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The impact of sensory and/or sensorimotor neuropathy on lower limb muscle endurance, explosive and maximal muscle strength in patients with type 2 diabetes mellitus

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ABSTRACT

Aims: The purpose of this study was to investigate the impact of diabetic neuropathy (dNP) on lower limb endurance, explosive and maximal muscle strength in patients with Type 2 Diabetes Mellitus (T2DM).
Methods: Fifty-four participants, aged between 55 and 85, were enrolled in this observational comparative study. The patients with T2DM had an average HbA1c of 7.4% (±1.03) and diabetes duration of 13 years. Participants were classified by means of electroneuromyography as T2DM without dNP (dNP-; $n = 8$), T2DM with sensory dNP (dNPs; $n = 13$), T2DM with sensorimotor dNP (dNPsm; $n = 14$), and healthy controls without neuropathy (C; $n = 19$). Maximal muscle strength and muscle endurance of the dominant knee and ankle were measured by dynamometry, while explosive muscle strength was evaluated by mechanography.
Results: Muscle endurance "total work" in knee extension and ankle plantar flexion was higher in the healthy controls compared to dNP-, dNPs and dNPsm, in knee flexion compared to dNPs and dNPsm, and in ankle dorsiflexion compared to dNPsm only ($p<0.05$). Furthermore, relative explosive muscle strength "total power/body weight" and relative maximal muscle strength "peak torque/lean body mass of the dominant leg" considering knee flexion, ankle plantar flexion and dorsiflexion, were higher in healthy controls compared to the dNPsm group, and for maximal muscle strength ankle dorsiflexion even between dNP- and dNPsm ($p < 0.05$).
Conclusions: Muscle endurance is impaired in patients with T2DM, independent of the presence of dNP. Explosive and maximal muscle strength are more likely affected by the presence and severity of dNP.

1. Introduction

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disease, associated with considerable macrovascular (i.e. coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (i.e. diabetic neuropathy (dNP), nephropathy, and retinopathy) with dNP affecting approximately 50% of patients with T2DM.[1]

DNP can be classified into sensory dNP (dNPs), characterized by isolated sensory complaints without motor impairment (e.g. reduced tactile function, pain sensation, and proprioception) and sensorimotor dNP (dNPsm), affecting the neuromuscular system and leading to muscle weakness and atrophy of the leg and foot musculature.[2]

A considerable body of evidence exists on reduced lower limb maximal muscle strength[3–13] and muscle mass[5–7,9,12] in patients with T2DM, with or without dNP, compared to healthy controls. In general, the available studies showed an additive negative effect of dNP, further aggravating the decrease in muscle strength and mass in patients with T2DM. Both T2DM and dNP are associated with metabolic and inflammatory changes that possibly accelerate the age-related deterioration of muscle strength and mass, and are also related to impaired balance and gait, which will in turn increase the risk of falls. Accordingly, this negative spiral of diabetes and ageing will contribute to an enhanced development of disability in activities of daily living and can eventually lead to a quicker loss of independence.[14,15]

In contrast to the well-established findings on maximal muscle strength, little is known about the impact of T2DM and dNP on muscle endurance and explosive muscle strength. As both are crucial muscle function parameters, closely related to activities of daily living and quality of life,[15,16] this flaw in knowledge and insight may be responsible for suboptimal treatment effects of exercise and rehabilitation. Particularly

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in the elderly, decreased maximal muscle strength, force steadiness (i.e. strength-endurance), and power (i.e. explosive strength) are strongly associated with an increased risk for functional limitations, disabilities, and with higher probability of falls.[17] Fatigability of skeletal muscles can limit the performance of daily tasks that require repeated or sustained contractions.[18,19] Explosive strength (i.e. rapidly available strength) is also of functional significance in order to avoid falls and hip fractures in older adults.[20,21]

To our knowledge, only two studies examined muscle endurance in T2DM patients with dNP, and reported reduced levels of lower limb endurance in these patients. These findings were associated with impaired mobility and poor quality of life.[16,22] Additionally, in a T2DM population with exclusion of clinically suspected dNP, Senefeld et al. provided pioneering work on the contribution of neural (i.e. (supra)spinal) and muscular (i.e. contractile) mechanisms to a greater fatigability in the knee extensor muscles compared to healthy participants after a dynamic fatiguing task.[18] Yet, the influence of T2DM and dNP on explosive muscle strength remains unexplored.

Currently, it is unclear whether the different measures of muscle strength and muscle mass are differently affected in patients with either dNPs or dNPsm. We hypothesized that both muscle endurance and explosive muscle strength are affected in T2DM patients without and with neuropathy compared to a healthy control group in the same age category. This affection is hypothesized to increment from patients without diabetic neuropathy, over patients with sensory diabetic neuropathy into patients with sensorimotor diabetic neuropathy.

In order to both optimize and customize the recommendations for strength training, the aim of this study was to examine the impact of sensory and sensorimotor dNP on lower limb endurance, explosive and maximal muscle strength, compared to T2DM patients without dNP and healthy controls.

2. Participants, materials and methods

2.1. Study design and participants

In this observational comparative study, 35 patients with T2DM and 19 healthy volunteers (C) were included ($N = 54$). Patients were classified into the following groups: T2DM patients without dNP (dNP-; $n = 8$), with sensory dNP (dNPs; $n = 13$) and those with sensorimotor dNP (dNPsm; $n = 14$).

In order to be eligible for this study, participants had to be male, aged between 55 and 85, had to be able to understand Dutch instructions and to walk independently with or without walking aids. Participants were excluded when they experienced (i) neurological conditions (e.g. stroke, dementia, other causes of nerve injury and/or non-diabetic neuropathy), (ii) musculoskeletal disabilities (e.g. foot ulcerations and lower extremity 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 by endocrinologists at the Department of Endocrinology (Ghent University Hospital) or by general practitioners. T2DM was diagnosed according to the ADA-criteria.[23] Only controls without neuropathy were eligible and incorporated into the study by means of online advertising, flyer distribution, and from acquaintances of the researchers.

The present study was carried out with the approval of the Ethical Committee of the Ghent University Hospital (B670201112900) and all participants provided a written informed consent for participation.

2.2. Participant characteristics

Demographic data were gathered during anamnesis. Relevant medical history (e.g. medication and the duration of diabetes) was asked or obtained through medical files.

2.2.1. Anthropometric data

Height and weight were measured and body mass index (BMI) was calculated.

Total-body dual-energy X-ray absorptiometry (DXA) was performed to determine total lean body mass (LBM^{tot}; kg), total fat mass (FM^{tot}; kg) and LBM of the participant's dominant leg (LBM^{leg}; kg) using a Hologic QDR 4500 DXA Discovery A device (Hologic Inc., Bedford, MA, USA). Peripheral quantitative computed tomography (pQCT; CXT-2000, Stratec Medizintechnik, Pforzheim, Germany) was used to scan the dominant leg (66% of the tibia length) in order to assess muscle density (mg/cm^3).

2.2.2. Blood samples

HbA1c, glucose and lipid profile (total cholesterol, LDL, HDL and triglycerides) were assessed in fasting venous blood. HbA1c levels were 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 (cholesterol oxidase-PEG), triglycerides (glycerol phosphate-PAP) and total cholesterol (cholesterol oxidase-PAP). LDL-C was calculated from total cholesterol, HDL-C and triglycerides.

2.2.3. Habitual behavior assessments

The level of physical activity was recorded by the Baecke questionnaire.[24] Smoking habits were recorded as 'currently smoking' or 'ever smoked', and were quantified in packyears. Habitual alcohol drinkers were defined as participants who consumed at least 20 g of pure alcohol in one day at least three times per week.

2.2.4. Measurements of arterial stiffness, limited joint mobility and neuropathy

The ankle-brachial index was automatically calculated by means of the Microlife WatchBP Office ABI (Microlife®, Florida, USA).

A goniometer was used to detect limited joint mobility with passive range of motion measurements at the dominant knee and ankle.

The presence (and potential type and severity) of NP was determined in all participants by a board-certified neurologist at the Department of Neurology (Ghent University Hospital) using electroneuromyography (CareFusion Nicolet EDX®, Middleton, USA) with synergy software analysis (Version 20.0 EDX®). The electrodiagnostic reference values for these upper and lower limb nerve conduction studies in adult populations were used according to Chen et al.[25] The motor nerve conduction of the N. Peroneus communis, N. Tibialis, and N. Ulnaris was evaluated at the most affected limb, indicated by the participant's complaints, and was reported as compound muscle action potential (mV) and motor nerve conduction velocity (m/s). The sensory nerve action potential (μV) and sensory nerve conduction velocity (m/s) were measured using an antidromic technique and consisted of stimulation of the N. Suralis and N. Radialis on both sides of the body (Table A.1). These sensory measurements were obtained while skin temperature, recorded over the dorsum of the hand and foot, was maintained at a minimum of 30 °C.

2.3. Measurements of maximal muscle strength and muscle endurance

An isometric (IM) and isokinetic (IK) evaluation was performed by using dynamometry (Biodex; Biodex Corporation, Shirley, NY, USA) in order to measure the maximal voluntary muscle strength of the extensors and flexors of knee and ankle. Test procedures were followed as described in the Biodex Manual and were performed at the dominant leg.

IM and IK maximal peak torque per lean leg mass (PT/LBM^{leg}; Nm/kg) were measured and calculated. All IM assessments were performed twice and lasted for 5 s each, with a resting interval of 60 s between the assessments, preceded by two trial tests. For optimal IM functioning, the knee was positioned and fixed at 60° flexion to assess knee extension and at 30° for knee flexion; the reference angle of the ankle was 0°. The

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

IK assessments were also used to measure muscle endurance by means of total work (J) and by calculating the work-fatigue ratio, which is the percentage decrease in torque output between work$^{1/3}$ and work$^{3/3}$, divided by work$^{1/3}$. These concentric and eccentric IK torques were assessed at 180°s^{-1} and consisted of 30 repetitions for the knee and 20 for the ankle, and were verbally encouraged by the same researcher.

It is noteworthy that isokinetic endurance dynamometry is a psychophysical test, requiring full cooperation of the participant. Therefore, the evaluations of strength at knee and ankle were obtained with an intra-individual variation (i.e. coefficient of variance) of <10%.[26]

2.4. Measurements of explosive muscle strength and functional performance

In this study, the single two leg jump (s2LJ) test and the chair rising test (CRT), respectively representing explosive muscle strength and functional performance, were carried out according to Taani et al., in random sequence on the LEONARDO mechanography ground reaction force platform (NOVOTEC Medical Gmbh, Pforzheim, Germany).[27] In both tests, peak force (N), power/BW (W/kg), and maximum velocity (m/s) were calculated. Additionally, maximum height (m) was estimated in the s2LJ test. The Esslinger Fitness Index, calculated in both s2LJ and CRT, represents the maximum jump power relative to BW for one's age- and gender-matched reference population[28].

2.5. Statistical analysis

Data were analyzed using IBM Statistical Package for Social Sciences (SPSS version 25) and an alpha level of 0.05 (two-tailed) was used. The approximate normality of data was examined by the Shapiro–Wilk test. Descriptive statistics for anthropometric, biochemical and muscle parameters are presented as mean (±SD) unless otherwise stated. Participant's characteristics were analyzed with a univariate ANOVA to compare subgroups.

A Pearson Chi-Square test was used for smoking habits, ethyl consumption and use of medication in order to detect all between-group differences.

Between-groups analysis of knee and ankle endurance was performed using ANCOVA with LBM^{leg} as covariate. Explosive muscle strength and functional performance outcomes (total force, velocity, estimated height, and the Esslinger Fitness Index) were analyzed by means of ANCOVA with total BW as covariate. Relative total power (corrected for total BW) and relative maximal muscle strength (corrected for LBM^{leg}) were analyzed using ANOVA. Post hoc comparisons were performed by means of the Sidak test.

3. Results

3.1. Participant characteristics

Table 1 reports on general and clinical participant characteristics. Age and habitual behavior assessments (level of physical activity, smoking habits, and alcohol consumption) were not different between healthy controls and the subgroups of T2DM patients. Also, anthropometric characteristics (BMI, LBM^{tot}, LBM^{leg}, and FM^{tot}) were not significantly different between the different groups. Only leg muscle density

Table 1
General and clinical participant characteristics.

	C (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)
BMI (kg/m^2)	27 (3.3)	29 (3.5)	29 (6.0)	31 (4.0)
Body height (m)	1.75 (0.066)	1.76 (0.529)	1.77 (0.063)	1.76 (0.064)
Body weight (kg)	82.6 (11.18)	91.2 (14.72)	90.2 (18.88)	95.2 (12.72)
LBM^{tot} (kg)	61.5 (6.9)	66.1 (9.57)	65.7 (10.01)	68.7 (8.41)
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)
Leg muscle density (mg/cm^3)	73.3 (3.76)	72.9 (3.81)	72.5 (4.02)	69.2 (5.10)
Level of PA (/15)	8.0 (6.25–9.63)	8.5 (5.50–9.50)	8.00 (5.13–10.13)	7.6 (6.63–10.25)
Smoking habits:				
Currently smoking (%)	33.3	16.7	41.7	25.0
Ever smoked (%)	88.9	66.7	66.7	91.7
Packyears (n)	16.9 (16.20)	18.0 (21.16)	14.1 (16.81)	14.9 (18.39)
Habitual alcohol drinkers (%)	44.4	12.5	23.1	21.4
Diabetes duration (years)	NA	10 (7.8)	13 (6.8)	15 (9.6)
HbA1c				
(%)	5.6 (0.22)	7.4 (0.84)*	6.9 (0.58)*	7.8 (1.29)*
(mmol/mol)	38.3 (2.36)	57.0 (9.10)*	51.9 (6.25)*	61.7 (14.13)*
Glucose (mg/dl)	99.5 (13.19)	147.4 (39.59)	195.8 (153.78)	176.0 (58.66)
Cholesterol total (mg/dl)	200.4 (46.49)	164.6 (27.07)	163.4 (38.97)	168.2 (48.10)
LDL (mg/dl)	112.4 (40.48)	85.6 (21.67)	89.5 (31.41)	79.9 (37.00)
HDL (mg/dl)	63.3 (18.24)	58.1 (15.65)	51.6 (14.12)	54.8 (31.82)
Triglycerides (mg/dl)	120.6 (67.78)	102.0 (32.11)	110.9 (43.98)	193.9 (225.68)
RoM				
Knee (°)	131 (119–140)	140 (125–140)	135.5 (110–154)	130 (50–140)
Ankle (°)	60 (37–88)	52 (50–90)	59 (35–70)	52 (23–78)
ABI (ratio)	1.3 (0.15)	1.3 (0.06)	1.2 (0.20)	1.2 (0.17)

Data are expressed as mean (SD), with exception for the level of PA ($n = 39$) and RoM, both expressed as median (min-max).
The percentages of participants with a history of smoking and ethyl consumption are presented.
C, healthy controls without neuropathy; dNP-, patients without diabetic neuropathy (dNP); dNPs, patients with sensory dNP; dNPsm, patients with sensorimotor dNP; BMI, body mass index; LBM^{tot}, total lean body mass; LBM^{leg}, lean body mass of the dominant leg; FM^{tot}, total fat mass; PA, physical activity; RoM, range of motion; ABI, ankle-brachial index; NA, not applicable.
* p <0.05 compared to C.

(pQCT) showed a tendency towards significance between healthy controls and dNPsm ($p = 0.051$).

In the overall patient group, diabetes duration ranged from 2 to 31 years with a mean of 13 years with an average HbA1c of 7.4% (±1.03). All patients used oral anti-diabetes medication and/or insulin. In the healthy control group, the average HbA1c level was ≤6.0% without intake of glucose-lowering medication (Table A.2).

No significant differences between healthy controls and the diabetes groups were found in both ankle and knee range of motion and in the ankle-brachial index.

3.2. Muscle endurance in the distal lower dominant limb

Work$^{1/3}$, work$^{2/3}$, work$^{3/3}$ and total work (J), expressed as area under the curve, are presented in Fig. 1(A–D). Additionally, Table A.3 presents an overview of the raw data.

Total work in IK knee extension and ankle plantar flexion was higher for the healthy controls compared to dNP- ($p = 0.023$ and $p = 0.002$), dNPs ($p = 0.043$ and $p = 0.001$), and dNPsm ($p = 0.004$ and $p = 0.000$).

Furthermore, the healthy controls scored significantly higher in total work knee flexion compared to dNPs ($p = 0.011$) and dNPsm ($p = 0.001$), and in total work ankle dorsiflexion compared to dNPsm only ($p = 0.000$).

The work-fatigue ratio did not reveal significant differences between the four groups.

3.3. Explosive muscle strength and functional performance

Both total power and the Esslinger Fitness Index of the single two leg jump test were significantly higher in the healthy controls compared to dNPsm ($p = 0.004$ and $p = 0.020$). Also, a tendency towards significance between the healthy controls and dNPsm was observed for velocity and estimated maximum height ($p = 0.057$ and $p = 0.079$).

No significant differences were found between the four groups neither for the single two leg jump total force, nor for functional performance (chair rising test) (Table 2).

3.4. Relative maximal muscle strength in the distal lower dominant limb

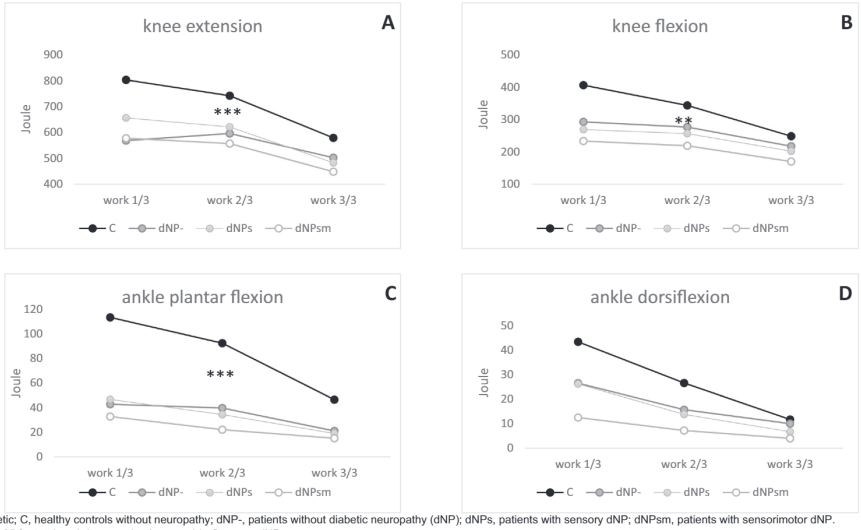
Table 3 reports on relative IM and IK maximal knee extension and flexion muscle strength, with only significantly higher IK maximal knee flexion muscle strength in the healthy controls compared to dNPsm ($p = 0.013$). Considering the ankle, significantly better results for IK maximal plantar flexion muscle strength were found in the healthy controls compared to dNPsm ($p = 0.002$).

Relative IM and IK maximal dorsiflexion muscle strength revealed significantly higher values in the healthy controls compared to dNPsm ($p = 0.035$ and $p = 0.003$). Additionally, relative IM and IK dorsiflexion strength values were better in dNP- compared to dNPsm ($p = 0.021$ and a tendency towards significance ($p = 0.085$) respectively).

4. Discussion

4.1. Main findings

In this study, a reduction in lower limb endurance was demonstrated by means of lower levels for total work in knee extension/flexion (20–30%) and ankle PF/DF (50–60%) in patients with T2DM (with or without dNP) compared to healthy controls. No noticeable differences



IK, isokinetic; C, healthy controls without neuropathy; dNP-, patients without diabetic neuropathy (dNP); dNPs, patients with sensory dNP; dNPsm, patients with sensorimotor dNP.
* $p<0.05$ for total work (area under the curve) in C versus dNPsm
** $p<0.05$ for total work (area under the curve) in C versus dNPs, and in C versus dNPsm
*** $p<0.05$ for total work (area under the curve) in C versus dNP-, in C versus dNPs, and in C versus dNPsm

Fig. 1. Absolute IK muscle endurance expressed in work 1/3, work 2/3, and work 3/3 in (A) knee extension, (B) knee flexion, (C) ankle plantar flexion, and (D) ankle dorsiflexion. IK, isokinetic; C, healthy controls without neuropathy; dNP-, patients without diabetic neuropathy (dNP); dNPs, patients with sensory dNP; dNPsm, patients with sensorimotor dNP. *$p < 0.05$ for total work (area under the curve) in C versus dNPsm. **$p < 0.05$ for total work (area under the curve) in C versus dNPs, and in C versus dNPsm. ***$p < 0.05$ for total work (area under the curve) in C versus dNP-, in C versus dNPs, and in C versus dNPsm.

Table 2
Explosive muscle strength and functional performance.

	C ($n = 19$)	dNP- (n = 8)	dNPs (n = 13)	dNPsm (n = 14)
Explosive muscle strength: s2LJ test				
Total force max (kN)	1.88 (0.370)	1.85 (0.427)	1.83 (0.403)	1.97 (0.222)
Total power max/BW (W/kg)	38.11 (6.303)	28.79 (7.044)	29.81 (5.234)	26.65 (8.124)*
Velocity max (m/s)	2.16 (0.192)	1.82 (0.300)	1.83 (0.261)	1.71 (0.445)
Estimated height max (m)	0,33 (0,038)	0,24 (0,068)	0,25 (0,058)	0,23 (0,106)
E.F.I. (%)	98.4 (13.73)	77.3 (17.37)	82.4 (18.11)	73.6 (19.47)*
Functional performance: CRT				
Total force max (kN)	1.16 (0.135)	1.25 (0.173)	1.22 (0.246)	1.27 (0.181)
Total power max/BW (W/kg)	11.41 (3.846)	8.87 (2.074)	9.01 (1.483)	9.09 (2.438)
Velocity max (m/s)	1.10 (0.251)	0.95 (0.138)	0.91 (0.126)	0.90 (0.174)
E.F.I. (%)	101.3 (12.57)	90.0 (14.96)	93.2 (21.62)	84.1 (20.18)

All data are expressed as mean (SD).
C, healthy controls without neuropathy; dNP-, patients without diabetic neuropathy (dNP); dNPs, patients with sensory dNP; dNPsm, patients with sensorimotor dNP; s2LJ, single two leg jump; BW, body weight; E.F.I., Esslinger Fitness Index; CRT, chair rising test.
* $p < 0.05$ compared to C.

in the work-fatigue ratio between all study groups were found. Both explosive and maximal muscle strength were significantly reduced in dNPsm compared to healthy controls.

The results of this study indicate a deteriorating effect on explosive and maximal muscle strength due to the presence of sensorimotor neuropathy, while T2DM as such predominantly affects muscle endurance.

4.2. Muscle endurance

Our findings on lower limb fatigability are in line with the scarce literature using comparable muscle endurance protocols. Allen et al. found a significant reduction in the average time to exhaustion between T2DM patients with dNP (dNP+) and age- and gender-matched healthy controls.[22] IJzerman et al. reported no significant differences in work-fatigue ratio based on the index of Moreau et al.,[29] comparing dNP-, dNP+ and healthy controls, except for the knee flexor outcome in dNP- versus healthy controls.[16] Additionally, Senefeld et al., compared patients with T2DM without clinical signs of dNP to age-, BMI- and physical activity-matched healthy controls, revealing a greater fatigability of the patient's knee extensor muscles. The greater fatigability was primarily associated with an impaired glycemic control and altered contractile mechanisms.[18] Bearing in mind that in previous research no further distinction was made between the type and severity of dNP, our results may give more in-depth information on the impact of dNP on muscle strength.

The absence of a compelling difference in lower limb endurance between patients with and without dNP, together with the lower values in our T2DM cohort in general, may indicate that the T2DM pathogenesis rather than the presence of dNP affects muscle endurance. A possible explanation for this discrepancy between healthy participants and patients with T2DM could be the impact of chronic hyperglycemia on the ageing process of skeletal muscle fibers. Indeed, there is a large body of evidence showing an age-related muscle fiber type shift towards a higher proportion of type I fibers.[30,31] Interestingly, opposite findings have been demonstrated in the T2DM population with a shift towards a higher proportion of type II muscle fibers.[16,32–35] This could explain the decreased muscle endurance in patients with T2DM, knowing that the slow-twitch oxidative muscle fibers (type I) are predominantly activated by endurance stimuli. The consequent weakness in the diabetic muscles may be induced by altered cellular metabolism (e.g. insulin resistance, metabolic inflexibility, reduced mitochondrial function, accelerated advanced glycation end products, …) and contractile mechanisms. This may result in an age-related decline in muscle strength prior to the reduction of muscle mass, predominantly pronounced in elderly patients with T2DM.[18,36,37]

Table 3
Relative maximal muscle strength of the lower limb (dominant knee and ankle).

	C ($n = 19$)	dNP- ($n = 8$)	dNPs ($n = 13$)	dNPsm ($n = 14$)
Knee extension				
IM max PT/LBM^{leg} (Nm/kg)	15.5 (3.05)	13.6 (3.15)	12.9 (2.94)	13.1 (3.69)
IK max PT/LBM^{leg} (Nm/kg)	14.3 (3.44)	11.9 (2.86)	12.6 (2.50)	11.7 (3.26)
Knee flexion				
IM max PT/LBM^{leg} (Nm/kg)	10.5 (1.58)	8.5 (1.40)	8.7 (2.49)	8.9 (2.25)
IK max P/LBM^{leg} (Nm/kg)	7.4 (1.36)	6.5 (0.91)	6.3 (1.21)	5.8 (1.73)*
Ankle plantar flexion				
IM max PT/LBM^{leg} (Nm/kg)	9.2 (2.70)	6.6 (3.01)	7.5 (1.64)	6.8 (2.57)
IK max PT/LBM^{leg} (Nm/kg)	5.8 (2.04)	5.0 (2.96)	3.5 (1.24)	2.6 (1.45)*
Ankle dorsiflexion				
IM max PT/LBM^{leg} (Nm/kg)	3.3 (1.17)	3.5 (1.06)	2.7 (1.08)	2.0 (0.71)*,**
IK max PT/LBM^{leg} (Nm/kg)	2.4 (0.70)	2.2 (0.50)	2.0 (0.53)	1.5 (0.41)*

All data are expressed as mean (SD).
C, healthy controls without neuropathy; dNP-, patients without diabetic neuropathy (dNP); dNPs, patients with sensory dNP; dNPsm, patients with sensorimotor dNP; IM, isometric; PT, peak torque; LBM^{leg}, lean body mass of the dominant leg; IK, isokinetic.
* $p < 0.05$ compared to C.
** $p < 0.05$ compared to dNP-.

4.3. Explosive and maximal muscle strength

Although muscle endurance was reduced in all patients with T2DM, a different pattern was identified with regard to both explosive and maximal muscle strength. Actually, both strength parameters were mainly influenced by the presence of dNPsm, suggesting a more dominant impact of neuropathic disturbances.

Our results concerning maximal muscle strength are in line with previous findings, claiming that the presence of dNP is associated with reduced maximal muscle strength values in patients with T2DM.[3–13,22] However, no distinction was made between dNPs and dNPsm in these publications. Due to the fact that explosive muscle strength is strongly determined by maximal muscle strength,[38] reduced maximal muscle strength in the lower limbs may have influenced the outcome on the s2LJ test.

Explosive and maximal muscle strength are influenced by various neural and morphological mechanisms, with motor unit loss or axonal loss as a feature of dNP. Subclinical motor involvement is often detected on electrophysiological studies in non-diabetic patients with idiopathic

sensory polyneuropathy.[39] According to Gutierrez et al., the presence of mild diabetic neuropathy leads to a decrease in the rapidly available ankle strength in the frontal plane and to a distal impairment in lower extremity sensory function, which increases fall risk.[21]

Allen et al. observed that this motor unit loss is accompanied by a loss of muscle strength and mass.[12] Furthermore, the same researchers reported that the muscle weakness in patients with dNP is related to the severity of neuropathy, which provides an explanation for our finding that patients with dNPsm have the lowest levels of maximal muscle strength. In our study, a significant reduction of maximal muscle strength was also observed in patients with dNPsm for knee flexors as well as for ankle plantar and dorsiflexors. Concerning muscle mass, we could not observe differences in LBM^{lcg} (DXA).

Additionally, muscle torque or force is also influenced by muscle density (pQCT), indicating fat infiltration in the muscle.[40] Goodpaster et al. showed that reduced quadriceps muscle density accounted for differences in maximal muscle torque, which is not attributed to muscle mass.[41] Besides, Allen et al. showed that a greater loss of motor units (e.g. caused by denervation of muscle fibers) is associated with greater proportions of non-contractile intramuscular tissue (fat and/or connective tissue) and with a proportional loss of contractile tissue. This process will impact the muscle quality negatively (reduced strength per unit muscle mass).[12,42]

In this study, pQCT data revealed a decreased leg muscle density outcome in the dNPsm group versus healthy controls with a tendency towards significance ($p = 0.051$), indicating an increased fat infiltration in this subgroup, and most likely resulting in poor muscle quality.

A critical note has to be mentioned concerning muscle mechanography. First, the s2LJ test is measuring peak torque and explosive strength, but it is also a very complex coordination and balance task. Second, CRT is most commonly used for geriatric purposes as it determines whether elderly meet the minimum criteria for ADL. Second, CRT is most commonly used for geriatric purposes as it determines whether elderly meet the minimum criteria for activities of daily living.[43] Consequently, caution is also needed when interpreting these unimpaired results, as activities-specific balance, confidence and diverse performance skills, such as core stability, determine the performance of this functional test.[27,44,45]

4.4. Practical implications.

Exercise training is a keystone intervention in patients with T2DM (besides pharmacological and dietary interventions[37]), in order to maintain quality of life and to reduce risk of falls.[15,46] Based on our results, it can be suggested to target strength training programs depending on the presence or absence of neuropathy in patients with T2DM. While endurance and strength training should generally be recommended in patients with T2DM, muscle strength training programs with high intensities, whether or not combined with higher velocities (power training), seem to be of crucial importance in patients with dNPsm in order to preserve both explosive and maximal muscle strength.[47]

4.5. Strengths and limitations

In the present study, electroneuromyographic examinations were performed in order to allocate each patient with T2DM to either the dNP- group or dNPs and dNPsm, since this is the gold standard for the diagnosis of neuropathy.

This is the first study that evaluates three major domains of muscle strength (endurance, explosive and maximal) in patients with dNPs and dNPsm, in comparison to dNP- and healthy controls.

Due to the nature of this cross-sectional study design, the future challenge is to establish adequately powered longitudinal research to determine the influence of ageing, the impact of long-term hyperglycemia exposure and the effect of lifestyle adjustments such as physical exercise on muscle strength in T2DM patients without dNP and in those with dNPs or dNPsm compared to healthy controls.

All participants were asked to report their medication intake. Patients with T2DM using confounding medication that could limit functional testing due to an affected neuromuscular status were not excluded. However, notwithstanding the larger heterogeneity of the groups, this limitation results in a sample size that is more representative for the Flemish population with T2DM.

The limited amount of differences between dNP- and patients with more severe neuropathy (dNPs and dNPsm) may be explained by the low number of patients in dNP- ($n = 8$), jeopardizing the power of our results. However, a posteriori power analysis of the primary outcomes (i.e. muscle endurance and explosive muscle strength) between the four groups (i.e. C, dNP-, dNPs, and dNPsm) exceeds 80% for total work ankle PF/DF and for the s2LJ test.

Generally, muscle strength can also be influenced by a variety of factors, including nutritional status (e.g. vitamin D exposure, protein intake,…) and muskuloskeletal pain. Unfortunately, we did not assess these features in this research.

4.6. Conclusion

In conclusion, this study presents evidence that diabetes has a significant degrading impact on muscle endurance, while explosive and relative maximal muscle strength were more influenced by sensorimotor diabetic neuropathy.

CRediT authorship contribution statement

Birgit L.M. Van Eetvelde: Conceptualization, Methodology, Investigation, Formal analysis, Writing - original draft, Writing - review & editing.**Bruno Lapauw:**Investigation, Formal analysis, Writing - review & editing.**Pascal Proot:**Investigation, Formal analysis, Writing - review & editing.**Karsten Vanden Wyngaert:**Investigation, Formal analysis, Writing - review & editing.**Bert Celie:**Investigation, Formal analysis, Writing - review & editing.**Dirk Cambier:**Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Patrick Calders:**Conceptualization, Methodology, Formal analysis, Writing - original draft, Writing - review & editing.

Declaration of competing interest

No potential conflicts of interest relevant to this article were reported.

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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. and B.C. 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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Appendix A

Table A.1
Electroneuromyography data.

	C (n = 19)	dNP- (n = 8)	dNPs (n = 13)	dNPsm (n = 14)
SNCV				
N. Suralis (m/s)	46.0 (6.56)	41.3 (7.48)	33.4 (23.67)	21.0 (31.84)
N. Radialis	41.6 (5.21)	46.5 (8.93)	41.8 (3.74)	38.1 (5.48)
SNAP				
N. Suralis (μV)	5.2 (3.09)	7.3 (3.78)	3.2 (3.37)**	0.4 (0.83)*,**
N. Radialis	10.3 (4.30)	17.6 (14.70)	12.5 (6.01)	9.8 (2.73)
MNCV				
N. Tibialis (m/s)	43.3 (3.47)	42.0 (4.53)	40.1 (5.80)	36.2 (2.82)*
N. Ulnaris	57.0 (3.38)	59.0 (3.75)	52.9 (6.07)	48.9 (5.08)*,**
N. Peroneus	49.9 (7.84)	49.0 (5.25)	46.6 (7.48)	47.1 (15.10)
CMAP				
N. Tibialis (mV)	9.4 (4.50)	8.6 (1.94)	5.7 (2.57)	2.9 (2.69)*
N. Ulnaris	8.7 (2.24)	7.6 (1.16)	7.5 (1.63)	5.1 (2.23)*
N. Peroneus	5.6 (1.51)	6.8 (2.06)	4.9 (1.44)**	3.5 (2.50)

All data are expressed as mean (SD).
C, healthy controls without neuropathy; dNP-, patients without diabetic neuropathy (dNP); dNPs, patients with sensory dNP; dNPsm, patients with sensorimotor dNP; SNCV, sensory nerve conduction velocity; SNAP, sensory nerve action potential; MNCV, motor nerve conduction velocity; CMAP, compound motor action potential; N, nervus.
* $p < 0.05$ compared to C.
** $p < 0.05$ compared to dNP-.

Table A.2
Medication.

	C (n = 19)	dNP- (n = 8)	dNPs (n = 13)	dNPsm (n = 14)
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

The percentages of each participant's relevant medication intake are presented.
C, healthy controls without neuropathy; dNP-, patients without diabetic neuropathy (dNP); dNPs, patients with sensory dNP; dNPsm, patients with sensorimotor dNP; DM, diabetes mellitus; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table A.3
Muscle endurance of the lower limb (dominant knee and ankle).

	C (n = 19)	dNP- (n = 8)	dNPs (n = 13)	dNPsm (n = 14)
IK knee extension				
Total work (J)	2124,8 (480,33)	1667,6 (141,05)*	1761,3 (480,04)*	1583,6 (681,77)*
Work-fatigue (%)	25,6 (13,35)	4,3 (41,91)	25,6 (16,20)	17,9 (17,73)
$Work^{1/3}$ (J)	803,3 (214,87)	568,7 (119,53)*	656,6 (167,36)	578,0 (265,65)*
$Work^{3/3}$ (J)	579,3 (121,08)	502,6 (114,65)	483,2 (153,46)*	448,4 (184,46)*
IK knee flexion				
Total work (J)	998,9 (291,43)	787,3 (234,22)	728,0 (316,33)*	622,6 (375,91)*
Work-fatigue (%)	37,9 (21,39)	24,5 (38,99)	23,3 (29,41)	27,9 (27,53)
$Work^{1/3}$ (J)	406,5 (125,23)	292,9 (89,05)*	269,2 (107,78)*	233,6 (151,31)*
$Work^{3/3}$ (J)	248,6 (89,04)	217,5 (101,63)	202,2 (107,91)	170,1 (99,09)
IK ankle plantar flexion				
Total work (J)	252,6 (80,27)	103,9 (55,32)*	100,4 (60,12)*	70,3 (92,84)*
Work-fatigue (%)	56,0 (15,97)	61,2 (22,31)	62,0 (37,71)	67,3 (24,18)
$Work^{1/3}$ (J)	113,5 (40,98)	42,9 (26,76)*	46,8 (20,25)*	32,9 (39,56)*
$Work^{3/3}$ (J)	46,6 (14,72)	21,2 (18,15)*	19,1 (19,64)*	15,2 (20,97)*
IK ankle dorsiflexion				
Total work (J)	82,0 (26,02)	52,5 (45,57)	47,0 (44,81)	24,1 (29,74)*
Work-fatigue (%)	71,9 (28,35)	71,9 (36,29)	81,9 (30,91)	51,1 (47,62)
$Work^{1/3}$ (J)	43,5 (11,57)	26,6 (12,70)*	26,3 (17,61)*	12,6 (12,99)*,**,***
$Work^{3/3}$ (J)	11,8 (11,30)	10,1 (15,32)	6,8 (12,96)	4,1 (7,82)

All data are expressed as mean (SD).
C, healthy controls without neuropathy; dNP-, patients without diabetic neuropathy (dNP); dNPs, patients with sensory dNP; dNPsm, patients with sensorimotor dNP.
* $p < 0.05$ compared to C.
** $p < 0.05$ compared to dNP-.
*** $p < 0.05$ compared to dNPs.

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