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Original Article

The impact of diabetic neuropathy on the distal versus proximal comparison of weakness in lower and upper limb muscles of patients with type 2 diabetes mellitus: a cross-sectional study

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Abstract

Objectives: This study aimed to determine the impact of diabetic neuropathy (dNP) on the distal versus proximal comparison of weakness in lower and upper limb muscles of patients with type 2 Diabetes Mellitus (T2DM). **Methods**: 19 healthy male controls without neuropathy (HC) and 35 male T2DM patients, without dNP (n=8), with sensory dNP (n=13) or with sensorimotor dNP (dNPsm; n=14), were enrolled in this study. Maximal isometric (IM) and isokinetic (IK) muscle strength and IK muscle endurance of the dominant knee, ankle and elbow, and maximal IM handgrip strength were measured by means of dynamometry. **Results**: Ankle muscle endurance was lower compared to the knee, independently of dNP (p<0.001). Maximal IK ankle muscle strength was also lower compared to the knee, albeit only in dNPsm (p=0.003). No differences were found between maximal IM handgrip and elbow strength. **Conclusions**: Our results suggest an impact of T2DM -with or without dNP- on lower limb muscle strength more distally than proximally, while this was not observed in the upper limb. The gradient of dNP seemed to be a determining factor for the maximal muscle strength, and not for muscle endurance, in the lower limb.

Keywords: Diabetic Neuropathy, Distal Versus Proximal Comparison, Lower And Upper Limb, Muscle Strength, Type 2 Diabetes Mellitus

Introduction

Diabetic neuropathy (dNP) affects approximately 50% of the patients with type 2 diabetes mellitus (T2DM). This complication accelerates age-related declines in muscle strength and muscle mass and contributes to an increased risk of falls and the development of difficulties in mobility and functionality. Accordingly, dNP can have a paramount impact on daily life activities and is associated with loss of independence and a reduced quality of life[1-7].

This neuropathic disorder most often affects the sensory nerves. Thus, initially, sensory dNP (dNPs) presents with sensory disturbances such as neuropathic pain and a decreased sense of vibration, temperature and light touch. At a later stage, also sensorimotor dNP (dNPsm) may develop with motor disturbances such as skeletal muscle weakness and atrophy[3,8]. These symptoms can be observed in the lower limbs, starting at the ankles and usually progressing in a distal-to-proximal way towards the knee[9].

The T2DM disease itself[10-17], but also the presence of dNP[5,18-25], contributes to the deterioration of *maximal muscle strength* in the ankle and knee joints compared to healthy controls (HC). In contrast to the extensive knowledge on maximal muscle strength in patients with T2DM, available

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data on *muscle endurance* and *explosive strength* or power in this population are scarce[5,11]. In 2020, our research group already reported a negative impact of the presence of dNPsm on maximal muscle strength and explosive strength, but not on muscle endurance, which was only affected by the T2DM disease as such[26].

The first symptoms of dNP become manifest at the lower limbs. However, symptoms at the upper limbs can develop as well, especially when dNP is present for at least 20 years[3,27]. In 2014, it was reported that muscle weakness in the hand may occur the moment dNP advances from the ankle to the level of the knee[3]. To our knowledge, a comparison of muscle weakness in the distal (hands) versus proximal (elbow) part of the upper limb, eventually due to the length-dependent nature of dNP, has not been discussed in literature.

Furthermore, the impact of sensory and motor impairments on functional domains such as activities of daily living and self-care may be more significant in the upper limb compared to the lower limb[28]. However, no data were found on the association between dNP and the physical performance of the upper limb.

Based on these knowledge gaps in literature, the aim of this study was to determine whether muscle weakness was more pronounced in the distal (ankle) compared to proximal (knee) part of the lower limb and in the distal (hands) compared to proximal (elbow) part of the upper limb in patients with T2DM and, if present, whether this was affected by the presence and severity of dNP.

Materials and methods

Participants

This observational comparative study presents data of 35 patients with T2DM and 19 healthy controls (HC). Inclusion criteria comprised male gender, aged between 55 and 85 years, able to adequately respond to instructions and to walk independently with or without walking aids.

Participants with the following conditions were excluded: (i) major neurological conditions (stroke, Parkinson's disease, dementia, other causes of nerve injury and/or non-diabetic neuropathy, e.g. radiculopathies), (ii) musculoskeletal disabilities (e.g. upper and lower extremity ulcerations and/or amputations), (iii) severe cardiovascular diseases (e.g. chronic heart failure), (iv) respiratory diseases (chronic obstructive lung diseases), and (v) severe liver dysfunction and/or renal failure.

Patients with T2DM were recruited at the Department of Endocrinology of Ghent University Hospital or by their general practitioner. T2DM was diagnosed in accordance with criteria established by the American Diabetes Association[29]. HC were recruited by online advertising and flyer distribution, and from acquaintances of the researchers. The HCs were only eligible to participate when neuropathy was diagnostically excluded, based on electroneuromyography (ENMG) performed by an experienced specialist at the Department of Neurology of Ghent University Hospital.

The present study was carried out with the approval of the Ethical Committee of Ghent University Hospital (B670201112900), according to the World Medical Association Declaration of Helsinki — Ethical Principles for Medical Research Involving Human Subjects. All participants provided a written informed consent for participation.

Participants characteristics

Demographic data were gathered by anamnesis, and the medical history (e.g. medication and the duration of diabetes) was asked or obtained through medical records.

Anthropometric data and body composition

Body height and weight were measured, and the body mass index (BMI) was calculated. Body composition was measured by total-body dual-energy X-ray absorptiometry (DXA). Total fat mass (FM^{tot}; kg), and total lean body mass (LBM^{tot}; kg), LBM of the subject's dominant arm (LBM^{arm}; kg) and leg (LBM^{leg}; kg) were determined using a Hologic QDR 4500 DXA Discovery A device (Hologic Inc., Bedford, MA, USA)[30].

Fasting venous blood samples

HbA1c, glucose, and lipid profile (total cholesterol, LDL-C, HDL-C and triglycerides) were determined. HbA1c was determined using a Menarini HA-8140 analyzer. Glucose was analyzed by the hexokinase method (COBAS, Roche). The lipid variables were evaluated using diagnostic kits (Roche Diagnostics) for HDL-C, triglycerides and total cholesterol. LDL-C was calculated from total cholesterol and HDL-C[26].

Habitual behavior assessments

The level of physical activity was recorded by the Baecke questionnaire, a short survey on activities of daily living[31]. Smoking habits were recorded as 'currently smoking', 'ever smoked' or 'never smoked', and were quantified in pack years[26]. Habitual alcohol drinkers were identified when the alcohol consumption exceeded 20 g of pure alcohol in one day at least three days per week[32].

Measurements of neuropathy

Each participant underwent an electrophysiological examination at the most affected limb indicated by the participant in order to determine the presence (and potential type and severity) of dNP. This ENMG was performed by a board-certified specialist, who was blinded for the physical examinations. This procedure has been comprehensively described elsewhere[26]. Based on this method, patients were allocated to a group without dNP (dNP-; n=8), a group with sensory dNP (dNPs; n=13) or a group with sensorimotor dNP (dNPsm; n=14).

Measurements of muscle strength

The extensors and flexors of elbow, knee and ankle joints

were measured by means of an isometric (IM) and isokinetic (IK) maximal voluntary muscle strength test battery on the Biodex® dynamometer (Biodex® Corporation). The protocol as described in the Biodex® manual was used and measurements were performed at the dominant upper and lower limb[33]. Data are reported as absolute value and as maximal elbow peak torque per lean arm mass (PT/LBM^{arm}; Nm/kg), and knee and ankle peak torque per lean leg mass (PT/LBM^{leg}; Nm/kg).

All IM assessments were performed twice and lasted for five seconds each, with a resting interval of 60 seconds between consecutive assessments, preceded by two trial tests. For optimal IM functioning, the elbow was positioned and fixed at 90° flexion, the knee at 60° flexion to assess knee extension and at 30° for knee flexion, the reference angle of the ankle was 0° [33].

The concentric and eccentric IK torques were assessed at 60°·s^{-1} and consisted of five repetitions. The highest value was considered. After one trial test, the participants were asked to push and pull as hard and fast as possible over the full range of motion with verbal encouragement of the researcher.

IK assessments at the elbow, knee and ankle joints were performed as well to measure muscle endurance. Data are reported as total work (J). Muscle endurance was assessed at 180°·s^{-1}, consisted of 25, 30 and 20 repetitions for elbow, knee and ankle in respective order, and were all verbally encouraged by the same researcher.

The handgrip strength (HGS; kg) was measured isometrically at the dominant side using the Jamar® dynamometer (Sammsons Preston Rolyan Inc.), according to the American Society of Hand Therapists guidelines[34-36]. A 15-second interval was used between consecutive measurements and the strongest of three attempts was retained as maximal grip strength[37].

Data management and statistical analysis

Data were analyzed using IBM Statistical Package for Social Sciences (SPSS version 26) and an alpha level of 0.05 was used. The normality of data was examined by Q-Q plots and by the Shapiro-Wilk test. Descriptive data are presented as mean and standard deviations (±SD) unless otherwise stated. Subject characteristics were analyzed with a univariate analysis of variance, i.e. one-way ANOVA with post-hoc Sidak. A Pearson Chi-Square test was used to compare alcohol consumption and smoking habits between the four groups[26].

The raw data of lower limb were already published in a previous article by Van Eetvelde et al, 2020[26]. For the purpose of this publication, other statistical analyses on upper and lower limb strength were implemented.

For distal versus proximal comparison, the summation of knee flexion and extension (IM and IK maximal peak torque, and IK total work separately) was compared to the summation of ankle plantar flexion (PF) and dorsiflexion (DF). The summation of elbow flexion and extension (IM and IK maximal peak torque, and total work separately) was compared to the summation of knee flexion and extension to analyze whether upper and lower limbs were differently affected. Then, the authors followed the analytical approach of Gosselinck et al., who expressed respiratory and peripheral muscle strength of 44 patients with COPD as a percentage of the control subjects' value (% control) (HC; n=22) with the difference that Gosselink et al. could rely on normalized values (expressed as a percentage of predicted value) of the in- and expiratory muscle strength in healthy, age-, weight-, and gender-matched controls, while no normalized values of peripheral muscle strength are available[38]. So, ratios of each of the three T2DM groups to the HC were calculated for relative maximal muscle strength in hand, elbow, knee and ankle and for muscle endurance in elbow, knee and ankle. These ratios were calculated by subtracting the mean value of the control group (HCm) from the individual strength value of the diabetic group (dNPi), divided by the mean value of the control group, i.e. (dNP-^{i} – HC^{m}) / HC^{m}), (dNPs^{i} – HC^{m}) / HC^{m}) and (dNPsm^{i} – HC^{m}) / HC^{m}).

Repeated measures ANOVA was carried out to detect (i) significant differences between groups (dNP-, dNPs, and dNPsm ratios) within a specific joint (hand, elbow, knee or ankle), (ii) and significant differences within groups (dNP-, dNPs, or dNPsm ratios) between two joints of our interest (e.g. knee versus ankle for distal-proximal evaluation, elbow versus knee for upper-lower evaluation, ...). For this test, the level of significance was set at $p<0.05$. When significant differences were found for (i) a post-hoc analysis was performed with an independent sample t-test, and for (ii) with a paired sample t-test. Based on the Sidak post-hoc correction for multiple testing, the formula $(1-(1-\alpha)^{1/nmt})$ was used with 'α=0.05' and 'nmt' being 'number of multiple tests'. Then, the level of significance was defined (i) at p<0.0253, and (ii) at p<0.0169.

Results

Participants

Age, habitual behavior assessments and all other anthropometric characteristics were not different between HC and the subgroups of patients with T2DM. The overall patient group had a diabetes duration ranging from 2 to 31 years with a mean of 13 years and an average HbA1c value of 7.4% (±1.03)[26]. Furthermore, LBM^{arm} and LBM^{leg} did not differ between HC, dNP-, dNPs and dNPsm. Age, level of PA, DXA body composition data, use of medication and a list of T2DM related complications can be consulted in Supplementary Table 1.

Table 1a displays the results of between-groups analyses of maximal IM muscle strength of the dominant hand (one-way ANOVA) and the relative maximal IM and IK muscle strength of the dominant elbow, knee and ankle (one-way analysis of covariance (ANCOVA) with LBM^{arm} and LBM^{leg} as respective covariates). Table 1b presents the absolute data of elbow, knee and ankle IK muscle endurance total work (one-

Table 1a. Maximal IM muscle strength of the dominant hand and relative maximal IM and IK muscle strength of the dominant elbow, knee and ankle.

	HC (n=19)	dNP- (n=8)	dNPs (n=13)	dNPsm (n=14)
Maximal IM muscle strength				
HGS max *(kg)*	49.8 (±9.08)	42.5 (±5.71)	40.8 (±9.99)	**39.1 (±9.18)[a]**
Elbow extension max PT/LBM^{arm} *(Nm/kg)*	12.8 (±1.96)	10.6 (±1.25)	11.6 (±3.26)	10.7 (±2.54)
Elbow flexion max PT/LBM^{arm} *(Nm/kg)*	17.4 (±3.80)	14.4 (±3.16)	14.6 (±2.64)	**14.0 (±2.41)[a]**
Knee extension max PT/LBM^{leg} *(Nm/kg)*	15.5 (±3.05)	13.6 (±3.15)	12.9 (±2.94)	13.1 (±3.69)
Knee flexion max PT/LBM^{leg} *(Nm/kg)*	10.5 (±1.58)	8.5 (±1.40)	8.7 (±2.49)	8.9 (±2.25)
Ankle extension (PF) max PT/LBM^{leg} *(Nm/kg)*	9.2 (±2.70)	6.6 (±3.01)	7.5 (±1.64)	6.8 (±2.57)
Ankle flexion (DF) max PT/LBM^{leg} *(Nm/kg)*	3.3 (±1.17)	3.5 (±1.06)	2.7 (±1.08)	**2.0 (±0.71)[ab]**
Maximal IK muscle strength				
Elbow extension max PT/LBM^{arm} *(Nm/kg)*	12.6 (±2.87)	9.6 (±1.04)	10.5 (±3.63)	**8.8 (±1.82)[a]**
Elbow flexion max PT/LBM^{arm} *(Nm/kg)*	13.8 (±2.73)	12.0 (±2.16)	**11.3 (±2.14)[a]**	**11.0 (±1.75)[a]**
Knee extension max PT/LBM^{leg} *(Nm/kg)*	14.3 (±3.44)	11.9 (±2.86)	12.6 (±2.50)	11.7 (±3.26)
Knee flexion max PT/LBM^{leg} *(Nm/kg)*	7.4 (±1.36)	6.5 (±0.91)	6.3 (±1.21)	**5.8 (±1.73)[a]**
Ankle extension (PF) max PT/LBM^{leg} *(Nm/kg)*	5.8 (±2.04)	5.0 (±2.96)	3.5 (±1.24)	**2.6 (±1.45)[a]**
Ankle flexion (DF) max PT/LBM^{leg} *(Nm/kg)*	2.4 (±0.70)	2.2 (±0.50)	2.0 (±0.53)	**1.5 (±0.41)[a]**

All data are expressed as mean (±SD). HC, healthy controls; dNP-, patients without diabetic NP; dNPs, patients with sensory dNP; dNPsm, patients with sensorimotor dNP. IM, isometric; HGS, handgrip strength; PT, peak torque; LBM^{arm}, lean body mass of the dominant arm; LBM^{leg}, lean body mass of the dominant leg; PF, plantar flexion; DF dorsiflexion; IK, isokinetic. [a] p<0.05 compared to HC. [b] p<0.05 compared to dNP-.

Table 1b. IK muscle endurance of the dominant elbow, knee and ankle.

	HC (n=19)	dNP- (n=8)	dNPs (n=13)	dNPsm (n=14)
Elbow extension total work *(J)*	841.1 (±236.06)	653.4 (±148.11)	**650.1 (±273.84)[a]**	**597.2 (±197.73)[a]**
Elbow flexion total work *(J)*	898.9 (±324.56)	698.4 (±116.98)	690.3 (±252.65)	**670.2 (±225.18)[a]**
Knee extension total work *(J)*	2124.8 (±480.33)	**1667.6 (±141.05)[a]**	**1761.3 (±480.04)[a]**	**1583.6 (±681.77)[a]**
Knee flexion total work *(J)*	998.9 (±291.43)	787.3 (±234.22)	**728.0 (±316.33)[a]**	**622.6 (±375.91)[a]**
Ankle extension (PF) total work *(J)*	252.6 (±80.27)	**103.9 (±55.32)[a]**	**100.4 (±60.12)[a]**	**70.3 (±92.84)[a]**
Ankle flexion (DF) total work *(J)*	82.0 (±26.02)	52.5 (±45.57)	47.0 (±44.81)	**24.1 (±29.74)[a]**

All data are expressed as mean (±SD). HC, healthy controls; dNP-, patients without diabetic NP; dNPs, patients with sensory dNP; dNPsm, patients with sensorimotor dNP. IK, isokinetic; PF, plantar flexion; DF dorsiflexion. [a] p<0.05 compared to HC.

Table 2. Ankle-knee comparison for IK muscle endurance total work, maximal IK and IM muscle strength.

	dNP-	dNPs	dNPsm	ankle-knee comparison	joint*group interaction
total work ankle ratio	**-53.3 (±18.9)[a]**	**-55.8 (±25.69)[a]**	**-71.8 (±33.94)[a]**	***p*<0.001**	*p*=0.555
total work knee ratio	-21.4 (±10.90)	-20.3 (±21.97)	-29.4 (±32.71)		
max IK ankle ratio	-12.5 (±38.97)	-32.7 (±16.94)	**-49.8 (±19.41)[a,b]**	***p*=0.003**	***p*=0.049**
max IK knee ratio	-15.1 (±16.96)	-12.9 (±15.41)	-19.3 (±22.05)		
max IM ankle ratio	-17.7 (±30.60)	-17.2 (±12.66)	-26.3 (±21.61)	*p*=0.258	*p*=0.240
max IM knee ratio	-14.7 (±16.34)	-17.1 (±17.67)	-15.6 (±21.41)		

Data (%) are expressed as mean (±SD). IK, isokinetic; IM, isometric; dNP-, patients without diabetic NP; dNPs, patients with sensory dNP; dNPsm, patients with sensorimotor dNP. [a] p<0.017 all dNP groups: ankle compared to knee. [b] p<0.025 ankle: dNPsm compared to dNP-.

way ANOVA). All post-hoc comparisons were performed by means of the Sidak test.

In seven patients' data for ankle PF and/or DF strength parameters were missing. As the data of all seven patients were similar to the baseline characteristics of the cohort, we decided to include their HGS, elbow and knee strength data in the final analysis (Supplementary Table 2).

Distal versus proximal lower limb comparison between dNP-, dNPs, and dNPsm

At the ankle, total work ratios were more negative compared to the knee ($p<0.001$) with an effect size (Partial Eta Squared; η^2) of 0.629. In dNP-, dNPs and dNPsm, the paired sample t-test of the ankle-knee comparison revealed significant lower ankle values (resp. $p=0.005$, $p=0.005$, and $p=0.001$). As no significant joint*group interaction was detected, this effect was independent of the presence of dNP ($p=0.555$) (Table 2).

Significant lower maximal IK ankle ratios were found compared to the knee ratios ($p=0.003$; $\eta^2=0.290$). A significant joint*group interaction ($p=0.049$; $\eta^2=0.200$) for maximal IK ratios was observed, indicating that the most negative maximal IK ratios were dependent on the presence of dNPsm. Specifically, at the ankle, the dNPsm group was significantly more affected than the dNP- group ($p=0.010$) and, additionally, more negative values of the ankle compared to the knee were observed within the dNPsm groups ($p<0.001$) (Table 2).

For the IM muscle strength ratios, no significant differences were found in the ankle-knee comparison (Table 2).

Distal versus proximal upper limb comparison between dNP-, dNPs, and dNPsm

The maximal IM HGS ratios (%) in the dNP-, dNPs and dNPsm group were respectively -14.6 (±11.47), -18.0 (±20.07) and -21.5 (±18.44). For maximal IM elbow strength in the dNP-, dNPs and dNPsm group, the ratios (%) were respectively -17.4 (±13.25), -13.4 (±11.79) and -18.3 (±14.79). The distal versus proximal upper limb comparison for maximal IM muscle strength did not show any significant differences within (hand-elbow comparison; $p=0.652$) and between the different groups (joint*group interaction; $p=0.725$).

Upper versus lower limb comparison between dNP-, dNPs, and dNPsm (elbow-knee)

The IK muscle endurance elbow total work ratios (%) in the dNP-, dNPs and dNPsm group were respectively -22.3 (±14.58), -23.0 (±29.55) and -27.2 (±23.35). For IK muscle endurance knee total work in the dNP-, dNPs and dNPsm group, the ratios (%) were respectively -21.4 (±10.90), -20.3 (±21.97) and -29.4 (±32.71). The upper versus lower limb comparison for IK muscle endurance total work did not show any significant differences within (elbow-knee comparison; $p=0.922$) and between the different groups (joint*group interaction; $p=0.889$).

The maximal IM elbow strength ratios (%) in the dNP-, dNPs and dNPsm group were respectively -17.4 (±13.25), -13.4 (±11.79) and -18.3 (±14.79). For maximal IM knee strength in the dNP-, dNPs and dNPsm group, the ratios (%) were respectively -14.7 (±16.34), -17.1 (±17.67) and -15.6 (±21.41).The upper versus lower limb comparison for maximum IM muscle strength revealed no significant changes in any group (elbow-knee comparison; $p=0.529$), nor between groups (joint*group interaction; $p=0.521$).

The maximal IK elbow strength ratios (%) in the dNP-, dNPs and dNPsm group were respectively -18.1 (±11.17), -17.4 (±20.60) and -25.1 (±12.66). For maximal IK knee strength in the dNP-, dNPs and dNPsm group, the ratios (%) were respectively -15.1 (±16.96), -12.9 (±15.41) and -19.3 (±22.05). The upper versus lower limb comparison for maximum IK muscle strength revealed no significant changes in any group (elbow-knee comparison; $p=0.072$), nor between groups (joint*group interaction; $p=0.808$).

Upper versus lower limb comparison between dNP-, dNPs, and dNPsm (hand-ankle)

The maximal IM HGS ratios (%) in the dNP-, dNPs and dNPsm group were respectively -14.6 (±11.47), -18.0 (±20.07) and

-21.5 (±18.44). For maximal IM ankle strength in the dNP-, dNPs and dNPsm group, the ratios (%) were respectively -17.7 (±30.60), -17.2 (±12.66) and -26.3 (±21.61). The distal versus proximal upper limb comparison for maximal IM muscle strength did not show any significant differences within (hand-ankle comparison; p=0.652) and between the different groups (joint*group interaction; p=0.725).

Discussion

The main objective of this study was to determine whether muscle weakness was more pronounced in the distal (ankle) compared to proximal (knee) part of the lower limb and in the distal (hands) compared to proximal (elbow) part of the upper limb in patients with T2DM and, if present, whether this was affected by the presence and severity of dNP.

For muscle endurance total work, the ankle ratios were significantly more negative compared to the knee ratios, independently of the presence of dNP. Concerning maximal IK strength, the ankle ratios were significantly more negative compared to the knee ratios, dependent on the presence of dNP as the lowest values were only present in the dNPsm group. Regarding the upper limb, no significant differences in ratios between subgroups were found. This might suggest a more pronounced impact of dNP on the distal compared to proximal muscles in the lower limb versus upper limb.

Distal versus proximal lower limb comparison between dNP-, dNPs, and dNPsm

The main finding in the lower limb is a more distinct muscle weakness in the ankle versus the knee. This is in line with the results of our previous research and certainly provides more in-depth information about the impact of dNP-, dNPs and dNPsm on lower limb muscle weakness[26].

This study revealed that muscle endurance of the ankle is more affected than the knee in all patients with T2DM, independent of the presence of dNP. The impact of chronic hyperglycemia and impaired glycemic control on top of the ageing process of skeletal muscle fibers should not be neglected. Furthermore, altered contractile mechanisms and cellular metabolism (e.g. insulin resistance, metabolic inflexibility, reduced mitochondrial function and accelerated advanced glycation end products) play a role in the deterioration of muscle endurance[39]. Allen et al., 2015, proposed that dNP-related loss of muscle endurance is partially attributed to neuromuscular transmission instability under conditions that stress the capacity of the system, such as fatiguing contractions, and to possibly pathological alterations in the above-mentioned cellular metabolism or blood flow[11,13]. Another approach to clarify the decreased muscle endurance in this population is the well-documented muscle fiber type shift in T2DM patients over the years towards a higher proportion of type II muscle fibers, knowing that the slow-twitch oxidative muscle fibers type I are predominantly activated by endurance stimuli[4,5,40-42]. Additionally, we hypothesize that smaller muscle groups at smaller joints could be more vulnerable to metabolic changes than larger muscle groups at larger joints. The ankle and hand joints consist of smaller muscle groups with lower muscle mass, less adequate microvascular blood supply, and are possibly more affected due to mitochondrial dysfunction and impaired free fatty acid metabolism.

Interestingly, the maximal IK muscle strength of the ankle also revealed lower values compared to the knee, only in the dNPsm group. Hence, we postulate that, additional to the metabolic factors caused by the disease itself, the presence and severity of dNP has a negative impact on maximal muscle strength. This may be due to fiber length-dependent or progressive centripetal degeneration of peripheral nerve axons in combination with an impaired regeneration, causing length-dependent neurological complications. As sensory neurons are less resistant than motor neurons to the dysfunction and degeneration associated with the disease itself, injuries due to lack of sensation may be noticed before muscle strength decreases. Nevertheless, the damages to the sensory and motor nervous system progress in a distal-to-proximal way, generally starting at the toes, extending over the feet and sometimes spreading to/over the lower legs or higher above the knee level, depending on the intensity of the peripheral nerve lesions[10,12-14,18,21,43].

Finally, the reduced lower limb muscle strength in patients with T2DM may have a high impact on their functionality and mobility. Upper leg muscles are larger, bigger and stronger than lower leg muscles, and thereby play a more important role in gait and functional mobility[44]. However, the muscles of the ankle play a key role in the biomechanics of gait (e.g. foot to roll over from heel to toe in a natural way) and, consequently, have large impact on gait quality[14].

Distal versus proximal upper limb comparison between dNP-, dNPs, and dNPsm

No significant differences were found between the handgrip and the elbow strength, indicating that total upper limb muscles might not be as much influenced by dNP as lower limb muscles, apparently being more progressively affected. It might be assumed that upper limb muscles are better preserved than lower limb muscles, which may be due to the length-dependent differences in upper and lower nerves.

Upper versus lower limb comparison between dNP-, dNPs, and dNPsm

Purely based on the stronger reduction in muscle strength in ankle compared to knee and no significant differences between hand and elbow, it can be suggested that there is a different impact of dNP on upper and lower limb muscle strength. Unfortunately, this was not supported by the comparison of the maximal muscle strength of the reciprocal joints (elbow versus knee and hand- versus ankle).

Often, when the loss of sensory axons and/or motor axons and units extends above the knee level, progressively, the fingers, hand and forearm can be affected too, following the

same fiber length-dependent pattern as in the lower limbs. Occasionally, the neuropathy may even affect the sensory nerve fibers of the intercostal nerves[43].

Lynch et al., 1999, found a more distinct decline in the maximal peak torque of lower limb muscles compared to the peak torque of upper limb muscles, which was definitely age-related[45]. Ageing may induce more inherent morphological changes in the leg than in the arm and, therefore, leg muscles might be more susceptible to loss of lean muscle mass. Another possible explanation for the more intact upper limb in the elderly is the quantity (level and intensity) of the activities of daily living, performed by the arm muscles, such as dressing, cooking, bathing, rising from a chair or sitting down, and activities of self-care in general[46,47].

Clinical implications

We investigated the maximal muscle strength and muscle endurance of lower and upper limbs, as these can be considered as important components of physical fitness and function. Minimum levels of both are needed to perform activities of daily living, to maintain functional independence while ageing, and to participate in active leisure-time activities without strains, stress or fatigue[48].

Generally, muscle weakness of lower limbs may definitely impact gait and balance, may increase risk of falls, and may negatively influence gait rehabilitation. Besides muscle weakness, the functional shortcoming in this ageing population can be caused by loss of proprioception, decreased joint mobility, and impaired vision[11,12,14]. Nowadays, the American Diabetes Association recommends aerobic exercises (e.g. walking and bicycling) in combination with gradually increased resistance exercises (e.g. exercises using machines and elastic resistance bands), predominantly in order to strengthen larger lower limb muscles to reduce risk factors such as insulin resistance, cardiovascular components, and overweight[44,49]. However, the majority of exercise therapy researchers lay focus on the musculature of the knee as they claim that knee extensors are a major antigravity muscle group, responsible for propelling and controlling the body during gait. Consequently, T2DM patients with dNP who experience knee muscle weakness can suffer from impaired balance, reduced gait speed, increased incidence of falls, and severe injuries with hospitalization[18,44]. Besides the alterations in the cartilage, ligaments and tendons of the knee, an increased thickness of the Achilles tendon and plantar fascia has been observed, leading to decreased flexibility of the ankle joint and limited dorsiflexion during walking[18]. Therefore, future research should rather investigate the effect of a refined training program focusing on smaller muscle groups such as ankle and hand musculature. Optimized and strengthened muscles around the smaller joints are necessary for the patients' functionality in order to stay as mobile as possible. Initially, physical therapy should be concentrated on analytical exercises. Later on, this training program could be combined with a more functional approach to focus on the physical component.

Strengths and limitations

Dyck et al., 2010, showed that a clinical diagnosis of dNP is unreliable and inaccurate[50]. Therefore, we relied on the more accurate ENMG testing, which is and remains the gold standard for the diagnosis of dNP[3].

We decided to incorporate DXA data into our study, as this is described as the preferred method for both research and clinical use[34].

In our study, the Biodex® dynamometer was consequently used for all IM and IK elbow, knee and ankle assessments at the dominant side. However, as maximal IM HGS was executed by using the Jamar® dynamometer, it was difficult to compare HGS ratios with maximal IM elbow and/or ankle ratios. In future research, we recommend the use of the Biodex® dynamometer in order to assess maximal IM and IK wrist palmar flexion and dorsiflexion, and to compile muscle endurance total work results.

As already mentioned in our previous publication, the power of the results may be jeopardized by the limited number of dNP- patients compared to the dNPs and dNPsm groups[26].

In our study, the median age (min-max) in three of the four groups was approximately equal (HC 64 (55-76), dNP- 64 (61-70) and dNPs 66 (55-76)). Contrary to this, the dNPsm group showed a wider range in age (67 (58-82)), albeit not significant different from the other groups. It is well known that healthy subjects reach their maximal muscle strength at the age of 30 with relatively stable values until the age of 60-65[51,52]. Thereafter, an age-dependent progressive loss of muscle mass and strength can be observed, described as 'sarcopenia', which can result in functional impairment leading to falls, injuries, and loss of independence in the healthy ageing population[34,51,52]. Meanwhile, in our target population, the diabetes health state should be taken into consideration as sarcopenia may occur earlier in patients with T2DM (often between 50 and 60 years), and as dNP on top of the age-dependent muscular degeneration could induce a synergistic detrimental impact on muscle mass and strength[51,53].

As the Baecke questionnaire for activities of daily living was used in this study, we did not segregate the level and intensity of daily use of upper and lower limbs. In future research, the investigators could question the daily use of arms and legs separately to get more insight into differences in frequency and intensity.

Furthermore, the normalization method used in this study, may have biased the statistical analysis of the obtained results due to the absence of a large dataset in healthy, age-, weight-, and gender-matched controls[38].

Finally, muscle strength can also be influenced by nutritional status and musculoskeletal pain, which was not assessed in this study[26].

Future research directions

The design of future studies should rather be longitudinal and prospective as it is of very high importance to investigate

the possibility of a distal-to-proximal progression of muscle weakness in lower and upper limbs of patients with T2DM, eventually due to the length-dependent nature of dNP, in order to preserve functionality and independence, and to reduce the risk of falls.

Conclusion

This study suggests a more pronounced weakness in the ankle compared to the knee regarding maximal muscle strength due to the presence and a gradient in severity of dNP. Moreover, this phenomenon was only present in the lower limb compared to the upper limb. Muscle endurance total work revealed significantly lower ankle ratios in all three diabetic groups compared to the knee, and thus independent of the presence of dNP. Therefore, our research group suggests that metabolic disturbances in patients with T2DM are probably responsible for these negative values.

These findings are of major importance to construct optimal and appropriate analytical strength programs in lower and upper limbs in order to maintain functional independence, and in particular tailored to T2DM patients with or without dNP.

Disclosure

The data of this paper have been presented as a poster at the 56th Virtual EASD Annual Meeting, 21-25 September 2020.

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Authors' contributions

B.V.E., D.C. and P.C. conceived and designed the study, analyzed data, wrote, edited, and reviewed the manuscript. B.V.E., B.L., P.P., K.V.W., S.H. and J.S. researched data, contributed to the discussion and interpretation of data, and edited and reviewed the manuscript. All authors gave final approval for publication. B.V.E. and P.C. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Supplementary Table 1. Additional information of the participants.

	HC (n=19)	dNP- (n=8)	dNPs (n=13)	dNPsm (n=14)
Age *(years)*	64 (±6.7)	65 (±3.2)	66 (±6.9)	67 (±8.3)
Level of PA *(/15)*	8.0 (6.3-9.6)	8.5 (5.5-9.5)	8.0 (5.1-10.1)	7.6 (6.6-10.3)
LBM^{tot} *(kg)*	61.5 (±6.90)	66.1 (±9.57)	65.7 (±10.01)	68.7 (±8.41)
LBM^{arm} *(kg)*	3.6 (±0.56)	3.9 (±0.78)	3.8 (±0.76)	3.9 (±0.57)
LBM^{leg} *(kg)*	9.6 (±1.10)	10.0 (±1.50)	9.8 (±1.49)	10.1 (±1.50)
FM^{tot} *(kg)*	18.5 (±5.00)	22.3 (±5.80)	21.6 (±10.00)	23.4 (±6.47)
DM medication oral *(%)*	0	100	84.6	71.4
Metformin® *(%)*	0	62.5	69.2	42.9
Januvia® *(%)*	0	12.5	0	7.1
DM insulin injection *(%)*	0	37.5	50.0	85.7
Lantus® *(%)*	0	0	23.1	28.6
Humalog® *(%)*	0	12.5	0	7.1
Novorapid® *(%)*	0	12.5	15.4	14.3
Other medication *(%)*	57.9	87.5	69.2	78.6
NSAIDs *(%)*	0	12.5	0	0
Anticoagulants *(%)*	15.8	50.0	46.2	71.4
Cholesterol-lowering *(%)*	31.6	75.0	23.1	57.1
Antihypertensive *(%)*	26.3	62.5	53.8	71.4
DM complications other than dNP	0	2	2	5
retinopathic	0	0	0	1
nephropathic	0	0	1	2
cardiovascular	0	2	2	2
orthopedic (LJM)	0	1	0	0
dermatologic (ulcer)	0	0	0	2

Age, LBM and FM data are expressed as mean (±SD); level of PA is expressed as median (min-max). The percentages of each participant's relevant medication intake are presented. The number of patients with DM related complications (other than dNP) are presented. HC, healthy controls without neuropathy; dNP-, patients without diabetic neuropathy (dNP); dNPs, patients with sensory dNP; dNPsm, patients with sensorimotor dNP. PA, physical activity; LBM^{tot}, total lean body mass; LBM^{arm}, lean body mass of the dominant arm; LBM^{leg}, lean body mass of the dominant leg; FM^{tot}, total fat mass; DM, diabetes mellitus; NSAIDs, nonsteroidal anti-inflammatory drugs; LJM, limited joint mobility.

Supplementary Table 2. Main characteristics of the seven participants with missing ankle DF/PF ratios.

Patient	#1	#2	#3	#4	#5	#6	#7
ENMG	dNP-	dNPs	dNPs	dNPs	dNPsm	dNPsm	dNPsm
Age *(yrs)*	62	59	65	72	71	60	68
BMI *(kg/m^2)*	27.7	36.9	30.0	22.9	28.5	33.5	32.1
Diabetes duration *(yrs)*	3	13	10	10	6	26	10
HbA1c *(%)*	6.0	7.1	6.6	7.2	5.5	10.0	8.0
LBM^{arm} *(kg)*	4.0	5.2	3.8	3.7	3.9	3.9	3.3
LBM^{leg} *(kg)*	11.0	12.4	9.3	8.6	9.1	11.0	9.8

DF, dorsiflexion; PF, plantar flexion; ENMG, electroneuromyography; dNP-, patients without diabetic NP; dNPs, patients with sensory dNP; dNPsm, patients with sensorimotor dNP; BMI, body mass index; LBM^{tot}, total lean body mass; LBM^{arm}, lean body mass of the dominant arm; LBM^{leg}, lean body mass of the dominant leg.