5	3.8 ± 0.5	0.8 ± 0.8	0.0093*
NSS (range 0 to 10)	2.2 ± 0.5	2.6 ± 0.5	0.0 ± 0.0	0.0430*
NIS-LL (range 0 to 88)	8.7 ± 1.8	10.0 ± 2.0	0.4 ± 0.4	<0.0001***
SSR (positive)	3	3	0	N/A
SNAP (µV)				
LSN	10.2 ± 1.2	10.1 ± 1.4	10.4 ± 1.5	0.69 (ns)
RSN	11.5 ± 1.3	11.2 ± 1.4	13.5 ± 2.9	0.35 (ns)
CMAP (mV)				
LTN	15.5 ± 1.4	15.9 ± 1.6	13.3 ± 1.9	0.48 (ns)
RTN	15.2 ± 1.3	15.2 ± 1.5	15.3 ± 3.6	0.92 (ns)
LPN	7.0 ± 0.7	6.5 ± 0.7	9.8 ± 1.1	0.08 (ns)
RPN	6.0 ± 0.6	5.5 ± 0.7	9.1 ± 1.0	0.0432*
DML (ms)				
LTN	3.7 ± 0.1	3.6 ± 0.1	3.7 ± 0.2	0.68 (ns)
RTN	3.4 ± 0.2	3.4 ± 0.2	3.4 ± 0.1	0.58 (ns)

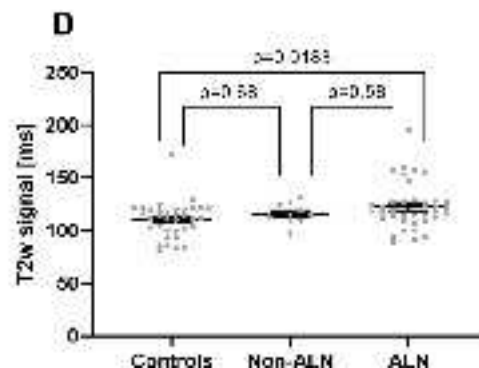
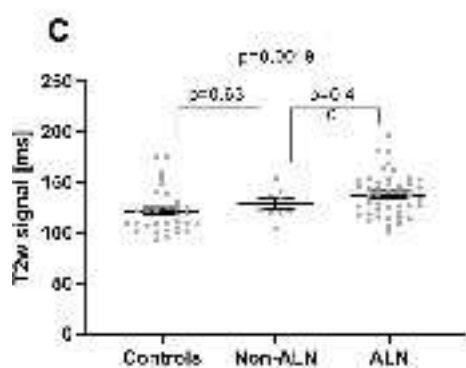
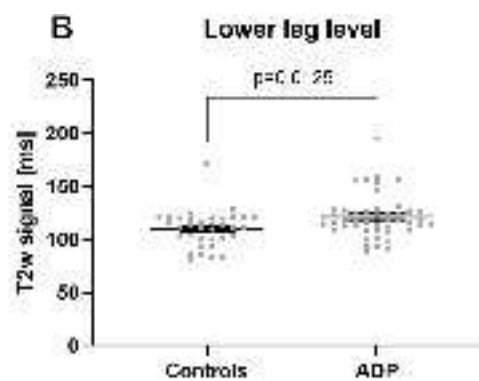
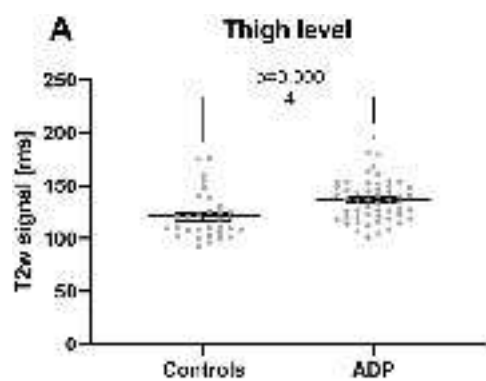
LPN	4.0 ± 0.1	4.1 ± 0.1	3.6 ± 0.2	0.07 (ns)
RPN	3.8 ± 0.2	3.8 ± 0.2	3.5 ± 0.2	0.08 (ns)
F-wave (ms)				
LTN	50.2 ± 1.0	50.6 ± 1.1	48.5 ± 2.2	0.26 (ns)
RTN	49.5 ± 1.0	50.3 ± 1.1	45.1 ± 1.3	0.0489*
LPN	48.3 ± 1.0	49.1 ± 1.0	43.9 ± 1.3	0.0329*
RPN	47.9 ± 1.1	48.8 ± 1.1	43.2 ± 1.9	0.0390*
NCV (m/s)				
LTN	47.9 ± 0.9	47.4 ± 1.1	50.4 ± 1.4	0.36 (ns)
RTN	49.1 ± 0.7	48.6 ± 0.7	52.4 ± 1.8	0.11 (ns)
LPN	46.3 ± 0.8	45.3 ± 0.9	51.2 ± 1.0	0.0011*
RPN	46.6 ± 0.8	45.7 ± 0.8	52.3 ± 0.9	0.0029*
LSN	48.9 ± 1.1	49.3 ± 1.2	47.1 ± 2.6	0.42 (ns)
RSN	50.1 ± 1.0	50.0 ± 1.1	50.9 ± 2.9	0.41 (ns)

Table 2: Summary of MRN results in ADP, Non-ALN, and ALN

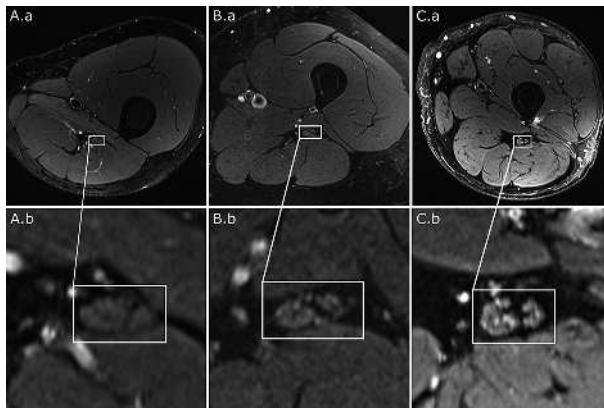
Parameter	Controls	ADP	p value Controls vs. ADP	Non-ALN	ALN	p value ALN vs. Non-ALN
T2w signal (ms)						
TN thigh	121.2 ± 3.9	136.5 ± 2.7	p = 0.0004***	128.3 ± 4.9	138.1 ± 3.1	p = 0.40 (ns)
TN LL	110.2 ± 2.9	121.2 ± 3.0	p = 0.0125*	115.9 ± 3.1	122.7 ± 3.7	p = 0.58 (ns)
PN thigh	122.1 ± 3.5	137.1 ± 2.4	p = 0.0015*	129.5 ± 8.5	138.6 ± 2.8	p = 0.41 (ns)
ρ (a.u.)						
TN thigh	407.6 ± 6.3	474.4 ± 7.1	p < 0.0001***	464.5 ± 10.6	476.4 ± 8.2	p = 0.77 (ns)
TN LL	408.0 ± 8.4	461.0 ± 10.0	p = 0.0002***	452.0 ± 18.4	463.5 ± 11.8	p = 0.86 (ns)
PN thigh	410.0 ± 8.2	482.3 ± 9.1	p < 0.0001***	470.8 ± 28.8	490.9 ± 9.2	p = 0.62 (ns)
T2_{app} (ms)						
TN thigh	69.6 ± 0.8	76.3 ± 1.3	p = 0.0046*	69.8 ± 2.3	77.6 ± 1.4	p = 0.0214*
TN LL	67.6 ± 1.2	69.6 ± 1.1	p = 0.18 (ns)	66.3 ± 2.9	70.5 ± 1.1	p = 0.23 (ns)
PN thigh	66.7 ± 0.8	74.1 ± 1.3	p = 0.0003***	66.9 ± 1.9	75.6 ± 1.4	p = 0.0064*
CSA (mm³)						
TN thigh	59.6 ± 1.2	67.3 ± 1.4	p = 0.0004***	65.9 ± 3.0	67.6 ± 1.6	p = 0.87 (ns)
TN LL	34.0 ± 1.5	35.6 ± 1.0	p = 0.25 (ns)	33.2 ± 2.0	36.2 ± 1.1	p = 0.50 (ns)
PN thigh	27.5 ± 1.0	33.0 ± 0.9	p = 0.0003***	31.6 ± 1.2	33.2 ± 1.1	p = 0.74 (ns)



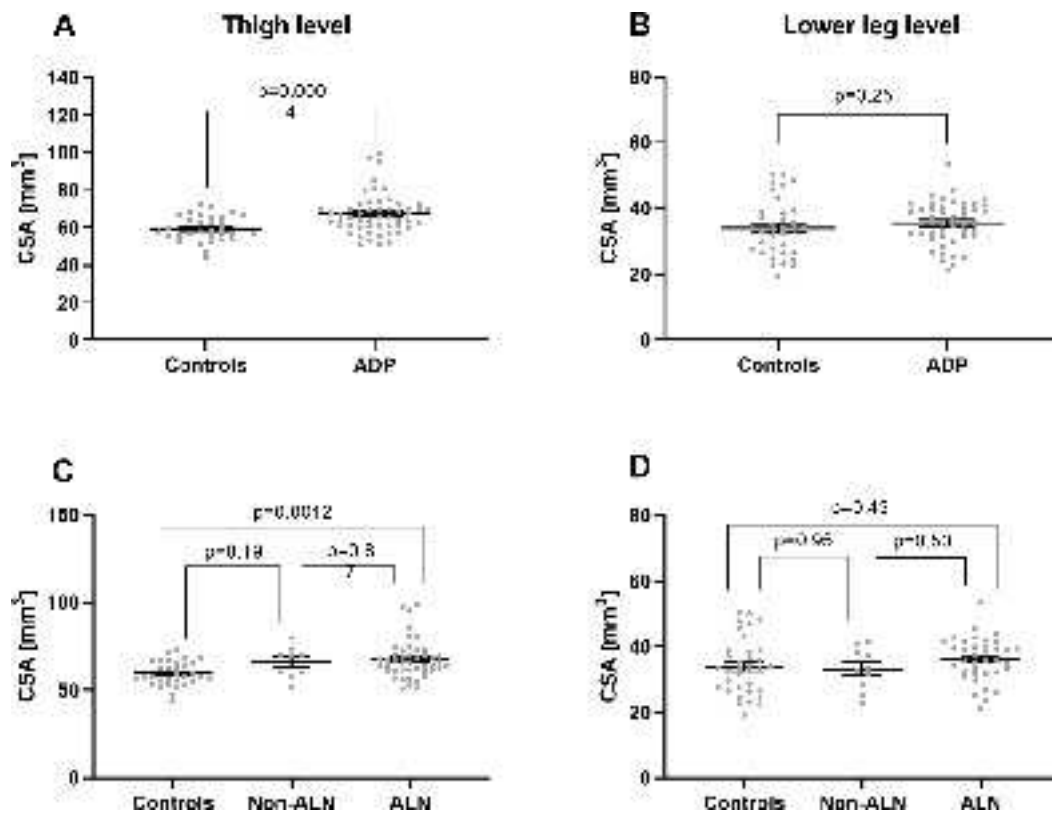
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