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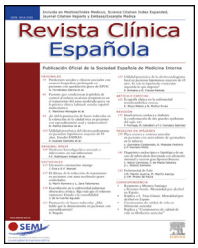

ORIGINAL ARTICLE

Initial handgrip strength as a predictive factor for amputation risk in diabetic foot patients

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KEYWORDS
Diabetic foot;
Diabetes mellitus;
Handgrip strength;
Dynapenia;
Amputation

Abstract
Background: We aimed to analyze the prognostic significance of handgrip strength as predictor of lower extremity amputation at 1 year follow up in patients with type 2 diabetes.
Methods: We evaluated 526 patients with type 2 diabetes between August 2020, and, June 2022. We collected from the electronic medical records demographic variables, laboratory data and history of amputation. The handgrip strength was assessed using a handheld Smedley digital dynamometer following the NHANES Muscle Strenght/Grip Test Procedure. Low handgrip strength was defined for women as less than 16 kg and for men less than 27 kg. Outcome variable was major or minor lower extremity amputation.
Results: A total of 205 patients with complete data entered the study. Patients mean age was 59 years old, 37% were women and the mean diabetes disease duration was 14 years. Seventy-seven (37%) patients suffered from lower extremity mputations (26 major and 51 minor amputations). After controlling for age, gender, presence of peripheral artery disease, body mass index and white cell counts as confounder variables, patients with low handgrip had an increased risk for amputations (Odds Ratio 2.17; 95% confidence Interval: 1.09–4.32; <0.001).
Conclusion: Low handgrip stregth is an independent prognostic marker for lower limb amputation at one year in patients with diabetes.

PALABRAS CLAVE
Pie diabético;
Diabetes mellitus;
Fuerza de agarre manual;
Dinapenia;
Amputación

La fuerza de presión inicial como factor predictivo del riesgo de amputación en pacientes con pie diabético

Resumen
Antecedentes: Nos propusimos analizar la significancia pronóstica de la fuerza de agarre manual como predictor de la amputación de extremidad inferior en el seguimiento de 1 año en pacientes con diabetes tipo 2.

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Métodos: Evaluamos a 526 pacientes con diabetes tipo 2 entre agosto de 2020 y junio de 2022. Recopilamos de los registros médicos electrónicos variables demográficas, datos de laboratorio e historial de amputación. La fuerza de agarre manual se evaluó utilizando un dinamómetro digital manual Smedley siguiendo el Procedimiento de Prueba de Fuerza Muscular/Agarre de NHANES. Se definió una baja fuerza de agarre manual para las mujeres como menos de 16 kg y para los hombres menos de 27 kg. La variable de resultado fue la amputación de extremidad inferior, ya sea mayor o menor.
Resultados: Un total de 205 pacientes con datos completos ingresaron al estudio. La edad media de los pacientes fue de 59 años, el 37% eran mujeres y la duración media de la enfermedad de la diabetes fue de 14 años. Setenta y siete (37%) pacientes sufrieron amputaciones de extremidad inferior (26 amputaciones mayores y 51 menores). Después de controlar la edad, el género, la presencia de enfermedad arterial periférica, el índice de masa corporal y los recuentos de células blancas como variables de confusión, los pacientes con baja fuerza de agarre manual tuvieron un mayor riesgo de amputaciones (*odds ratio* 2,17; intervalo de confianza del 95%: 1,09−4,32; <0,001).
Conclusión: La baja fuerza de agarre manual es un marcador pronóstico independiente para la amputación de miembro inferior a un año en pacientes con diabetes.

Introduction

What is already known on this topic?

Older patients with type 2 diabetes and diabetic foot disease had a higher rate of low handgrip strength.

Low handgrip strength was significantly associated with the occurrence of diabetic foot ulcers and directly correlated with Wagner score in geriatric patients with type 2 diabetes.

What this study adds?

This prospective study on diabetic foot patients reveals the significance of initial handgrip strength as a valuable predictor for the risk and level of amputation.

How this study might affect research, practice or policy?

The importance of taking initial handgrip strength into account in clinical assessments is highlighted by this study, which is remarkable for being the first to design and evaluate the risk of amputation based on this parameter prospectively.

Diabetic foot patients

Diabetic foot ulcers are significant contributors to morbidity and mortality in diabetic patients, impacting 6.3% of the population.[1] Although diabetes patients have a 19–34% lifetime risk of having foot ulcers, there is a 40% chance of recurrence in the first year after healing.[2,3] Patients with diabetic foot wounds had lower quality of life, higher rates of morbidity and mortality, and a six-year shorter life expectancy.[4] Amputation is necessary in 20% of instances involving infections that affect individuals with diabetic foot ulcers, which affect about 50% of patients.[5]

The most frequent reason for non-traumatic amputations in individuals with diabetes is foot ulcers, which account for the majority of amputations performed in this population.[6] A substantial reduction in quality of life and an increased risk of depression are observed in patients with major lower extremity amputations, which account for approximately 10% of perioperative deaths.[7] According to research, the 3-year death rate following amputation of a diabetic foot ranged from 35 to 50%.[8] A recent study found a link between grip strength and wound healing, which may serve as a guide to avoid this disastrous outcome.[9]

Grip strength is very important in daily activities which makes it used as a marker of nutritional status and daily activities.[10–12] Moreover, grip strength is a measure of factors including frailty and nutritional state.[10,13–15] Intriguingly, a recent study found a significant association between low handgrip strength and the coexistence of diabetic foot ulcers in elderly patients.[16] However, the relation between grip strength and amputation necessity in diabetic patients is unknown. In this, study we aimed to study diabetic foot patients with and without amputation and investigate the relation between amputation necessity and grip strength.

Methods

Study design

The research was conducted at outpatient clinics in Gaziantep, Turkey, where diabetic foot patients with type 2 diabetes mellitus who had visited the endocrinology outpatient clinic between August 2020 and June 2022 were

included. The patients were divided into two groups based on their initial handgrip strength as low and normal and called for follow-up and observed whether they had undergone amputation prospectively. In total, the study included 205 individuals, 100 with low grip strength and 105 with normal grip strength.

Participants

The patients were divided into two groups based on the necessity of amputation, as patients with or without any amputation. The exclusion criteria for the study included patients who were diagnosed Type 1 diabetes, undergoing hemodialysis, having a history of cancer, using any amount and duration of steroids within the past year, with missing data of handgrip strength measurement, suffering from other neurological conditions that impacted muscle strength like Parkinson's Disease, multiple sclerosis, or Alzheimer's, or experiencing mobility problems, myopathy, or quadriplegia due to a stroke.

Variables and definitions

Clinical and demographic information was extracted from patient records stored within our hospital's computerized database. This information encompassed details such as the presence of microvascular and macrovascular issues, the duration of diabetes, the occurrence of concurrent medical conditions, amputations, amputation levels and the medications prescribed. Additionally, the body mass index (BMI) was determined by considering height and weight. In terms of assessing glycemic control, this study utilized anthropometric measurements from the examination, as well as data from our institution's measurements of fasting plasma glucose (FPG) and HbA1c levels. To calculate the glomerular filtration rates (GFR) of the patients, the Modification of Diet and Renal Disease (MDRD) equation (GFR = 186 $\times$ [Creatinine/88.4] -1.154 $\times$ [Age]-0.203 $\times$ [0.742 if female] $\times$ [1.210 if black]) was employed. The severity of ulcers was assessed using the Wagner score (n = 5). The Wagner classification, established by Meggitt in 1976 and subsequently modified by Wagner in 1981, is the most commonly used method for grading diabetic foot ulcers. The Wagner scores categorize diabetic foot ulcers into six classes (ranging from G0 to G5) based on the ulcer's depth. Major amputation was defined as any amputation level proximal to ankle joint, and minor amputation is described as ankle and more distal levels.

To evaluate muscular strength, handgrip strength was assessed using a handheld Smedley digital dynamometer (Baseline 12-0286 Digital Smedley Dynamometer, Fabrication Enterprises Inc., Elmsford, NY). The score for each patient was computed based on the mean value of all measurements. Measurements were taken in each hand three times, with one-minute intervals between each measurement. The NHANES Muscle Strength/Grip Test Procedure was followed for conducting handgrip strength measurements.[18] Low handgrip strength was defined as handgrip strength below 16 kg for females and 27 kg for males.

The biochemical readings from the preceding month were recorded using hospital records. Using colorimetric enzymatic techniques (Siemens Advia System, Deerfield, IL, USA), the following parameters were measured: total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and fasting plasma glucose. An Advia 1650 Chemistry system from Siemens (USA) was used to measure serum creatinine levels, and an Advia 2400 Chemistry system from Siemens Healtcare Diagnostics Inc. was used to measure HbA1C utilizing the immune-inhibition method.

Study size

Power analysis was performed using G-Power software, version 3.1.9.4, to determine the required effective sample size for our study. Based on data from a previous investigation, an a priori power analysis for sample size estimate showed that 80 patients were required to achieve 95% power at a 5% error rate and an effect size of 0.46.[17] After adjusting for the 5% error rate of the post hoc power analysis approach, which was based on the discovery of amputations owing to handgrip strength and involved 205 participants, the study's power was found to be 96%.

Statistical methods

All statistical analyses were performed using the statistical program SPSS (Statistical Package for the Social Sciences) v.22.0 (IBM Corp., Armonk, NY, USA), which was accessible via our network. Data were evaluated as mean (+/−) standard deviation for continuous variables (FPG, weight, lipid profile), and as number (n) and percentage (%) values for categorical variables (sex, etc.). The normal distribution was investigated using the Kolmogorov-Smirnov test. An independent sample t-test or Mann–Whitney U variance analysis test was used, presuming a normal distribution. Depending on the assumption of normal distribution, the dependent sample t-test or Wilcoxon test was employed to compare numerical data among dependent groups. The chi-square test was used to compare the category data. We compared the progression to amputation of subpopulations due to the grip strength via a Kaplan-Meier survival analysis.

The main exposure in the study was dynapenia, assessed through handgrip strength measurements using a handheld dynamometer. Potential confounders were age, gender, BMI and body weight, hemoglobin and albumin levels, peripheral arterial disease, renal function, plasma ALT and AST levels, and white blood cell count.

The association between low handgrip strength and the numerical data (HbA1c, creatinine, fasting glucose level, etc.) was ascertained using the Spearman correlation analysis. Cramer's V is used to assess the relationship between two dichotomous categorical variables. The rank-biserial correlation coefficient, or r rb, is used for dichotomous nominal data vs ranks (ordinal). Logistic regression was used to look at possible baseline risk variables for diabetic foot ulcers. A statistically significant result was defined as a p-value of 0.05 or less.

The study protocol, which was conducted at the Endocrinology and Metabolism Outpatient Clinics in compliance with the Declaration of Helsinki and the Harmonization

Guidelines for Good Clinical Practice, was approved by the institutional ethical committee. Every participant gave their informed consent both verbally and written.

Results

Participants and descriptive data

Total patient count was 526. After patients without handgrip strength measuremetnt and patients with missed data criteria were excluded, 205 patients were included in the study (Fig. 1).

Assessment of clinical characteristics, laboratory results, and comorbidities of patients according to amputation

The demographics, clinical traits, biochemical findings, and comorbidities of diabetic foot patients with and without amputations were listed in the table (Table 1). Seventy seven of the 205 type 2 diabetic patients (37.5%) had an amputation. The statistical results revealed that Diabetic foot patients with amputations had a significantly higher prevalence of peripheral artery disease ($p < 0.001$), WBC count ($p < 0.001$), and a significantly higher prevalence of low initial handgrip strength ($p < 0.001$), while diabetic foot patients without amputations had a significantly higher BMI ($p = 0.001$), body weight ($p = 0.021$), hemoglobin ($p < 0.001$) and albumin ($p < 0.001$). When initial handgrip strength was evaluated considering genders, male diabetic foot patients without amputations had significantly higher strength ($p = 0.001$), however results of female gender were not statistically significant ($p = 0.089$). The Wagner scores were found to be significantly higher in the diabetic foot patients with amputation compared to patients without amputation ($p < 0.001$). When the distribution of geriatric patients was compared according to gender in amputated patients, it was found to be similar ($p = 0.614$). Additionally, no significant difference was found in amputated patients when the ages of male and female patients were compared ($p = 0.327$).

Medication use

Drug and insulin therapy usage based on the presence of amputation were evaluated and listed in a table (Table 1). Diabetic foot patients with amputations were found to have a significantly lower total daily insulin dose compared to the patients without amputations ($p = 0.006$). Between the two groups, there was no discernible difference in the use of any oral antidiabetic drugs, beta-blockers ($p = 0.326$), calcium channel blockers ($p = 0.803$), acetylsalicylic acid ($p = 0.109$), ACE inhibitors or ARB ($p = 0.138$). Insulin treatment duration did not reveal any difference between the two groups ($p = 0.745$).

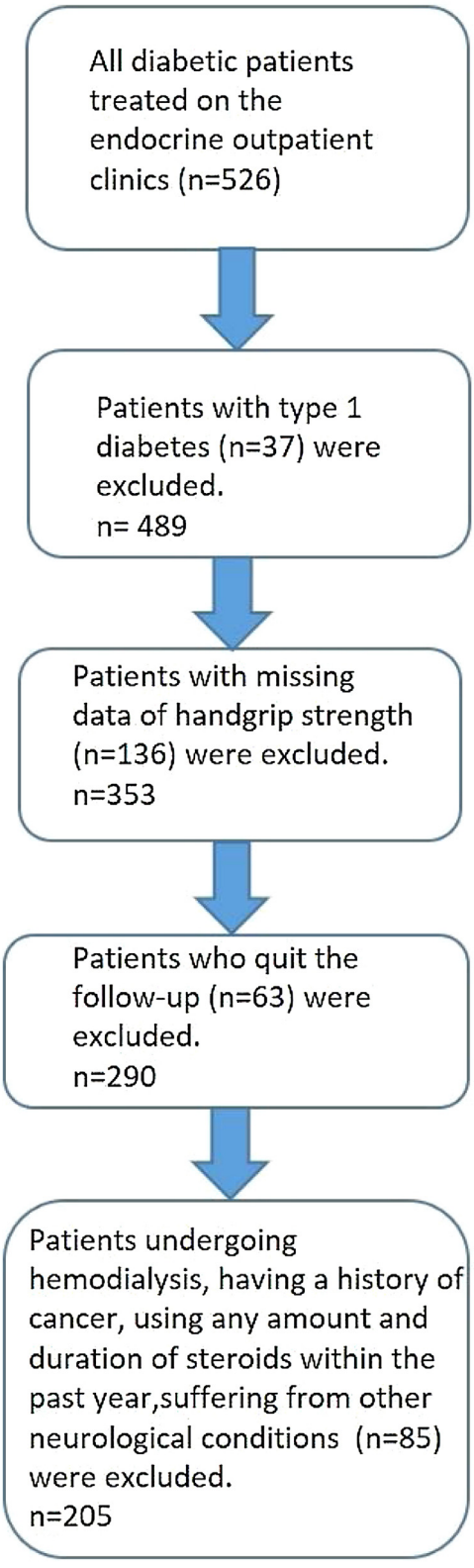

Figure 1 Flowchart diagram showing the inclusion and exclusion of selected patients.

Table 1 Demographics, clinical characteristics, biochemical results, comorbidities and the comparison of the drugs and insulin therapy in type 2 diabetic patients with and without amputations.

	Diabetic foot patients with any amputations n = 77	Diabetic foot patients without amputations n = 128	P value
Gender (Female) (n,%)	24 (31.2%)	52 (40.6%)	0.175
Age (year)	60.67 ± 10.78	59.60 ± 8.60	0.462
Duration of diabetes (year)	14.59 ± 7.15	14.34 ± 6.54	0.800
Diabetic retinopathy (%)	31 (40.3)%	43 (33.6%)	0.336
Complaints of neuropathy (%)	68 (87.1%)	116 (91.3%)	0.324
eGFR <60 ml/min/1.73 m^2	28 (36.4%)	41 (32.0%)	0.525
Hypertension (n,%)	43 (55.8%)	74 (57.8%)	0.982
Hyperlipidemia (n,%)	55 (71.4%)	92 (71.9%)	0.945
Coronary artery disease (n,%)	37 (48.1%)	46 (35.9%)	0.106
Peripheral artery disease (%)	40 (51.9%)	23 (18.0%)	**<0.001**
Smoking (n,%)	32 (42.1%)	44 (34.3%)	0.349
Body mass index (kg/m^2)	27.34 (8.50)[a]	31.23 (4.15)[a]	**0.001**
Bodyweight (kg)	77.00 (20.00)[a]	80.25 (17.30)[a]	**0.021**
FPG (mg/dl)	249.00 (190.30)[a]	215.00 (158.80)[a]	0.734
HbA1c (%)	10.05 (4.39)[a]	10.46 (3.13)[a]	0.791
Triglycerides (mg/dl)	155.00 (132.0)[a]	186.00 (88.0)[a]	0.092
HDL cholesterol (mg/dl)	33.91 ± 13.09	40.01 ± 18.62	**0.024**
LDL cholesterol (mg/dl)	97.63 ± 34.53	98.35 ± 34.70	0.897
Non-HDL cholesterol (mg/dl)	133.67 ± 41.94	139.13 ± 48.33	0.492
Creatinine (mg/dL)	0.96 (0.61)[a]	0.87 (0.35)[a]	0.238
e-GFR (mL/dk/1.73 m^2)	81.00 (55.00)[a]	85.50 (35.00)[a]	0.200
Uric acid (μg/L)	5.07 ± 1.74	5.44 ± 1.62	0.156
AST (U/L)	18.00 (12.80)[a]	16.00 (11.00)[a]	0.927
ALT (U/L)	16.50 (11.30)[a]	15.50 (9.80)[a]	0.487
Albumin (g/dL)	3.40 (0.72)[a]	4.05 (0.67)[a]	**<0.001**
WBC (/mm^3)	12130.00 (8780.00)[a]	9665.00 (4000.00)[a]	**<0.001**
Hemoglobin (g/dL)	11.65 ± 2.08	13.17 ± 2.26	**<0.001**
Metformin (n,%)	46 (59.7%)	91 (71.1%)	0.095
Dpp-4 inhibitor (n,%)	35 (45.5%)	67 (52.3%)	0.388
Sglt-2 inhibitor (n,%)	14 (18.2%)	28 (21.9%)	0.526
Sulfonylurea (n,%)	13 (16.9%)	19 (14.8%)	0.697
Thiazolidinedione (n,%)	4 (5.2%)	12 (9.4%)	0.280
Glinid (n,%)	2 (2.6%)	6 (4.7%)	0.454
Statin (n,%)	12 (15.6%)	23 (18.0%)	0.720
Fenofibrate (n,%)	4 (5.2 %)	13 (10.2%)	0.222
Acetyl salicilic acid (n,%)	48 (62.3%)	65 (50.8%)	0.109
ACE inhibitor/ARB use (n,%)	24 (31.2%)	54 (42.2%)	0.138
Calcium channel blocker (n,%)	18 (23.4%)	28 (21.9%)	0.803
Beta blocker (n,%)	21 (27.3%)	27 (21.1%)	0.326
Insulin users (n,%)	65 (84.4%)	97 (75.8%)	0.141
Duration of insulin treatment (year)	8.00 (6.50)[a]	8.00 (6.50)[a]	0.745
Total daily insulin dose (U/day)	40.00 (30.00)[a]	50.00 (32.50)[a]	**0.006**
Low initial handgrip strength (n/%)	50 (64.9%)	50 (39.1%)	**<0.001**
Initial handgrip strength (kg force)			
Female patients	15.41 (6.31)[a]	17.04 (4.70)[a]	0.089
Male patients	22.36 (10.33)[a]	29.09 (10.19)[a]	**0.001**
Wagner score			
Wg 1	0 (0.0 %)	17 (13.3 %)	
Wg 2	5 (6.5 %)	39 (30.4 %)	
Wg 3	21 (25.9 %)	56 (43.7 %)	**<0.001**
Wg 4	41 (53.2 %)	16 (12.5 %)	
Wg 5	10 (12.9 %)	0 (0.0 %)	

F, female; FPG, fasting plasma glucose; M, male, Wg, Wagner; eGFR, estimated glomerular filtration rate, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein.

[a] Calculated by non-parametric tests (Mann–Whitney U test) (median/IQR).

Table 2 Demographics, clinical characteristics, biochemical results, and comorbidities of type 2 diabetic patients according to handgrip strength.

	Patients with Low initial handgrip strength n = 100	Patients with normal initial handgrip strength n = 105	p-value
Age (year)	62.06 ± 9.01	58.05 ± 9.51	**0.002**
Gender (F/M), (n)	35/65	41/64	0.566
Duration of diabetes (year)	13.00 (10.50)*	15.00 (9.00)*	0.395**
Bodyweight (kg)	77.00 (15.00)*	82.00 (20.50)*	0.107**
Body mass index (kg/m^2)	29.21 (6.80)*	31.22 (9.57)*	0.147**
Hypertension (n,%)	62 (62.0%)	55 (52.4%)	0.087
Hyperlipidemia (n,%)	73 (73.0 %)	74 (70.5%)	0.757
Ischemic heart disease (n,%)	47 (47.0%)	36 (34.3%)	0.067
Peripheral artery disease (%)	42 (42.0 %)	21 (20.0 %)	**0.001**
Diabetic retinopathy (n,%)	36.0 (36.0%)	38 (36.2%)	1.000
Smoking (n,%)	33 (33.0%)	43 (40.9%)	0.245
AST (U/L)	16.00 (13.00)*	18.00 (11.50)*	0.191**
ALT (U/L)	15.00 (12.00)*	18.00 (8.50)*	**0.003****
FPG (mg/dl)	257.87 ± 129.36	236.13 ± 107.88	0.194
Hba1c (%)	10.36 ± 2.38	9.98 ± 2.15	0.233
Triglycerides (mg/dl)	166.00 (119.00)*	168.00 (107.00)*	0.248**
HDL cholesterol (mg/dl)	37.01 ± 12.41	38.60 ± 20.36	0.537
LDL cholesterol (mg/dl)	103.15 ± 39.25	93.91 ± 29.67	0.091
Non-HDL cholesterol (mg/dl)	140.25 ± 48.77	134.13 ± 43.27	0.430
Creatinine (mg/dl)	0.96 (0.58)*	0.87 (0.49)*	**0.009****
e-GFR (mL/dk/1.73 m^2)	66.96 ± 30.51	79.55 ± 28.78	**0.003**
Uric acid (μg/L)	5.50 ± 1.72	5.09 ± 1.61	0.111
Hemoglobin (g/dL)	12.02 ± 2.13	13.17 ± 2.35	**<0.001**
Insulin users (n,%)	78 (78.0%)	84 (80.0%)	0.725
Duration of insulin treatment (year)	9.00 (10.00)*	8.00 (7.00)*	0.508**
Total daily insulin dose (U/day)	50.00 (30.50)*	50.00 (42.00)*	0.680**
Wagner score	Wg 1 = 5 (5.0%)	Wg1 = 12 (11.4%)	
	Wg 2 = 19 (19.0%)	Wg2 = 25 (23.8%)	
	Wg 3 = 36 (36.0%)	Wg3 = 41 (39.0%)	0.081
	Wg 4 = 32 (32.0%)	Wg4 = 25 (23.8%)	
	Wg 5 = 8 (8.0%)	Wg5 = 2 (1.9%)	
Amputation (n,%)	50 (50.0%)	27 (25.7%)	**0.001**
Major/minor amputation (n/n)	21/29	5/22	**0.038**

F, female; FPG, fasting plasma glucose; M, male, Wg, Wagner; eGFR, estimated glomerular filtration rate, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein.
* Median (IQR).
** Mann–Whitney U-test was used to compare the median of continuous variables.

Assessment of clinical characteristics, laboratory results, and comorbidities of patients according to handgrip strength

According to handgrip strength, diabetic foot patients with and without amputation had their demographic, clinical, laboratory, and comorbidity data evaluated and brought to a table (Table 2). One hundred (40.9%) of the 205 individuals with type 2 diabetes had low grip strength. Patients with low initial handgrip strength were found to be significantly older (p = 0.002), had a significantly higher prevalence of peripheral arterial disease (p = 0.001), amputations (p = 0.001), and both major and minor amputations (p = 0.038) and had higher creatinine levels (p = 0.009) and lower e-GFR levels (p = 0.003). Patients with normal initial handgrip strength were found to have higher hemoglobin, albumine and ALT levels compared to those with low initial handgrip strength (p < 0.001, p = 0.005, p = 0.003 respectively).

Outcome data

After one-year follow up, 77 (37%) out from 205 patients suffered from amputations. Major amputations occurred in 21 (21%) patients in the low initial handgrip strength, and in 5 (5%) patients with normal initial handgrip strength (Odds Ratio 5.27 [OR]; 95% confidence intervals [CI]: 1.98–16.33; P = 0.0004). Minor amputations occurred in 29 (29%) patients in the initial low handgrip strength, and in 22 (22%) patients with normal initial handgrip strength (OR: 1.53; IC: 0.81—0.94; P = 0.188). Overall, low initial handgrip strength was associated with any kind of amputation major or minor (OR: 2.87; CI: 1.60–5.23; P = 0.0003).

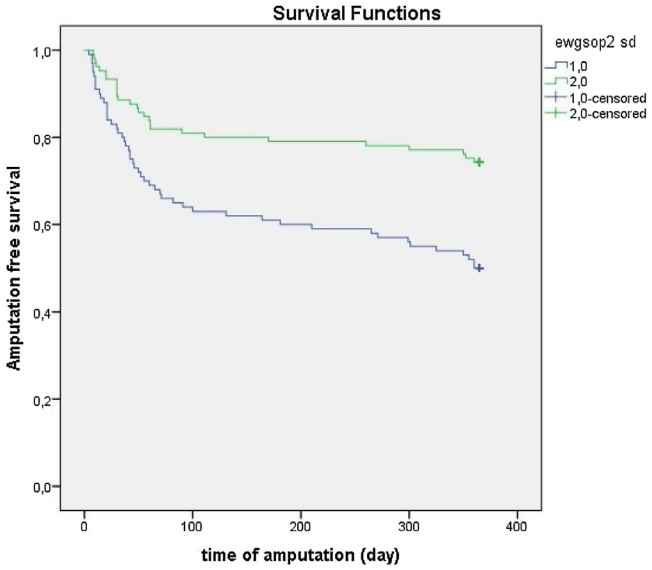

Figure 2 Kaplan–Meier survival analysis.

Correlation and regression analysis

Initial low handgrip strength was correlated with amputation requirement in the follow-up ($r = 0.251$, $p < 0.001$) and major amputation ($r = 0.237$, $p = 0.038$), age ($r = 0.214$, $p = 0.002$), plasma ALT level ($r = -0.206$, $p = 0.003$), hemoglobin level ($r = -0.258$, $p < 0.001$), peripheral arterial disease ($r = 0.238$, $p = 0.001$), and eGFR < 60 ml/min ($r = 0.152$, $p = 0.030$). Amputations were correlated with BMI ($r = -0.238$, $p = 0.001$), bodyweight ($r = -0.165$, $p = 0.020$), hemoglobin level ($r = -0.311$, $p < 0.001$), peripheral arterial disease ($r = 0.357$, $p < 0.001$) and WBC level ($r = 0.292$, $p < 0.001$). Major amputations were correlated with WBC levels ($r = 0.315$, $p = 0.006$), and peripheral arterial disease ($r = 0.412$, $p < 0.001$).

Logistic regression analysis was done and results were brought to a table (Table 3). Initial low handgrip strength was found to be independently linked to amputation in univariate analyses. Amputation frequency was 2.89 times higher among those with poor initial grip strength than those with good initial grip strength. Also, initial low grip strength was found to be independently associated with amputation in multivariate analysis.

Survival analysis

The Hazard Ratio of 1.33 (CI:1.01–1.76, $p < 0.001$) suggests a moderate increase in the risk of the amputation in the low initial handgrip strength group compared to normal initial handgrip strength group, and clinically, these findings suggest that low initial handgrip strength patient group was found to be associated with an increased risk of the amputation, warranting further investigation and consideration in the context of the specific study or clinical scenario (Fig. 2).

Discussion

This prosopective study revealed that diabetic foot patients with low initial grip strength have higher risk and frequency of amputation in the prospective one year follow-up when compared to diabetic foot patients with normal initial grip strength. A study similar to this study, demonstrated that wound healing was improved in those with normal muscle strength, and our study also supports this result.[9] However, the result obtained in the literature was unexpected considering the design of the study, and this study is the first prospective study to evaluate the risk of amputation according to initial handgrip strength. The survival analysis of this study based on progression to amputation revealed that the risk of amputation was significantly higher in diabetic foot patients with low initial grip strength. The reason for this result may be the decrease in muscle strength and functionality as a result of the catabolic process experienced by patients after the development of diabetic foot ulcer, the effect of inflammatory cytokines secreted in this process, and the effect of malnutrition experienced by patients due to the catabolic process. In addition, conditions such as peripheral artery disease and diabetic neuropathy, which are frequently associated with diabetic foot patients, may be important in this process.[18,19] In our study, BMI and body weight were found to be significantly higher in patients without the need for amputation, which supports the effect of the catabolic process and malnutrition. At the same time, low HDL values in amputated patients may be related to the peripheral artery disease.[20] Moreover, multivariate logistic regression analysis showed that low initial low hangrip strength was associated with the need for amputation. The initial low handgrip strength should be used as a predictor for the progress towards amputation.

The rate and number of major amputations were found to be higher in patients with low grip strength. Furthermore, multivariate logistic regression revealed an assocation of major amputation with peripheral arterial disease and high leukocyte count. This result may be related to the catabolic processes and malnutrition. But there was no associaton between low initial handgrip strength and major amputation risk. These results suggest that prospective studies involving more patients should be conducted to understand the role of muscle strength better as an indicator of the risk of major amputation.

Initial low handgrip strength was found significantly more common in patients who needed amputation. Nevertheless, a significantly low initial handgrip strength was observed only in amputated male patients with diabetic foot disease when grip strength was examined in kg-force by gender. In the literature, a study conducted using the DEXA method in diabetic foot patients reported that sarcopenia is more common in diabetic foot patients.[21] Another study in the literature demonstrated that the measurement of sarcopenia at the L3 level on CT is also associated with mortality in amputated diabetic foot patients.[22] The results of this study suggest that dynapenia, a parameter used in screening and diagnosis of sarcopenia, may be a predictive factor for amputation risk and is associated with the prognosis of diabetic foot disease. The authors of this study also consider

Table 3 Multivariate binary logistic regression analysis models.

Variable	Dependent variable	Independent variable	Odds ratio/%95 confidence interval	p-value	R^2 of the model	P value of the model
Univariate	Amputation	Initial low handgrip strength	2.890 (1.605–5.208)	**<0.001**	0.084	**<0.001**
Univariate	Major Amputation	Initial low handgrip strength	3.184 (1.037–9.803)	**0.043**	0.080	**0.043**
Age and gender-adjusted	Amputation	Initial low handgrip strength	2.824 (1.545–5.181)	**0.001**	0.094	**0.002**
		Age	1.003 (0.971–1.036)	0.834		
		Male gender	1.494 (0.801–2.787)	0.206		
Age and gender-adjusted	Major Amputation	Initial low handgrip strength	3.205 (0.968–10.526)	0.056	0.144	**0.038**
		Age	1.022 (0.972–1.075)	0.382		
		Male gender	0.417 (0.142–1.229)	0.113		
Model 1	Amputation	Initial low handgrip strength	2.173 (1.095–4.329)	**0.027**	0.296	**<0.001**
		Age	1.003 (0.966–1.039)	0.891		
		Male gender	1.190 (0.563–2.517)	**0.649**		
		Peripheral Artery Disease	3.033 (1.470–6.250)	**0.003**		
		BMI	0.959 (0.902–1.021)	**0.195**		
		WBC	1.002 (1.001–1.003)	**0.001**		
Model 2	Major amputation	Inıtial Low handgrip strength	3.831 (0.939–15.625)	**0.061**	0.410	**<0.001**
		Age	1.015 (0.959–1.072)	0.602		
		Male gender	0.311 (0.078–1.234)	0.097		
		Peripheral Artery Disease	9.148 (2.325–35.714)	0.002		
		WBC	1.002 (1.001–1.003)	0.023		

that sarcopenia indirectly indicates the risk of amputation in diabetic foot patients.

The peripheral artery disease was more common in patients with low initial low grip strength and amputations, and according to the results of multivariate analysis, peripheral artery disease and leukocyte count was found to be associated with the risk of major amputation. This result reveals that peripheral artery disease and severity of infection affect the amputation level.

In diabetic foot patients with initial low handgrip strength, lower level of albumin, which is a negative acute phase reactant, and higher leukocyte count, which is related to the severity of the infection, and lower hemoglobin are considered as parameters indicating the severity of the infection developing in diabetic foot patients and the severity of the resulting catabolic process. When the literature was examined, in a meta-analysis conducted in 2021, hemoglobin and albumin were found to be negatively associated with sarcopenia.[23] In a study conducted in 2019, high leukocyte count even within the normal range was found to be associated with sarcopenia.[24] The results of our study were found to be compatible with the literature.

Total insulin doses were found to be lower in patients who needed amputation in this study. In the literature, although insulin use was found to be more common in patients with diabetic foot ulcers than in patients without diabetic foot ulcers, the total insulin dose used was found to be similar.[16,17] In this study, unlike the literature, only diabetic foot patients were included. This result may have been due to the catabolic process in the patients, and may also

be related to the better adherence to treatment in patients who did not require amputation.

No difference was detected between the usage of SGLT-2 inhibitors in patients who developed the need for amputation and those who did not. Although there are findings in the literature that the use of SGLT-2 inhibitors increases the risk of amputation, there are also results indicating that it is not associated with such a risk.[25–27] In this study, no difference was found between patients with and without lower extremity amputations in terms of SGLT-2 inhibitor use, but this study was not designed with this purpose. There is a need for prospective studies on this subject, specifically designed and involving a larger number of patients, and for the experiences gained during the use of drugs to be reported in the literature.

In this study, patients with low initial low handgrip strength were found to be older than the normal group. Low muscle strength is a phenomenon that develops more in elderly patients and affects 10–16% of the elderly population.[28] The result of this study was compatible with the literature and was an expected result.

This study have some limitations. Although it was a prospective study, it was not designed as randomized and double blinded. This leads to bias and also weakens the cause-and-effect relationship. Only dynapenia was examined in the design of the study, and sarcopenia was not assessed. Studies that assess sarcopenia will provide more accurate results in identifying patients who are at risk of amputation. The progress to major amputation in cases with minor amputation and total healing of existing foot ulcers were not investigated. Additionally, no examination of the muscle strength measurement after a year was made and the changes in handgrip strength in a year time was not evaluated. Treatment adherence was not inquired and evaluated among the groups. Changes in weight and BMI during follow-up were also not monitored.

Conclusions

This prospective study on diabetic foot patients reveals intriguing perspectives into the significance of initial handgrip strength as a valuable predictor for the risk and level of amputation. The results are consistent with previous research demonstrating the positive correlation between muscle strength and wound healing. The importance of taking initial handgrip strength into account in clinical assessments is highlighted by this study, which is remarkable for being the first to design and evaluate the risk of amputation based on this parameter prospectively. The discovered correlations between amputation risk in this patient population and variables like age, infection severity, and peripheral vascular disease reflect the complex nature of this risk.

Conflict of interest

There are no competing interests for any author.

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