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A population-based follow-up study of maximal muscle strength and mobility in patients with myasthenia gravis

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Abstract

It is uncertain whether residual muscle weakness in myasthenia gravis (MG) can improve, and whether it reflects deficits and disability. In a population-based follow-up study of 107 patients with MG and 50 healthy controls, maximal shoulder, knee and ankle strength was measured using isometric dynamometry and related to the quantitative MG (QMG), the MG Composite (MGC), the MG-activities of daily living (MG-ADL), the MG quality of life 15-items (QOL15) and a 400 m walk test (400MWT). During a mean follow-up of 4.6 ($\pm$0.04) years, patients improved 10.8% ($P < 0.001$) in isometric shoulder strength, whereas their isometric knee strength did not improve (3.2%, $P = 0.151$). Higher age, longer disease duration and greater baseline impairment had no negative impact. Change in isometric shoulder and knee strength did not correlate with changes in the QMG, the MG-ADL or the QOL15. Change in isometric knee strength correlated with change in the 400MWT ($r = -0.357$), and the 400MWT correlated with changes in the QMG ($r = 0.439$), the MG-ADL legs subitem ($r = 0.419$) and the QOL15 ($r = 0.310$). Overall, muscle strength improved over time, and the MG clinical scales were related to impaired mobility and muscle strength. Change in residual muscle weakness was unrelated to disability (MG-ADL) and quality of life (QOL15).
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Keywords: Myasthenia gravis; Follow-up; Muscle strength; Mobility.

1. Introduction

Myasthenia gravis (MG) is an autoimmune, neuromuscular disease affecting ocular, bulbar, respiratory, trunk and extremity muscles. Autoantibodies in MG affect the neuromuscular transmission, resulting in muscle weakness mainly characterized by fatigability whereas maximal muscle strength is less affected [1]. Although this fluctuating muscle weakness is a hallmark of MG, studies show a 10% to 50% decreased maximal muscle strength [2–5]. These studies are cross-sectional [2–5], small [3,4], and restricted to patients with generalized MG [2,3], limiting assessment of temporal changes in a general MG population. Whereas maximal muscle strength improves during initial therapy

in newly diagnosed patients [4], one cross-sectional study reported decreased maximal muscle strength in a general MG population [5] despite standard clinical care. It is unknown if and how this residual muscle weakness persists in the general MG population during further treatment and follow-up. Although unsettled, persistent muscle weakness may contribute to the insufficient treatment response observed in some patients with continued disability or refractory disease despite treatment with currently available therapeutics. It remains unknown, however, whether the residual muscle weakness observed in MG populations reflects impairment as captured by the clinical MG scales, mobility assessments, activities of daily living and quality of life.

Several novel MG therapeutics aiming at improving symptoms in MG are currently being developed [6]. Accordingly, studies examining and clarifying factors contributing to persistent residual disability are needed. These patients with persistent disability represent an unmet need in

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current therapeutic management, and it is currently unsettled how muscle weakness contributes to these persistent residual symptoms. Thus, we performed a population-based follow-up study in patients with MG already receiving standard clinical care at baseline to examine whether maximal muscle strength improved during follow-up, and whether this weakness was related to relevant changes in functional performance and clinical scores.

2. Patients and methods

2.1. Study design and population

This follow-up study was conducted at Department of Neurology, Aarhus University Hospital in Denmark. Baseline population consisted of patients with MG and age and gender-matched healthy controls enrolled in two previous studies in 2012 to 2014 [4,5]. Briefly, the MG diagnosis was verified by $\geq$ one of the following characteristics: (1) autoantibodies against the acetylcholine receptor or muscle specific tyrosine kinase receptor, (2) abnormal decrement on repetitive nerve stimulation, (3) abnormal jitter on single-fiber electromyography, (4) a positive edrophonium test, or (5) unequivocal clinical response to pyridostigmine therapy. We excluded patients $\geq$ 90 years of age and patients with comorbidities potentially affecting muscle strength measurements and clinical rating (e.g. inflammatory myopathy, musculoskeletal diseases, cancer). These comorbidities were identified by chart review prior to assessments and by detailed patient history during study visits [4,5]. Prevalent MG cases who lived in the Central Denmark Region were identified in the Danish National Patient Registry, and those recruited at baseline were matched with healthy controls [5]. In addition to prevalent cases, incident MG cases at Department of Neurology, Aarhus University Hospital were consecutively enrolled at time of diagnosis [4]. Incident cases were examined prior to and following initiation of standard of care. Most recent measurements following initiation of treatment were used as baseline data in the present analysis.

The combined baseline population was subsequently recruited for follow-up assessments in the period from 2017 to 2019, either through letters or during outpatient visits. A reminder was sent to non-responders. Subjects were excluded at follow-up, if they were > 90 years of age or had intercurrent comorbidities affecting muscle strength measurements and clinical rating. These comorbidities were identified by chart review and patient history obtained by telephone prior to follow-up assessments.

2.2. Patient characteristics

Date of diagnosis, antibody type, neurophysiological assessments, edrophonium test result, documented response to pyridostigmine therapy, prior and current MG treatments, comorbidities, thymectomy and thymoma results were obtained from patient charts and detailed patient history

at baseline and follow-up. In case of discrepancies in the retrospective data prior to baseline assessments, a second critical chart review was performed at follow-up to identify and validate the information.

2.3. Clinical scales

Disease severity was classified according to the Myasthenia Gravis Foundation of America (MGFA) Classification. Clinical rating consisted of the quantitative myasthenia gravis (QMG) [7], the myasthenia gravis composite (MGC) [8], the myasthenia gravis activities of daily living (MG-ADL) [9], and the myasthenia gravis quality of life 15-items (QOL15) [10]. Clinical rating was performed by trained physicians at baseline (LV) and follow-up (JLST). Patients were examined while receiving their prescribed pyridostigmine treatment. First, the QMG was performed, followed by the MGC, the MG-ADL and the QOL15.

2.4. Lower limb performance and physical activity

Mobility was measured using a 400 m walk-test (400MWT). Subjects were instructed to walk 400 m as fast as possible back and forward on a 20 m course. Elapsed time was measured in seconds.

Proximal lower limb performance was measured using a 30 s chair stand test (30STS), counting the number of times subjects could get up from a chair with their arms crossed in front of their chest in 30 s.

Average daily physical activity was assessed using the Physical Activity Scale (PAS) questionnaire [11]. This questionnaire quantifies the daily average energy expenditure during various activities including exercise; the estimate is expressed as hours of metabolic equivalents (MET).

2.5. Maximal muscle strength

After clinical rating, maximal muscle strength was measured with a Biodex® System 3 dynamometer using the same standardized protocols and audio feedback at baseline and follow-up. An isometric protocol was used to limit the effects of muscle fatigability on measurements. Subjects rested 5 to 10 min between clinical rating and dynamometric measurements. To take the effect of age, gender, height, and weight on isometric muscle strength [12] into account, patients were compared to matched controls.

Maximal isometric muscle strength was determined as the highest peak torque in newton meters (Nm) based on three repeated maximal isometric contractions for right shoulder abduction, left knee extension and left ankle dorsal flexion. Each contraction lasted 5 s separated by 40 s of rest. Measurements were repeated following a few minutes of rest if shoulder variability was $\geq$ 15%, knee variability was $\geq$ 10%, or ankle variability was $\geq$ 10%.

2.6. Statistics

Results are presented as mean and standard error, or median and interquartile range. T-test, Wilcoxon's rank sum test or the chi-squared test was used to compare baseline data in patients and controls, as well as in participants and subjects lost to follow-up.

Changes in isometric muscle strength (peak torque, Nm), 400MWT (seconds) and 30STS (repeats) were analyzed using mixed effects regression on all subjects alive at follow-up to reduce potential bias. Due to skewed data and non-normality of random effects in a mixed linear regression, data were analyzed using a generalized mixed effects model with log-transformed (log-link) normal distribution (gaussian family). Patients were compared with controls using group (patients and controls) and visit (baseline and follow-up) as categorical fixed effects and subject as random effect. Factors affecting degree of improvement in patients were analyzed using visit as fixed effect with interaction subject age (continuous), MG duration (continuous), or baseline strength as percentage of healthy controls (three strata, cut-off at 80% and 60%). Associations between change in isometric muscle strength and clinical scores were analyzed in the mixed effects models using interaction between visit (categorical) and scores (continuous), the latter also applied in *test for trend* on MG scale subitems.

Correlations between change in isometric muscle strength, change in performance tests, and change in clinical scores were analyzed using Pearson correlation. These analyses were restricted to patients who completed follow-up.

STATA/IC 16.1 software for Windows (StataCorp LLC) was used for analyses.

2.7. Ethics and informed consents

The study was approved by the Central Denmark Region Committee on Health Research Ethics. This study complies with the Declaration of Helsinki. All patients provided written informed consent prior to inclusion.

3. Results

3.1. Participants

A total of 107 patients with MG and 50 healthy controls were included at baseline; 70 patients and 35 controls were reexamined at follow-up (Table 1). Mean follow-up duration was 4.6 (±0.04) years. At follow-up, 9 patients had died, 20 patients did not respond to follow-up letters or declined further participation, 1 was > 90 years, and 7 patients developed severe intercurrent comorbidities impeding further participation (dementia(1), cancer(1), lower extremity ischemia(1), bilateral leg amputation(1), recent bilateral knee surgery (1), subarachnoid haemorrhage (1), and rheumatic disease (1)). Among the controls, 12 did not respond or declined participation and 3 were excluded due to intercurrent comorbidities.

Table 1
MG characteristics at baseline and follow-up.

	Baseline ($n = 107$)	Follow-up ($n = 70$)
Gender, female% (n)	49.5% (53)	54.3% (38)
Age, years (IQR)	62 (48;69)	65 (53;72)
Height, cm (±SE)	170.1 (±0.80)	171.1 (±0.99)
Weight, kg (±SE)	80.7 (±1.33)	78.4 (±1.65)
MG duration†, years (IQR)	7 (2;14)	11.7 (6.5;18.7)
Antibody type,% (n)		
Acetylcholine receptor	84.1% (90)	82.9% (58)
Muscle-specific kinase	1.9% (2)	2.8% (2)
Negative	14.0% (15)	14.3% (10)
Thymectomy,% (n)	30.8% (33)	35.7% (25)
MGFA Classification,%		
Clinical remission[a]	5.6% (6)	17.1% (12)
Class I	11.2% (12)	7.2% (5)
Class II	60.8% (65)	67.1% (47)
Class III	21.5% (29)	7.2% (5)
Class IV	0.9% (1)	1.4% (1)

Abbreviations: MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America.
[a] No detectable symptoms on the QMG, the MGC and the MG-ADL.

Other than weight (mean kilograms, 80.7 vs. 75.9, $P = 0.04$), there were no baseline differences between patients and controls regarding gender distribution (% female, 49.5% vs. 58.0%, $P = 0.32$), age (median years, 62 vs. 58, $P = 0.38$), and height (mean centimeters, 170.1 vs. 171.4, $P = 0.39$).

Patients lost to follow-up were older at baseline (median 66 vs. 61, $P = 0.01$). There was no difference in gender distribution, weight or height in follow-up participants compared with subjects lost to follow-up (all $P > 0.05$). There was no difference in MG duration, QMG, MGC, MG-ADL and QOL15 scores in follow-up patients compared with patients lost to follow-up (all $P > 0.05$).

At follow-up, 79% received pyridostigmine treatment (81% at baseline, 6% initiated treatment, 36% had dose change), 14% were treated with corticosteroids (23% at baseline, 6% initiated treatment, 6% had dose change), 53% received non-steroid immunosuppressive agents (41% at baseline, 23% initiated a new type of treatment, and in 16%, the dose of existing treatment was changed). At follow-up, the non-steroid immunosuppressive agents encompassed azathioprine (37%), methotrexate (4%), mycophenolate (9%), cyclosporine (4%), maintenance immunoglobulin or plasma exchange (6%), rituximab within 1 year (1%), and eculizumab (1%).

3.2. Maximal muscle strength

At baseline, isometric muscle strength was lower in patients with MG compared with healthy controls including right shoulder abduction (−13.8%, $P = 0.015$), left knee extensors (−18.5%, $P = 0.001$), and left ankle dorsal flexors (−11.1%, $P = 0.022$) (Fig. 1). At follow-up, isometric shoulder strength had improved by 10.8% in patients ($P < 0.001$) whereas it was unchanged in controls ($P = 0.702$) (Fig. 1 and Table 2). Patients and controls had similar isometric shoulder strength at follow-up ($P = 0.379$) (Fig. 1). Isometric knee extensor strength did not improve in patients
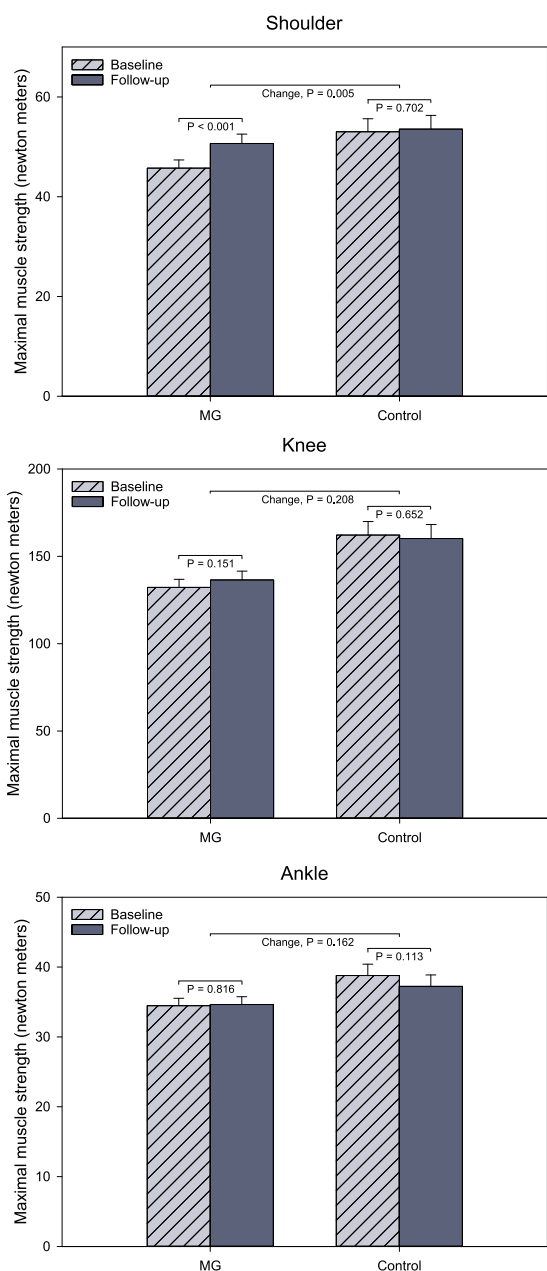
Fig. 1. Isometric muscle strength (mean and standard error) at baseline and follow-up in patients with MG and controls.
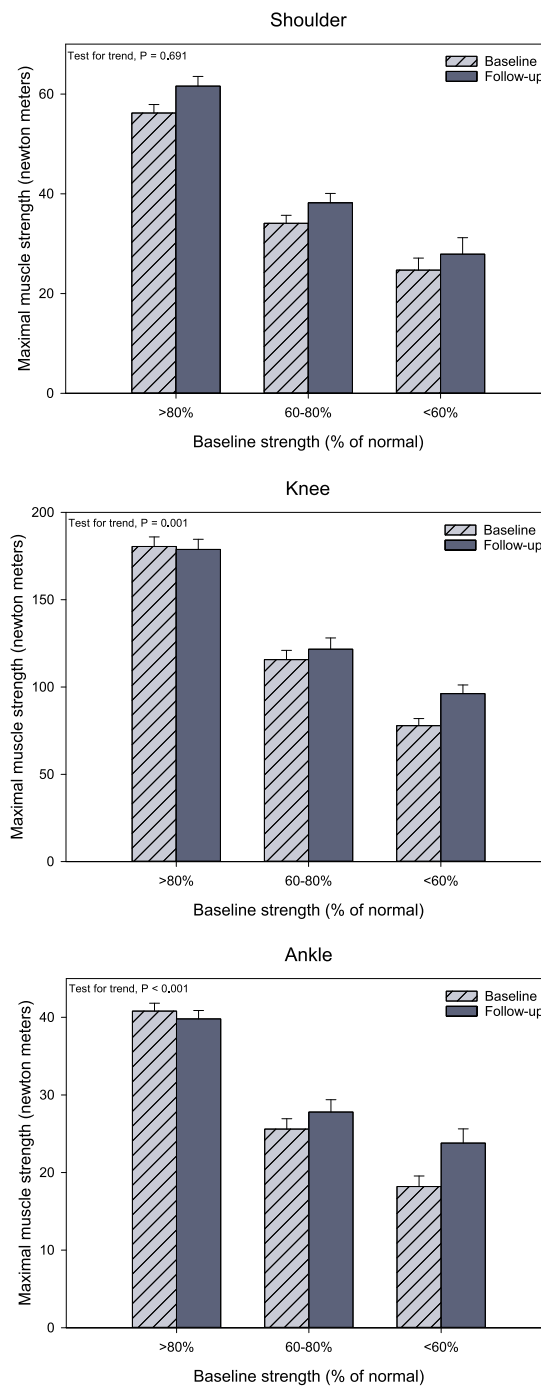

Fig. 2. Isometric muscle strength (mean and standard error) at baseline and follow-up in patients with MG, stratified by baseline isometric strength (percentage of normal).

Table 2
Change in isometric muscle strength (mean ±standard error and percentage of change from baseline) during follow-up in patients and controls.

	MG		Control		MG vs. control
	Nm (±SD)	%	Nm (±SD)	%	P-value
Shoulder	4.9 (±0.98)	10.8%	0.5 (±1.41)	1.0%	0.005
Knee	4.3 (±2.99)	3.2%	−2.0 (±4.36)	−1.2%	0.208
Ankle	0.2 (±0.68)	0.5%	−1.6 (±0.99)	−4.0%	0.162

($P = 0.151$) (Fig. 1), the change during follow-up was not different between patients and controls (Table 2), and it remained lower than in controls at follow-up (-14.8%, $P = 0.010$) (Fig. 1). Isometric ankle strength did not improve in patients ($P = 0.816$) (Fig. 2), but at follow-up ankle strength in patients was comparable to controls (Fig. 1 and Table 2).

In a sub-analysis, isometric shoulder strength improved in both incident (13.8%, $P = 0.002$) and prevalent cases (9.9%,
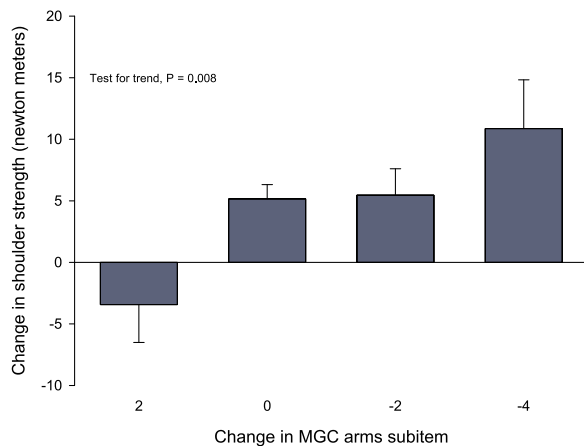
Fig. 3. Change in isometric shoulder strength (mean and standard error) stratified by change in MGC arm subitem during follow-up.

Fig. 4. Change in 400 m walk test (mean and standard error) stratified by change in MG-ADL leg subitem during follow-up.

$P < 0.001$). Neither incident nor prevalent cases improved in isometric knee or ankle strength. Patients in clinical remission and healthy controls had similar shoulder, knee, and ankle strength at baseline and follow-up (all $P > 0.05$).

Patients with the lowest baseline isometric knee (test for trend, $P=0.001$) and ankle strength (test for trend, $P < 0.001$) improved, whereas isometric shoulder strength improved independently of baseline strength (test for trend, $P=0.691$) (Fig. 2). The findings were similar if the analysis was limited to subjects with a baseline disease duration of at least 5 years (data not shown).

Neither disease duration nor age was related to change in isometric shoulder ($P > 0.05$), knee ($P > 0.05$) or ankle ($P > 0.05$) strength during follow-up. Current treatment with corticosteroids at follow-up did not result in less change in isometric shoulder ($P=0.402$), knee ($P=0.790$) or ankle strength ($P=0.118$) compared with patients treated with non-steroid immunosuppressive agents, when adjusting for disease severity based on the QMG score. Patients treated with corticosteroids did not have lower isometric muscle strength at follow-up (all $P > 0.05$). Cumulated corticosteroid dose within the last year prior to follow-up assessments (weight-adjusted dosing times number of days on treatment) did not correlate with change in shoulder ($r = -0.01$, $P=0.94$) or knee ($r=-0.04$, $P=0.74$) strength. Ankle strength improved more with increasing cumulated corticosteroid dose ($r=0.24$, $P=0.045$).

3.3. Isometric muscle strength and change in clinical scores

Change in isometric shoulder strength during follow-up was related to change in the MGC arm subitem (test for trend, $P=0.008$). However, isometric shoulder strength also improved in patients who remained stable on the MGC arms subitem ($P < 0.001$) (Fig. 3). Changes in the QMG right arm subitem ($P=0.487$), the MG-ADL arms subitem ($P=0.438$) and the QOL15 total score ($P=0.363$) were not related to change in isometric shoulder strength. Change in isometric knee strength during follow-up was not related to changes in
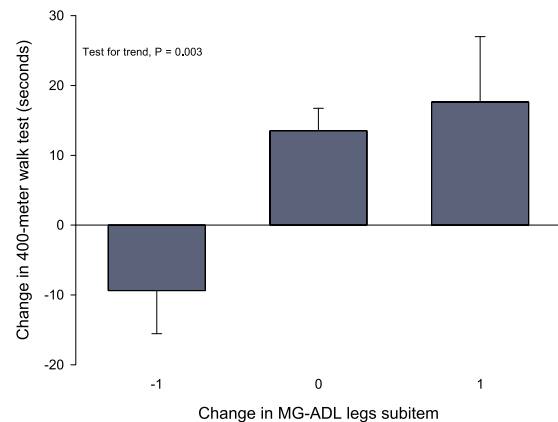
the MGC legs subitem ($P=0.06$), the QMG left leg subitem ($P=0.696$), the MG-ADL legs subitem ($P=0.850$) or the QOL15 total score ($P=0.309$).

3.4. Lower limb performance tests and physical activity

At follow-up, the 400MWT was completed by 84% of patients (9% exhausted, 3% dyspnea, 4% declined) and 97% of controls. The 30STS was completed by 87% of patients (9% exhausted, 4% declined) and 100% of controls at follow-up. The 400MWT ($P < 0.001$) and the 30STS ($P < 0.001$) were impaired in patients compared to controls at baseline (Table 3). There was no difference in change during follow-up on the 400MWT ($P=0.575$) and the 30STS ($P=0.865$) in patients compared with controls (Table 3). Patients in clinical remission and healthy controls had similar 400MWT and 30STS at baseline and follow-up (all $P > 0.05$).

At baseline, the median (IQR) PAS score in metabolic equivalents was 41.9 (39.4 to 47.7) in patients and 44.1 (41.5 to 47.7) in controls. There was no difference between patients and controls at baseline ($P=0.158$) or follow-up ($P=0.118$). The PAS score did not change in patients during follow-up (Wilcoxon signed-rank test, $P=0.393$).

3.5. Performance test correlations

During follow-up, change in the 400MWT correlated with change in isometric knee strength, QMG score, QOL15 score, and MG-ADL leg subitem score (Table 4). The 400MWT also worsened during follow-up in patients with no change in MG-ADL legs subitem score ($P < 0.001$) (Fig. 4). Change in the 30STS correlated with change in the QMG and QOL15 scores (Table 4). Change in the 400MWT or 30STS did not correlate with change in average daily physical activity (Table 4). Change in average daily physical activity was weakly correlated with change in shoulder strength ($r=0.324$, $P=0.01$), whereas it was not correlated with change in isometric knee strength ($r=0.0171$, $P=0.895$).

Table 3

Lower limb performance tests (mean ±standard error) at baseline and change during follow-up in patients and controls.

	MG		Control	
	Baseline	Change	Baseline	Change
400-m walk test (seconds)	258.7 (±4.62)	9.4 (±3.04)	217.5 (±5.16)	10.5 (±3.8)
30-s sit-to-stand (repeats)	12.6 (±0.38)	3.0 (±0.44)	15.5 (±0.49)	3.7 (±0.59)

Table 4

Correlations between change in performance tests and isometric muscle strength as well as MG scores during follow-up in patients with MG (Pearson correlation, *r*).

	400MWT	30STS
Isometric shoulder strength	0.0012	0.0470
Isometric knee strength	−0.3574*	−0.1468
Isometric ankle strength	−0.2091	−0.1639
QMG score	0.4393*	−0.3194*
QMG leg subitem	0.4400*	−0.2389
MGC score	0.0549	−0.1925
MGC legs subitem	0.1216	−0.1328
MG-ADL	0.2061	−0.1167
MG-ADL legs subitem	0.4187*	−0.1692
QOL15	0.3103*	−0.2948*
PAS	−0.0452	0.0677

Abbreviations: 400MWT = 400 m walk test; 30STS = 30-seconds sit-to-stand test; QMG = quantitative myasthenia gravis; MGC = myasthenia gravis composite; MG-ADL = myasthenia gravis activities of daily living; QOL15 = myasthenia gravis quality of life 15-items; PAS = Physical Activity Scale.

* $P < 0.05$.

4. Discussion

In this prospective population-based cohort study of patients with MG receiving standard optimal treatment, maximal shoulder strength improved and normalized during a 4½-year follow-up period. Accordingly, residual muscle weakness in a general MG population can improve, and the decreased maximal muscle strength found in cross-sectional studies [2–5] does not represent persistent impairments. Longer disease duration and greater baseline impairment did not result in less improvement, supporting the notion that optimizing treatment can alleviate the burden of symptoms and improve muscle strength despite long-standing and severe disease.

Whereas shoulder weakness normalized in patients in our study, knee weakness only improved in more severely affected patients and did not normalize. Some muscle groups are more frequently affected than others in MG, and distal extremity muscles are rarely affected [13]. Accordingly, ankle strength did not differ much at baseline and there was no detectable difference in change during follow-up. In contrast, knee strength remained lower in patients during follow-up. This may suggest a decreased therapeutic response on this muscle group and some degree of residual weakness, although other factors might contribute to the persistent impairment. Muscle weakness, fatigue and fatigability in

patients with MG may result in reduced exercise capacity and less physical activity compared with healthy individuals. This can subsequently result in muscle weakness and slower walking speeds. However, we found no association between the level of physical activity and knee strength or mobility impairment in patients with MG. The mechanisms accounting for this inconsistent finding on change in muscle weakness is unsettled and warrants further research.

The exact cause of muscle weakness in MG is poorly understood. In MG, autoantibodies target the post-synaptic receptors of the neuromuscular junction (NMJ). In most patients, these antibodies activate the complement system, resulting in receptor blockage, complement deposition and varying degrees of damage to the post-synaptic portion of the NMJ [1]. This destruction of the NMJ may result in irreversible damage, and it may subsequently result in more severe and permanent weakness. Our results do not support a detrimental effect of neither increasing disease duration nor higher baseline impairment on degree of improvement during follow-up. Treatment with corticosteroids might result in muscle weakness due to a steroid myopathy; however, we found no relation between steroid treatment and dose and change in shoulder or knee strength. Interestingly, ankle strength improved more with increasing steroid dose, and it is possible that a steroid myopathy has attenuated the observed change in knee strength. Further studies examining the effect of corticosteroids on muscle strength in MG are needed to clarify this relationship. Less physical activity may also result in decreased maximal muscle strength. However, only a weak correlation was observed between physical activity as assessed by the PAS questionnaire and shoulder strength in our study, and no association was observed with knee strength. Most patients with MG belong to the late-onset group [1], and muscle strength decrease with increasing age in healthy individuals [14]. Although this may lead to susceptibility to muscle weakness in most patients, we did not find less improvement in older patients.

We applied MG outcome measures designed to reflect relevant deficits and disability including two objective scores (MGC and QMG), one activity of daily living assessment (MG-ADL), and one quality of life questionnaire (QOL15). Whereas the QMG mainly reflects muscular fatigability using timed assessments, the limb and axial subitems of the MGC reflect muscle strength. Accordingly, the change in isometric shoulder strength correlated to change in the MGC arms subitem and not the QMG arm subitem, supporting the ability of dynamometry to distinguish muscle strength

from fatigability. Dynamometry was more sensitive to detect changes than the MGC, but this improvement did not translate to change in disability as assessed by the MG-ADL or change in quality of life as assessed by the QOL15. Accordingly, the MGC adequately captures clinically relevant muscle weakness in patients with MG. Dynamometry requires special equipment and is time consuming. Hence, it may be useful primarily in the early stages of drug development where the preliminary evidence of efficacy is examined.

Lower extremity weakness in MG is assessed by the MGC and the MG-ADL using hip flexor strength and inability to get up from a chair, respectively. However, impaired gait may negatively affect daily living, and weakness of knee extensors may negatively affect patients' mobility. Neither of these are directly assessed by the MGC or MG-ADL. Change in maximal knee strength was not related to change in the MGC, but it reflected physical disability assessed by the time walk test. Interestingly, this gait impairment was also captured by the MG-ADL. Hence, the MG-ADL adequately assesses lower extremity disability, and knee extensor strength is probably redundant when also examining hip flexor strength.

Lower extremity impairment is assessed by the 400MWT and 30STS. In daily clinical practice, the 30STS is easier to incorporate, but the 400MWT reflected overall disability better. Cross-sectional studies have used the 400MWT [5] and a 6 min walk test [15] in patients with MG. In this prospective study, the change in the 400MWT reflected muscle fatigability on the QMG, quality of life in the QOL15, and disability in the MG-ADL legs subitem. Correlations between change in the 400MWT and the clinical scores are in line with cross-sectional assessments [5,15], and they were stronger on lower-extremity specific subitems. Further, the 400MWT was more sensitive to change than the MG-ADL. Accordingly, the 400MWT can quantify gait impairment in MG and it reflects muscle fatigability, disability and quality of life. Severely affected patients may be unable to walk 400 m due to fatigability or dyspnea, and the 400MWT may thus predominantly supplement the floor-effects of the MG-ADL [16] and quantify impaired gait in mild and moderate cases of MG.

In this population-based follow-up study a large, unselected and heterogenous cohort of patients with MG were examined. Accordingly, muscle strength in our population was higher than in previously published convenience samples of patients with generalized MG only [2–4], and it likely provides a more correct estimate of weakness in the general MG population. Our baseline population did not include all available patients, which might introduce selection bias. However, baseline characteristics and treatment frequencies are in line with population-based studies in other countries [17,18], suggesting external validity. Although some patients and controls were lost during follow-up, the statistical imputations should reduce any bias introduced by this. Assessments of more muscle groups, especially hip flexors, could have strengthened our results. However, additional assessments would likely have resulted in fatigue and fatigability, which could subsequently affect measurements

and bias results. Thus, assessments were limited to a muscle group often affected (shoulder abductors), a potentially relevant muscle group not directly examined on the clinical scales (knee extensors), and a muscle group rarely impaired in MG (ankle dorsal flexors) serving as a negative control. Most patients were mildly affected, which might limit generalizability to more severe cases of MG. Interestingly, we found no evidence of less improvement in more severely affected patients. We do not have data on disease course preceding study participation, which may bias results due to long-standing disease. However, longer disease duration did not result in less improvement in our analyses. We consider improved shoulder strength to be the result of therapeutic optimization, which cannot, however, be determined based on our study. It is unsettled whether knee strength will normalize during further optimization and follow-up.

In conclusion, residual muscle weakness in patients with MG can improve. Our study showed that maximal shoulder strength normalized during follow-up, whereas maximal knee strength remained impaired and related to mobility impairment. Higher age, increasing disease duration and more severe baseline impairment did not result in less improvement. Although dynamometry and the timed-walk assessment quantified change over time in strength and mobility, change in residual muscle weakness was not related to disability and quality of life. Accordingly, other factors than muscle weakness are likely the main contributors to residual symptoms in patients with MG.

Declaration of Competing Interest

Jan Lykke Scheel Thomsen has received a speaker fee from Alexion. Lotte Vinge reports no relevant disclosures. Thomas Harbo reports no relevant disclosures. Henning Andersen has received research support from Sanofi Genzyme and CSL Behring, and received travel support and speaker fees from Novo, Alexion, Sanofi Genzyme, Octapharma and CSL Behring as well as served as a consultant on an advisory board for NMD Pharma.

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