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Lower extremity muscle strength is reduced in people with type 2 diabetes, with and without polyneuropathy, and is associated with impaired mobility and reduced quality of life

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ABSTRACT

Aim: The purpose of the present study was to distinguish the effects of both diabetes mellitus type 2 (DM2) and diabetic polyneuropathy (DPN) on mobility, muscle strength and health related quality of life (HR-QoL).

Methods: DPN patients ($n = 98$), DM2 patients without DPN (DC) ($n = 39$) and healthy subjects (HC) ($n = 19$) performed isometric and isokinetic lower limb muscle strength tests. Mobility was determined by a timed up and go test (TUGT), a 6 min walk test and the physical activity scale for the elderly questionnaire. HR-QoL was determined by the SF36 questionnaire.

Results: DPN patients had moderate polyneuropathy. In both DPN and DC patients leg muscle strength was reduced by 30–50% compared to HC. Muscle strength was correlated with mobility tests, and reduced muscle strength as well as impaired mobility were associated with a loss of HR-QoL (all $p < 0.05$). We did not observe major differences in muscle strength, mobility (except for the TUGT, $p < 0.01$) and HR-QoL between diabetic patients with and without DPN.

Conclusion: DM2 patients, with and without DPN, have decreased maximal muscle strength in the lower limbs and impaired mobility. These abnormalities are associated with a loss of HR-QoL. The additional effect of moderate DPN was small in our patients.

1. Introduction

Diabetes type 2 (DM2) is accompanied by a wide range of impairments and several studies have shown that DM2 is associated with a loss of mobility [1–4]. This limited mobility encloses a broad range of daily activities. Limited mobility can have a large impact on the independence of an individual once basic daily activities such as rising from a chair, walking stairs and doing groceries are impaired. Reduced muscle strength could be an important factor in this mobility loss and Andersen et al. [5] showed in an earlier study that DM2 is associated with loss of muscle strength around the ankle and knee joint. The loss of mobility and muscle strength of the lower extremities can enhance each other. Inactivity will lead to loss of muscle mass, resulting in decreased muscle strength and vice versa increased muscle weakness will lead to an increased effort to be physical active. This will result in a negative spiral of become less active, losing muscle strength,

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loss of independence and health related quality of life (HR-QoL) [6].

Several factors could be responsible for the limited mobility and decreased muscle strength in diabetic patients such as intrinsic abnormalities in diabetic muscle, impaired capillary recruitment, peripheral arterial disease and diabetic polyneuropathy (DPN) [5,7,8]. DPN occurs in approximately 20–40% of all diabetic patients [9,10]. Furthermore, neuropathy has been associated with impaired mobility, loss of muscle strength and decreased HR-QoL, as reviewed elsewhere [7]. Earlier studies found that patients with severe DPN have increased muscle weakness in lower extremities [5,11]. However, several studies have shown that diabetic patients without DPN also have decreased muscle strength and volume compared to healthy subjects [5,12,13]. The contribution of polyneuropathy to the limited mobility and reduced and reduced muscle strength is therefore still matter for debate.

In a recent accelerometer study we found that DPN and handgrip strength were each independently associated with an approximately 30% reduction in the daily number of steps/day during a 1 week period [14]. However, the role of impaired lower extremity muscle strength in the loss of mobility and QoL in DM2 patients with and without DPN remains unclear. Therefore, the aim of this study was to determine the effect of the diabetic state per se and of DPN on lower extremity muscle function, mobility and health-related QoL (HR-Qol). Furthermore, the relations between these primary outcome parameters were assessed.

2. Materials and methods

2.1. Subjects

Patients with DM2 (DC group) and DPN (DPN group) were recruited in one university and four district hospitals in the south of the Netherlands. Healthy subjects (HC group) were recruited from a database that contained healthy volunteers who participated in earlier studies. All subjects were at least 50 years and were excluded if diagnosed with severe cardiac disease, renal insufficiency (creatinin $>$ 180 μmol/L), intermittent claudication, muscular disorders or rheumatoid arthritis. In addition, DM2 patients were excluded if they had been diagnosed with foot ulcers in the last six months prior to the study, or had nerve damage not due to DPN. Written informed consent was obtained from all participants and the protocol was approved by the medical ethical committee of the Maastricht University Medical Centre+.

2.2. Clinical assessment of polyneuropathy

Peripheral polyneuropathy was diagnosed and classified based on a standardised clinical neurological examination (CNE) in which a CNE score $\geq$5 indicates the presence of peripheral neuropathy and a score of $\geq$15 is considered as severe DPN [15]. In short, the CNE score is determined by examining the Achilles tendon reflex, vibration awareness, sharp–blunt discrimination, touch sense, position sense of the hallux and manual assessment of extensor muscle strength of the hallux and flexor muscle strength of the foot in which all items are scored as either normal, impaired or absent (0–2 points). In addition, the scoring of light touch sense was related to the anatomical level below which it is impaired (toe, mid-foot, ankle, mid-calf and knee) (0–5 points). In an earlier study of our group, were a sub population of the current population was studied, EMG and CNE score resulted in the same diagnosis of DPN in our DM2 patients [16].

2.3. Isometric and isokinetic muscle strength

Two dynamometers, the Cybex II (CMSI, Stoughton, MA) and the Biodex System 3 (Biodex Medical Systems, New York), were used to determine isometric and isokinetic muscle strength of dorsal and plantar flexor muscles of the ankle joint and the extensor and flexor muscles of the knee joint. Both systems are frequently used in scientific studies and both dynamometers are validated systems. According Gosker et al. [17] both systems yield similar results. Half of all subjects were tested on the Biodex and half on the Cybex.

2.4. Isometric test

To determine maximal, voluntary ankle joint moments, participants were positioned in a 90° hip and knee flexion. The subject's ankle joint centre was aligned with the rotation centre of the dynamometer. The dorsal and plantar ankle joint moments were determined at four different angles; 80°, 90°, 105° and 120°, where 80° equals maximal dorsal flexion and 120° compares maximal plantar flexion. One single maximal voluntary contraction was maintained approximately 3 s. Between subsequent contractions subjects were allowed 2 min of rest. Passive ankle joint moments were measured one second before the contraction. This passive moment resulted from the weight of the foot, the tension of passive structures and the weight of the arm of the dynamometer. Depending on the joint angle, the passive moment could be in dorsal or plantar flexion direction. The recorded maximal moments were corrected for these passive moments. A similar protocol was used to determine maximal voluntary muscle strength for the knee joint flexors and extensors. Subjects were positioned in a 90° hip flexion. Maximal voluntary knee joint moments were assessed at five angles: 30°, 50°, 70°, 90° and 100°, where 0° represented a fully extended leg. All measurements were performed in the right leg.

Maximal strength was determined by fitting a second degree polynomial function to the joint moment data at subsequent joint angles. The highest value of this fitted polynomial was considered the maximal strength. All joint moments were normalized for body mass [16].

2.5. Isokinetic test

The subjects were positioned the same as during the isometric tests. The participants were asked to push and pull as hard and fast as possible over their maximal range of motion with verbal encouragement of the researcher. The joint angular velocity was set on 120°/s. Subjects performed 20 repetitions. The work of each of these plantar and dorsal flexion repetitions of the ankle and extension and flexion repetitions of the knee was calculated and expressed as Nm/kg. To

determine the fatiguability of the involved muscle groups an adapted formula of Moreau et al. was used [18]. For ankle dorsal and plantar flexion and for knee extension and flexion, the fatigue index (FI) was calculated as the ratio of the mean work of the 16th till 20th repetition over the mean work of the highest, five consecutive repetitions within the first eight repetitions. A FI approaching 100% indicates that work decline during the test is low. Results of muscle fatiguability were considered as missing if the highest consecutive five repetitions were not performed within the first eight repetitions.

2.6. *Mobility*

Three validated tests were used to assess mobility. In the 6 min walk test (6 MWT) subjects were asked to walk as far as possible within 6 min without running on a 220 m flat track; in the timed up and go test (TUGT) subjects were asked to stand up from a chair, walk three meters at comfortable speed, turn, walk back and sit down again. The Physical Activity Scale of the Elderly (PASE) questionnaire was used to determine the daily activity pattern. The higher the score at the PASE questionnaire the more active a subject is in daily life.

2.7. *Quality of life*

The SF36 questionnaire was used to determine HR-QoL. This questionnaire contains 36 items. It measures health on nine multi item dimensions, based on functional status, well being and overall evaluation of health [19]. The higher the score at the SF36, the more positive a subject was about experienced HR-QoL.

2.8. *Biochemical analysis*

Overnight fasting blood samples were drawn for measurement of glucose, glycated hemoglobin (HbA_{1c}) and creatinine.

2.9. *Statistical analysis*

Results are presented as mean ± standard deviation. Analysis of variance was performed to detect differences between the three experimental groups. We used analysis of covariance to test differences between groups in the muscle strength, mobility and QoL data; age and gender were entered as covariates. If main effects were significant, the Bonferroni test was used for post hoc analysis. Pearson's correlation coefficients were calculated between muscle function (muscle strength and fatiguability), the three mobility tests and the nine QoL items. Within the group of DPN patients, correlations between the level of nerve damage (CNE score) and maximal muscle strength, mobility and QoL were evaluated. A p-value of <0.05 was considered as significant.

3. Results

We included 98 DM2 participants with DPN, 39 DM2 patients without DPN and 19 healthy control subjects. Demographic, neurological and blood parameters are presented in Table 1. In general, we included elderly obese diabetic subjects with good to moderate blood glucose control. The DC group was 5 years younger than the HC group ($p < 0.01$). Height and creatinine were higher in the DPN group than the DC group ($p < 0.01$), whereas weight, BMI, HbA_{1c} and glucose were higher in both diabetic groups ($p < 0.001$) compared to the HC group. By definition, the CNE score was higher ($p < 0.001$) in patients with DPN compared to both other groups.

Table 1 – Demographic, neurological and blood parameters.

	DPN	DC	HC	P-value
N	98	39	19	
Sex (male/female)	80/18[b]	20/19	15/4[b]	0.001
Age (yr)	67 ± 8	62 ± 7[a]	68 ± 5	0.002
Height (m)	1.74 ± 0.08[b]	1.68 ± 0.10	1.72 ± 0.07	0.002
Weight (kg)	94 ± 18[a]	88 ± 15[a]	73 ± 8	<0.001
BMI (kg m^2)	30.8 ± 5.0[a]	31.2 ± 5.7[a]	24.4 ± 1.9	<0.001
CNE score	13 ± 5[a,b]	3 ± 2	1 ± 2	<0.001
HbA_{1c} (%)	7.3 ± 1.1[a]	7.1 ± 1.0[a]	6.0 ± 0.5	<0.001
Glucose (mmol/L)	8.5 ± 2.3[a]	8.0 ± 2.2[a]	5.6 ± 0.6	<0.001
Creatinine (μmol/L)	98 ± 30[b]	81 ± 22	89 ± 12	0.004

CNE = clinical neurological examination; P-value: main effect of the analysis of variance between the three groups.
[a] Post hoc analysis $p \leq 0.05$ compared to HC.
[b] Post hoc analysis $p \leq 0.05$ compared to DC.

3.1. *Muscle strength and relative fatigue*

Both DPN and DC groups had diminished, maximal, voluntary muscle strength in all parameters measured around the knee and ankle joints compared to the HC group (reductions of 34–47%), whereas no differences were observed between the DPN and DC groups (Fig. 1). Although all FI's were numerically lower in both diabetic groups compared to the HC group ($p > 0.1$), this was not statistically significant except for the fatiguability of the knee joint flexors. This muscle group had in

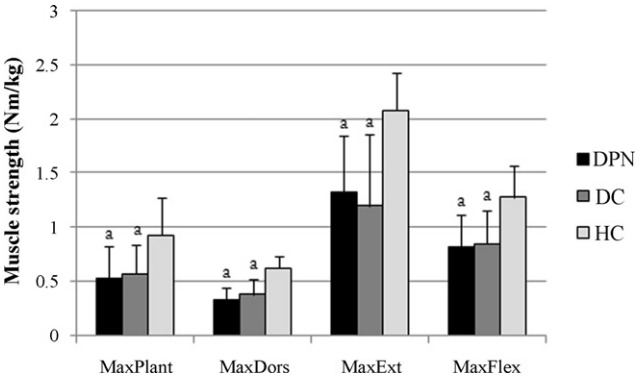

Fig. 1 – Normalized maximal isometric muscle strength of the plantar flexors (MaxPlant), dorsal flexors (MaxDors), knee extensors (MaxExt) and knee flexors (MaxFlex) (P-value: main effect of the analysis of variance between the three groups. Post hoc analysis $p \leq 0.001$ compared to HC. Joint moments were normalized for body mass MaxPlant.

Table 2 – Muscle strength, mobility and QoL parameters.

	DPN	DC	HC	P-value
FatiguePlant (%)	61 ± 20	57 ± 14	65 ± 14	0.315
FatigueDors (%)	42 ± 16	39 ± 14	47 ± 14	0.226
FatigueExt (%)	63 ± 13	66 ± 13	70 ± 8	0.159
FatigueFlex (%)	71 ± 10	70 ± 11[a]	78 ± 9	0.039
PASE	141 ± 81	151 ± 91	195 ± 72	0.06
6 MWT (m)	477 ± 89[a]	486 ± 87[a]	668 ± 68	<0.001
TUGT (s)	9.3 ± 2.8[a]	8.4 ± 2.4	7.2 ± 0.9	0.002
SF36 Physical functioning	68 ± 25[a]	71 ± 28[a]	91 ± 11	0.001
SF36 Social functioning	77 ± 23[a]	75 ± 28[a]	93 ± 15	0.02
SF36 Role limitations (physical problems)	66 ± 39[a]	62 ± 44[a]	97 ± 8	0.003
SF36 Role limitations (emotional problems)	78 ± 36	66 ± 44	91 ± 27	0.051
SF36 Mental heatlh	74 ± 20	71 ± 17[a]	85 ± 15	0.032
SF36 Vitality	61 ± 18[a]	60 ± 20[a]	79 ± 20	<0.001
SF36 Pain	71 ± 24[a]	68 ± 28[a]	91 ± 11	0.003
SF36 General health perception	50 ± 20[a]	50 ± 19[a]	77 ± 15	<0.001
SF36 Health change	46 ± 20	51 ± 25	54 ± 17	0.197

P-value: main effect of the analysis of variance between the three groups.
[a] Post hoc analysis $p \leq 0.05$ compared to HC. Fatigue index of the plantar flexors (FatiguePlant), dorsal flexors (FatigueDors), knee extensors (FatigueExt) and knee flexors (FatigueFlex).

the DC group a significant lower FI in comparison to the HC group (Table 2).

3.2. *Mobility*

Both diabetic groups showed a decreased mobility compared to the HC group. During the 6 MWT, participants in both diabetic groups walked significantly less far than HC participants (approximately 28%, Table 2). The 6 MWT distance for DC and DPN did not differ. The PASE score showed a similar, but no significant trend ($p = 0.06$) with HC participants reporting more daily physical activity than DC and DPN subjects. During the TUGT the DPN group needed significantly more time than HC group (an increase of 29%); no differences were observed between the other groups.

3.3. *Quality of life*

In the DPN group six of the nine SF36 items and in the DC group seven of the SF 36 items were significantly lower than in the HC group (Table 2). No differences were observed in perceived HR-QoL between both diabetic groups.

3.4. *Correlations*

Significant correlations were observed between all items of the SF36 and muscle strength, except for health change and role limitations related to emotional problems. The other seven items had significant positive correlations ($p < 0.05$) with dorsal and plantar flexion as well as knee flexion and extension maximal voluntary muscle strength. The correlation coefficients of these associations were between 0.19 and 0.41.

Similar results were found when the nine SF36 items were correlated with the mobility tests, except for health change and mental health. The other seven items were correlated ($p < 0.05$) with the 6 MWT and the PASE questionnaire with correlation coefficients between 0.20 and 0.59. The same seven items of the SF36 questionnaire had negative correlations with the TUGT (R between −0.29 and −0.46, $p < 0.05$).

Finally, all muscle strength parameters were correlated with the mobility parameters ($p < 0.05$), with correlation coefficients between 0.22 and 0.59.

No significant correlations were observed for the FI of the ankle and dorsal flexors and knee extensors and flexors and the QoL and mobility parameters.

The level of DPN (CNE score) had no significant influence on the majority of parameters, except that a correlation was observed between the severity of DPN and the TUGT (R = 0.28, $p < 0.05$).

4. Discussion

The present study clearly demonstrated that DM2 is associated with a marked reduction in lower leg muscle strength, that muscle strength was correlated with mobility and that loss of both lower leg muscle strength and of mobility is associated with a loss of HR-Qol in these elderly patients. We did not observe in this study major differences in muscle strength, mobility (except for the TUGT) and QoL between the diabetic patients with and without DPN. One of the innovative aspects of the current study was that we studied the triad leg muscle strength, mobility and quality of life in the same patients.

Although there are numerous studies on abnormal muscle metabolism and its role in the development of insulin resistance, the number of studies on muscle strength and its role in the development of impaired mobility and quality of life in DM2 is limited. Based on the present results we could conclude that DM2 has a major effect on maximal muscle strength with reductions of approximately 30–50% in both the upper and lower leg. Our findings are in line with previous studies that reported loss of muscle strength in patients with DM2, although the loss of muscle strength was in our study larger than the studies reported earlier [5,11,14,20–22]. In the Health ABC Study, elderly adults (mean age 74 years) with DM2 had a mean reduction of leg muscle strength of approximately 3% although muscle mass in their legs was greater than those without diabetes. Muscle quality (strength corrected for

muscle mass) was therefore reduced with approximately 7% [22]. We found a much larger reduction in muscle strength in our patients, that may be (in part) related to differences in the calculation of muscle strength. We corrected muscle strength for body weight, while this was not done in the Health ABC study [22]; if we recalculate the data of this latter study the diabetic patients had a reduction in muscle strength of approximately 10%, which is still less than in the present study. Another explanation could be that our control subjects were relative fit and had a higher muscle strength compared to the control subjects in the Health ABC study [22]. Several mechanisms, alone or in concert, could be responsible for the loss of muscle strength in DM2. As lack of physical exercise is one of the central mechanisms in the development of DM2, inactivity and disuse probably contribute to the relative poor muscle strength. Moreover, abnormal mitochondrial function, abnormal free fatty acid metabolism and an inadequate rise in microvascular blood supply during exercise [23,24] could further impair muscle function. In the current study we did not observe a relation between loss of nerve function and loss of muscle strength, in contrast to earlier studies [5,12]. One of the likely explanations is that the majority of our DPN patients had relative mild DPN. In the studies of Andersen et al. [5] and of Andreassen et al. [12] leg muscle weakness was in particular observed in patients with severe, symptomatic, neuropathy and not in patients with less severe DPN. These data suggest that additional loss of muscle strength is a relatively late phenomenon in the course of DPN and occurs at a severe stage of the disease. These data suggest that additional loss of muscle strength is a relatively late phenomenon in the course of DPN and occurs at in patients with a more severe and more advanced stage of disease than the patients included in the current study.

Muscle fatiguability, determined with an isokinetic protocol, was somewhat increased in our diabetic patients, but these differences were clearly less prominent than the decline of maximal voluntary muscle strength, determined with an isometric protocol. Oberbach et al. showed that patient with DM2 have increased proportion of muscle fiber type 2 (fast twitch fiber) and decreased proportion of muscle fiber type 1 (slow twitch and responsible for endurance capacity of a muscle) [25]. Changes in fiber composition could therefore (in part) explain the increased muscle fatiguability in patients with DM2. In contrast, in type 1 diabetic patients Andersen [26] observed, a significant higher FI of five percent in comparison to healthy volunteers while lower leg muscle strength was reduced, as in our type 2 patients. At this moment we cannot give an explanation for this discrepancy between type 1 and type 2 diabetic patients, but this might be related to underlying insulin resistance and impaired metabolic flexibility in type 2 diabetes [27]. We could not find a relation between muscle fatiguability and DPN, as also reported earlier [26]. However, research in the field of muscle fatiguability in DM2 patients is scarce and more (human) research is needed to gain a clear insight into this phenomenon.

Muscle strength is one of the important determinants of mobility in diabetic patients. In an earlier population based study we observed that hand grip strength predicted the number of steps taken during the day by patients with DM2 [14]. Our current data further extend this observation as reductions in muscle strengths in both the upper and lower leg were associated with the marked loss of mobility in our diabetic patients. As in our earlier study we did not observe a major impact of DPN on the mobility tests we performed, except the TUGT [14]. The TUGT was the most challenging mobility test for our subjects and poor performance during this test is probably (in part) related to the loss of propriocepsis in our DPN patients. DPN is associated with several changes in gait characteristics, such as reduced gait velocity, step length and frequency and postural instability, which in part may be related to loss of propriocepsis [28]; moreover in patients with DPN the timing of muscle activation is altered during walking as we recently observed [29]. In addition, although van Sloten et al. [14] did not find significant associations between DPN and functional mobility test in a laboratory setting, those DPN patients were significantly less active in daily life with a marked reduction in the number of steps/day when compared to subjects without DPN. These data of van Sloten et al. were in line with the conclusions of Allet et al. [28]; these authors found that diabetic patients, and in particular DPN patients, have deteriorated temporal and spatial gait parameters during walking tests in challenging daily life situations.

These studies suggest that (moderate) DPN does not have a large effect on the capability to be active, but more on mobility behavior and on gait characteristics, in particular in a more challenging environment. Future studies addressing the effect of DPN on mobility should therefore focus more on mobility and functional mobility tasks in daily life to determine the impact of DPN on the actual mobility capability in diabetic patients.

HR-QoL was decreased in our group of DM2 patients compared to healthy persons as shown in several studies [30] and the association between mobility and HR-QoL was observed by other authors [4,31]. Diminished muscle strength and mobility can result in infirmities and more dependence in daily life with negative influence on HR-QoL. The significant correlations between muscle strength, mobility and HR-QoL parameters showed this association clearly. In addition, there was no clear difference in HR-QoL between our DC and DPN group, in contrast with other studies [7]. An explanation can be found in the study Currie et al. [32], these authors concluded that diminished QoL in DPN is associated with the level of pain that is experienced. In the current study most patients had painless DPN and we did not observe differences in pain between the DC and DPN group.

Our study had some limitations. The mean age of the DC group was significantly lower than in the HC group. This could lead to an overestimation of the results of the DC subjects compared to the HC group. To correct for this, age was entered as a covariate in the statistical analysis. The results of the DC group are comparable with the DPN group who had similar age as the HC group. If there would have been an important age effect, we would have expected the DC group to have higher muscle strength, mobility and QoL than the DPN group. This turned out not to be the case. In addition, the DC group included relatively more female participants than both other groups and therefore we used also gender as a covariate in our statistical analysis.

In conclusion, in this study we demonstrated that DM2 patients have decreased maximal muscle strength of the

plantar and dorsal flexors of the ankle joint and of the extensors and flexors of the knee joint and that they suffer from impaired mobility. These abnormalities are associated with a loss of health related quality of life. The additional effect of moderate DPN was small in our patients. Physical exercise is one of the cornerstones in the prevention [33,34] and treatment of diabetes; our data suggest that in the future more emphasis could be placed on interventions to increase leg muscle strength to improve mobility in patients with type 2 diabetes.

Conflict of interest

The authors declare that they have no conflict of interest.

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