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The correlation between functional capacity and quality of life in patients with myasthenia gravis

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ABSTRACT

Objective. The objective of this study was to analyze the correlation between functional capacity with quality of life in patients diagnosed with myasthenia gravis (MG).

Method. This cross-sectional study included 23 patients with MG between July and August 2021 (7 men,16 women; mean age: 46.78 ± 6.24 years; range: 33-56 years). Using a 2-minute walking test (2MWT) for 2-minute walking distance (2MWD), maximum oxygen uptake (VO2Max), and metabolic equivalents (METs), the functional capacity was determined. The quality of life can be evaluated by the Myasthenia Gravis Quality of Life 15 (MG-QL15).

Result. Functional capacity was not significantly correlated with quality of life: (2MWD and MG-QoL15 r=-0.002, p=0.992), (VO2Max and MG-QoL15 r=0.190, p=0.386), and (METs and MG-QoL15 r=0.188, p=0.391). Multiple linear regression analysis showed that 2MWD, VO2Max, and METs of functional capacity have no significant effect on MG-QoL15 of quality of life but 2MWD, METs, and VO2Max had a stronger relationship strength with MG-QoL15 domain ranging from VO2Max, MET, and 2MWD. Quality of life and functional capacity of myasthenia gravis patients showed no regression relationship partially of current age, age at onset, length of medication, severity of disease using myasthenia gravis composite (MGC) score, and body mass index (BMI).

Conclusion. In MG patients, no significant correlation was observed between functional capacity and quality of life, and further research is required to determine the factors that influence functional capacity and quality of life.

Keywords: myasthenia gravis, functional capacity, quality of life

INTRODUCTION

Myasthenia gravis has a low mortality rate and a high morbidity rate. The low mortality rate is indicated by advances in diagnosis and treatment [1]. High morbidity is indicated by a high relapse rate even with long-term use of medication, which makes participation in daily life very difficult and impairs functional capacity [2]. The extent of QoL impairment cannot be determined because the impact of high functional capacity limitation is often overlooked [2]. Myasthenia gravis is a chronic illness that impairs QoL. Myasthenia gravis patients have a worse QoL than before their diagnosis of myasthenia gravis [3].

Muscle weakness, fatigue, cardiopulmonary effects, and exercise intolerance due to myasthenia gravis cause musculoskeletal limitations in activity and participation, leading to reduced physical activity and lifestyle [4,5]. The downside is that sedentary behavior increases exercise intolerance, which in turn leads to decreased functional capacity, leading to decreased healthy life expectancy, productivity, and QoL [4,5].

Symptoms of myasthenia range from weakness of the eyes, bulbar, extremities, and breathing to generalized respiratory arrest [6,7]. Patients with MG frequently exhibit a "myasthenic pattern" that involves decreased respiratory volume and muscle endurance

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on pulmonary function tests as a result of respiratory muscle dysfunction disease that impairs QoL. Due to respiratory muscle weakness and impairment, patients may experience shortness of breath during strenuous physical activity. Decreased respiratory muscle endurance leads to decreased cardiorespiratory endurance, leading to decreased performance in physical activity and daily living [8] and ultimately to exercise intolerance/decreased functional capacity [9].

Limited research has investigated the correlation between functional capacity with QoL in MG patients and an absence of functional capacity measurement in MG with 2MWT. A study by S. Birnbaum et al. (2021) found that walking ability of 6 Minute Walking Distance (6MWD) was not associated with the health related quality of life (HrQoL), hence this research was conducted. The purpose of this research was to analyze the correlation between functional capacity and QoL in MG patients. In patients with MG, our hypothesis was that functional capacity and quality of life are correlated.

MATERIAL AND METHODS:

The cross-sectional study was conducted at Physical Medicine and Rehabilitation the Outpatient Clinic between August 2022 and September 2022. The research sample was sampled from consecutive admittance till the desired sample size was obtained. This study uses a correlation coefficient hypothesis calculation to determine sample size. Data for sample size is derived from research examined myasthenia gravis patients' serum enzyme levels after aerobic and ischemic exercise [10]. Total research subjects are 20.

$n = \{(Z\alpha + Z) / (0.5 \ln [(1+r) / (1-r)])\}2 + 3 = 20.220$

n = sample size

Zα = Z value at a significance level of 5% = 1.96

Zβ = Z value at 95% power = 1.64

R = Desired correlation level = 0.7

The study included 23 MG patients (7 men and 16 women; mean age: 46.78±6.24 years; range: 33-56 years). The following are the criteria for inclusion: (*i*) patients with confirmed myasthenia gravis, (*ii*) cooperative, (*iii*) normal cognition, and (*iv*) agree to participate in the research and sign informed consent form. Exclusion criteria were as follow: (*i*) myasthenia crisis, (*ii*) Myasthenia Gravis of Foundation America (MGFA) class IIb or more, (*iii*) cardio-respiration disorder, (*iv*) systemic disorder, (*v*) pregnancy, (*vi*) balance disturbance, (*vii*) vision disturbance, (*viii*) presence of erythema, wound, ulcer, or gangrene on one of or both of feet, (*ix*) neuromuscular disease affected lower limb that disturb ambulation. Demographic and clinical features of the participants consisting of current age, age at onset, gender, duration of medication, body mass index, severity of disease based on MGC, and comorbid disease. The research flowchart is in Figure 1.

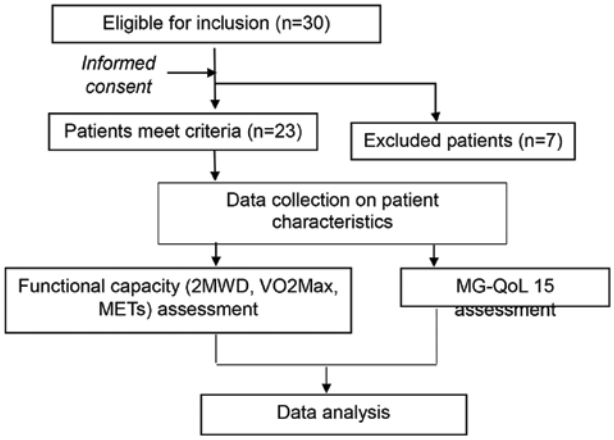

FIGURE 1. Research flowchart

Functional capacity was assessed using the 2MWT for 2-minute walking distance, VO2Max, and METs. Patients are instructed to consume pyridostigmine 1.5 to 2 hours before the 2MWT assessment in order to lower the risk of fatigue to general muscle weakness [11–13]. The time of medication, arrival at outpatient clinic, and evaluation of outcome measure were noted. On an unobstructed, rectangular path, patients walked 30 meters at a suitable pace for two minutes. Using track markings, the total distance in meter in 2 minutes was calculated and then converted to VO2max using the 2MWT formula [14].

$VO2Max\ (mL/KgBW/min) = 2.809 + (0.868 \times A) - (0.412 \times BW) - (0.0382 \times BH) - (0.474 \times WS)$

Note: mL = milliliter, KgBW = kilogram body weight, min = minute, A = age (years), BW = body weight (kilogram), BH = body height (cm), WS = walking speed (meter/minute).

VO2max was converted to give Metabolic Equivalent (METs) used to determine energy expenditure levels. METs = VO2Max / 3.5 [14,15].

The QoL was assessed using the MG-QoL15, which consists of 15 queries on 4 distinct domains, including mental. Score varying from 0 to 60 are given to each question of MG-QoL15 and higher score demonstrate decline in QoL. To assess health related QoL in myasthenia gravis patients, MG-QoL15 is regarded as a reliable and accurate instrument.

Ethics Committee Approval

Medicine Ethics Committee approved the study protocol (date: 31.05.2022, no: 0424/KEPK/V/2022). The research was performed according to with the Helsinki Declaration's principles.

Statistical Analysis

The research data was recorded and analyzed using IBM SPSS v 27.0 (IBM Corp., Armonk, NY, USA). The data obtained will be analyzed descriptively in the form of mean, standard deviation, minimum, maximum, number and percentage. Using the Shapiro-Wilk test for normality assumption, the distribution of the quantitative data was analyzed. Pearson correlation coefficients analyzed functional capacity and quality of life. Multiple linear regression analysis was performed to determine whether there was an effect of independent variables on the dependent variables. In the regression analysis, there will be a partial test and a coefficient of determination to figure out how each independent variable affects the dependent variables. Statistical significance was defined as $p < 0.05$ with a 95% confidence interval.

RESULTS

The 2MWD and MG-QoL15 scores of 23 participants had mean scores of 137.87 ±30.85 meter and 24.70±8.75 respectively (range: 66.81 to 189 meter and 9 to 46 score demographic and clinical characteristics are shown in Table 1.

Functional capacity and QoL variables in MG patients had normal distribution data that could be showed (2MWD (m) ($p = 0.747 > 0.05$), VO2Max ($p = 0.412 > 0.05$), MET ($p = 0.393 > 0.05$), MG-QoL scores ($p = 0.916 > 0.05$)) thus the data used met the requirements for using the Pearson correlation test. No significant correlations between functional capacity (2MWD, VO2Max, METs) with quality of life (MG-QoL15) ($p>0.05$; Table 2).

Multiple linear regression analysis showed that 2MWD, VO2Max, METs had no significant effects partially on movement, mental health, general satisfaction, and complaints domain in MG-QoL15 ($p > 0.05$, Table 3). Results of determination coefficients of 2MWD, VO2Max, METs for the movement, mental health, general satisfaction, and complaints domain of MG-QoL15 showed R square 0.000; 0.008; 0.008 (Table 4).

The analysis of multiple linear regression demonstrated that the current age, age of onset, duration of medication, severity of disease using MGC score, BMI had no significant effect partially on 2MWD, VO2Max, METs, and MG-QoL15 ($p > 0.05$, Table 5). Results of determination coefficient of current age, age of onset, duration of medication, severity of disease using MGC score,

TABLE 1. Demographic features of the participants

Variable	N (subject)	Min	Max	Mean	Std. Deviation	(%)
Current age (year)	23	33	56	46.78	6.24	-
Age at onset (year)	23	19	53	38.08	8.22	
Duration medication (year)	23	1	25	8.70	6.19	-
Body weight (kilogram)	23	36	86	60.57	13.72	-
Body height (centimeter)	23	144.50	173	159.76	7.46	-
BMI (kg/m^2)	23	15.38	35.11	23.70	5.00	-
MGC	23	0	10	3.65	3.01	-
MG-QoL 15	23	9	46	24.70	8.75	-
2MWD (meter)	23	66.81	189	137.87	30.85	-
VO2Max (ml/kg. minutes)	23	3.97	46.16	20.83	11.67	-
MET (ml/kg. minutes)	23	1.13	13.19	5.94	3.34	-
Gender						
Men						7 (30.4)
Women						16 (69.6)
Comorbidities						
Hypertension						4 (17.4)
Dyslipidemia						2 (8.7)
Atopic dermatitis						2 (8.7)
Hypertension, dyslipidemia						1 (4.3)
Nephrolithiasis						
Dyslipidemia, sinusitis						1 (4.3)
Post-polio lower limb D						1 (4.3)
Lipoma						1 (4.3)
None						11 (47.8)
BMI						
Underweight						3 (13.0)
Normal						8 (34.8)
Overweight						4 (17.4)
Obesity grade I						6 (26.1)
Obesity grade II						2 (8.7)

Min: Minimum, Max: Maximum; 2MWD: 2 Minute Walking Distance; VO2Max: maximum oxygen uptake; MET: Metabolic Equivalent; MGC: Myasthenia Gravis Composite; Std: Standard; BMI: Body Mass Index; D: Dextra; ml: milliliter; kg: kilogram; m: meter; MG-QoL 15: Myasthenia Gravis-Quality of Life 15.

TABLE 2. Correlation between functional capacity and QoL

Variable	r	p
2MWD (m) – MG-QoL 15	0.002	0.992
Vo2Max - MG-QoL 15	0.190	0.386
MET - MG-QoL 15	0.188	0.391

2MWD: 2 Minute Walking Distance; VO2Max: maximum oxygen uptake; MET: Metabolic Equivalent; MG-QoL 15: Myasthenia Gravis-Quality of Life 15; m: meter

Note: $p < 0.05$ (Significant)

TABLE 3. Regression analysis of movement, mental health, general satisfaction, complaints domain of MG-QoL

Variable	B	t-count	p-value
2MWD	0.000	0.002	0.998
Vo2Max	0.004	0.429	0.672
MET	0.013	0.425	0.675
Dependent variable: MG-QoL (movement, mental health, general satisfaction, complaints)/Reg Fact score 1 for analysis 2			
2MWD: 2 Minute Walking Distance; VO2Max: maximum oxygen uptake; MET: Metabolic Equivalent; MG-QoL 15: Myasthenia Gravis-Quality of Life 15			

Note: p < 0.05 (Significant)

TABLE 4. Determination coefficient result (movement, mental health, general satisfaction, complaints domain of MG-QoL)

Variable	R	R^2	Modified R2	Estimated Standard Error
2MWD	0.000[a]	0.000	-0.045	0.999
VO2Max	0.091[a]	0.008	-0.037	0.996
MET	0.090[a]	0.008	-0.037	0.996
a. Predictors: 2MWD, VO2Max, MET b. Dependent Variable: movement, mental health, general satisfaction, complaints domain of MG-QoL/Reg Fact score 1 for analysis 2				
2MWD: 2 Minute Walking Distance; VO2Max: maximum oxygen uptake; MET: Metabolic Equivalent; MG-QoL 15: Myasthenia Gravis-Quality of Life 15				

TABLE 6. Determination Coefficient Results (2MWD, VO2Max, METs, MG-QoL)

Variable	R	R^2	Modified R2	Estimated Standard Error
2MWD	0.463[a]	0.215	-0.329	35.56295
VO2Max	0.868[a]	0.754	0.584	7.53
METs	0.870[a]	0.757	0.589	2.138
MG-QoL 15	0.601[a]	0.361	-0.082	9.102
a. Dependent Variable: 2MWD, VO2Max, METs, MG-QoL b. Predictors: MGC, current age, age at onset, duration of medication, BMI				
2MWD: 2 Minute Walking Distance; VO2Max: maximum oxygen uptake; METs: Metabolic Equivalents; MG-QoL 15: Myasthenia Gravis-Quality of Life 15; Std: Standard				

BMI for 2MWD, VO2Max, METs, and MG-QoL15 showed R square 0.215; 0.754; 0.757; 0.361 (Table 6).

DISCUSSION

The total number of subjects was 7 men (30.4%) and 16 women (69.9%). The mean age of the study subjects was 46.78 ± 6.24 years, range 33-56 years, while age at onset was 38.08 ± 8.22, range 19-53 years. This is consistent with Andersen (2015) and Buboic et al (2020) which state that MG can affect male and female of all ages and races, although MG disease is considered a disease in young female (20-39 years) and old male (50-70 years) with a 3:1 incidence rate for female and male under 50 years [16,17].

A total of 23 subjects in this study had only 1 subject with ocular type and 22 subjects had general type, with a mean duration of treatment from onset of MG of 8.7 ± 6.19 years ranged from 1-25 years. Ocular MG (OMG) is an early sign of MG that affects the muscles around the eyes, the eyelids, or both. Depending on where the study was done, the change rates from OMG to generalized MG (GMG) range from 23.3% to 80% [18]. Most MG patients with ocular symptoms develop generalized within 2 years [19]. Patients with thymoma, aberrant facial RNS findings, shortened disease duration, and adult-onset OMG, and AChR-Ab positive have a significantly increased risk of generalization [20,21]. Using pyridostigmine and/or immunosuppressants and giving up smoking may cease the change to GMG [22].

In this study, there were 12 more subjects with comorbidities than subjects without comorbidities. This is consistent with studies by Laksoo (2021) and Cacho Diaz (2015), which found that MG patients had more comorbidities than those without comorbidities. Comorbidities in MG patients can worsen the prognosis of MG [23,24].

Subjects in this study had overweight and obese BMI more than normal. This condition is consistent with the study of Chang et al. (2021) pointed out that another condition associated with multiple comorbidities and metabolic disorders is obesity. Myasthe-

TABLE 4. Determination coefficient result (movement, mental health, general satisfaction, complaints domain of MG-QoL)

Variable	B				t-count				*p*-value			
	2MWD	VO2Max	METs	MG-QoL	2MWD	VO2Max	METs	MG-QoL	2MWD	VO2Max	METs	MG-QoL
Current age	10.762	2.086	0.599	-0.414	0.935	0.717	0.722	-1.252	0.362	0.482	0.480	0.227
Age at onset	-9.050	-2.519	-0.724	0.390	-0.788	-0.868	-0.874	1.182	0.441	0.397	0.393	0.253
Medication duration	-8.185	-2.267	-0.650	0.425	-0.703	-0.771	-0.774	1.270	0.491	0.451	0.449	0.220
BMI	1.929	1.601	0.460	0.029	1.550	5.094	5.119	0.801	0.139	0.000	0.000	0.434
MGC	0.626	0.081	0.017	0.063	0.230	0.118	0.085	0.800	0.821	0.907	0.933	0.434
Dependent variable: 2MWD, VO2Max, MET, MG-QoL/Reg Fact score 1 for analysis 2												
2MWD: 2 Minute Walking Distance; VO2Max: maximum oxygen uptake; METs: Metabolic Equivalents; MGC: Myasthenia Gravis Composite; BMI: Body Mass Index; MG-QoL: Myasthenia Gravis-Quality of Life.												

Note: p < 0.05 (Significant)

nia gravis alters the function and framework of the junction of neuromuscular, causing weakened muscles and alterations in body composition. The implications include diminished mass of muscle, elevated adiposity, and a rise in the prevalence of obesity [25].

The results of this research demonstrate no correlation between functional capacity with QoL in MG patients. These results are consistent with previous studies by Birnbaum et al (2021) and Paul et al (2001). Birnbaum et al (2021) studied generalized MG patients compared to controls and assessed physical activity from the tri-axial accelerometer, the 6-minute walk test (6MWT), and knee extension strength. The results of the research showed no relationship between physical activity/sedentary lifestyle and QoL, MG symptoms severity, and lower limb strength. Functional capacity as measured by 6MWT showed no association with HrQoL [26]. Paul et al (2001) studied 27 general MG subjects to measure QoL. The results revealed that functional capacity affected only physical domain of QoL to physical tasks completion and not-other domains of QoL. Overall QoL do not differ significantly from the general population [27].

There was no correlation between functional capacity and QoL in MG patients as there were confounding variables such as metabolic status, physical activity, daily intake. Individuals who are more active are less likely to develop metabolic syndrome [28]. Due to inactivity, the quantity of energy ingested outweighs the amount of energy used, resulting in an energy surplus that is stored in adipose tissue. This results in a resistance to insulin, which ultimately leads to the development of metabolic conditions such as type 2 diabetes (T2D). A sedentary life coupled with high intake of fats, carbohydrates, proteins which are risk factors for obesity, increases intracellular FFA [29].

In addition to metabolic diseases such as obesity and T2D, physical inactivity is also associated with heart problems such as coronary artery disease. Effects on sensitivity to insulin, metabolism of lipoprotein, blood pressure, fibrinolytic action, and hemostatic function can lead to cardiovascular problems [30]. Reduced cardiorespiratory fitness and physical activity due to metabolic syndrome because the symptoms of metabolic syndrome can increase unhealthy eating and lifestyle patterns, low energy levels, lack of exercise, and physical activity [31].

An important relationship between dietary quality and cardiorespiratory fitness is associated with improved cardiorespiratory fitness by decreasing exercise-induced oxidative stress by consuming a healthy diet. Oxidative stress is a major cause of aging. High-fiber diets associated with reduced levels of inflammation/oxidative stress, increased cardiorespiratory fitness, are important constituents of diet quality [32].

Assessments of functional capacity reflect an individual's ability to perform activities of daily living that require sustained aerobic metabolism and coordinated effort for cardiovascular, pulmonary, and musculoskeletal system [33]. The 2MWT is used to assess functional capacity [34]. Functional capacity describes the physical components (cardiorespiratory and muscle endurance) [35]. Physical component is movement domain of MG-QoL, other 3 domains of MG-QoL are not described. As we only measured cardiorespiratory endurance by 2MWT without muscular endurance, this may be one of the missing-relationship between functional capacity and QoL.

The MG-QoL15 is short in items, MG specific, correlates well with other quality of life questionnaires [36], good validity and reliability [3,34]. The MG-QoL15 is based on MG-QOL60 consisting of complaints (3 components), mental health (2 components), general satisfaction (1 component), and movement (9 components) [37]. MG-QoL15 can assess daily life, physical function, and social and psychological well-being of patients [37] so components of MG-QoL15 items include complex, multidimensional, and difficult to predict influencing factors [26]. No correlation between functional capacity and quality of life because there are uncontrolled influential factors and social psychological well-being components of MG-QoL were not measured.

This study had some limitations. First, there were some confounding variables that could not be controlled such as metabolic status, physical activity, and daily intake which might affect functional capacity and quality of life. Second, sedentary status or a specific questionnaire related to mental/psychological status of MG patients were not measured, making confounding factor in determining the impact on quality of life. Third, the absence of measurements pertaining to strength and endurance of the lower extremities and respiratory muscles as a predictive factor for functional capacity, thus becoming a confounder in determining QoL of MG patients. Fourth, the limited number of subjects so they could not strengthen correlation test and limited in the analysis of factors affecting quality of life levels.

CONCLUSION

No significant correlation was observed between functional capacity and QoL in MG patients, but 2MWD, METs, and VO2Max had a stronger relationship strength with MG-QoL15 domain ranging from VO2Max, MET, and 2MWD. There was no effect of age at present, age at onset, duration of treatment, BMI and degree of severity (MGC) on capacity of functional and QoL in MG patients. Presence of other factors affected the functional capacity and quality of life of MG patients.

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Patient consent for publication

Each patient provided their informed permission in the form of a written document.

Data sharing statement

The corresponding author can provide data supporting the results of this research upon reasonable request.

Authors contributions

Conceptualization, design, resources, data collection/processing, literature search, and writing: Y.D.A., Supervision, data analysis/data interpretation, critical reading: I.S., D.P., M.A., P.S., S.M. Materials: P.S., L.K.

Conflict of interest

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