

## Original Article

# Sarcopenia and Muscle Dysfunction in Osteogenesis Imperfecta: Insights from A Pilot Study

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## Abstract

**Objective:** This study aimed to assess the prevalence of sarcopenia in adult patients with osteogenesis imperfecta (OI) and to identify its associated factors. **Methods:** Seventeen adult OI patients and 17 adult healthy controls matched for age, sex, and BMI were included. Assessments included handgrip strength (HGS), ultrasonographic muscle measurements, the International Physical Activity Questionnaire (IPAQ), Upper and Lower Extremity Functional Indices (UEFI & LEFI), the SARC-F questionnaire, and laboratory markers. **Results:** Left-handgrip strength was significantly lower in OI patients than in controls ( $21.8 \pm 4.9$  kg vs.  $25.3 \pm 4.2$  kg,  $p = 0.034$ ). Four OI patients had a SARC-F score  $\geq 4$ , whereas none in the control group did. Handgrip strength was negatively correlated with thigh fat thickness ( $r = -0.604$ ,  $p = 0.010$ ) and free T4 levels ( $p < 0.05$ ) but positively correlated with gastrocnemius thickness, serum calcium, albumin, and triglycerides ( $p < 0.05$ ). **Conclusion:** Routine muscle strength assessments should be considered an integral component of OI management to optimize patient outcomes. This work is a pilot, hypothesis-generating study; its preliminary findings require confirmation in larger cohorts with formal power calculations.

**Keywords:** Handgrip Strength, Muscle Dysfunction, Osteogenesis Imperfecta, Sarcopenia

## Introduction

Osteogenesis imperfecta (OI), also known as “brittle bone disease,” is a rare genetic disorder characterized by impaired collagen synthesis, leading to bone fragility and recurrent fractures. The disease exhibits significant heterogeneity, with over 1,500 mutations identified in the COL1A1 and COL1A2 genes, which encode type I collagen—the primary structural component of the bone extracellular matrix<sup>1-2</sup>. Traditionally, OI has been classified into four major types according to the Silience classification, with additional subtypes being identified in recent years<sup>3-4</sup>.

Although OI has traditionally been regarded as a skeletal disorder, emerging research highlights the muscle-bone unit as a key determinant in its pathophysiology<sup>5,6</sup>. Patients with OI often exhibit muscle weakness, reduced muscle mass, and impaired functional capacity, suggesting an underlying neuromuscular component<sup>7,8</sup>. The interplay between bone fragility and muscle dysfunction remains poorly understood, yet emerging evidence suggests that impaired collagen structure, chronic inflammation, and altered mechanical loading contribute to muscle atrophy and sarcopenia in OI patients<sup>9,10</sup>.

Despite these insights, studies evaluating muscle function and sarcopenia in OI remain scarce, particularly in adults. Most research has focused on pediatric populations, genetic determinants, and bone-targeted therapies, while the role of muscle strength and its relationship with metabolic and biochemical parameters is less explored. A recent study by Coussens et al. (2022) demonstrated that adults with OI Type I exhibited lower muscle cross-sectional area, reduced trabecular and cortical bone mineral content, and impaired physical activity levels compared to healthy controls<sup>11</sup>.

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However, further investigation is needed to determine whether muscle dysfunction in OI aligns with established sarcopenia definitions and how it correlates with laboratory markers.

This study aims to evaluate muscle strength in individuals with OI in comparison to age- and sex-matched healthy controls, investigate the relationship between muscle function and biochemical markers such as serum calcium, albumin, and free T4, and assess the prevalence of sarcopenia in OI patients along with its potential impact on disease management.

## Materials and Methods

**Study Design and Setting:** This cross-sectional study was conducted in the Department of Endocrinology and Metabolism Diseases, Hacettepe University Hospital. The study fully adhered to the STROBE guideline. The present investigation was conceived as a pilot study; sample size was limited to the cases available. All statistical tests are exploratory, and the resulting p-values should be interpreted accordingly.

### Study Participants

The OI patient group consisted of 17 adult patients with a confirmed diagnosis of Osteogenesis Imperfecta (OI) who were routinely followed at the endocrinology outpatient clinic. Patients were included if they were 18 years or older, had a genetically or clinically confirmed diagnosis of OI, and had no recent fractures within the past six months. Patients were excluded if they had severe neurological disorders affecting muscle function, uncontrolled metabolic or endocrine disorders such as diabetes or hyperthyroidism, or had undergone major surgeries or experienced immobilization in the recent past.

### Control Group

The control group consisted of 17 healthy individuals, matched for age, sex, body mass index (BMI), height, and weight, with no history of muscle weakness, fractures, or metabolic disorders.

### Outcome Measures

The primary outcome of the study was handgrip strength, which was measured using a Jamar Hand Dynamometer (Lafayette Instrument, USA). Participants were positioned with their elbows flexed at 90° and forearms maintained in a neutral position during strength assessment. Handgrip measurements were performed on the patients' dominant hands. Each hand was tested three times, with a 30-second rest interval between attempts, and the highest recorded value in kilograms was used for analysis. This method has been validated for muscle strength assessment in clinical and research settings.

The secondary outcomes of the study included

ultrasonographic muscle assessment, physical activity and functional assessments, and blood biomarker analysis. Ultrasonographic muscle assessment was conducted using a high-resolution ultrasound device (Mindray DC-70, 7.5 MHz linear probe). The measurements were performed by an experienced radiologist who was blinded to group allocation. All ultrasound assessments were performed on the dominant leg, determined by asking each participant, "Which leg would you use to kick a ball?" Participants were positioned in a supine position with their legs extended and muscles relaxed. The parameters measured included gastrocnemius muscle thickness (cm), pennation angle (°), and fat tissue thickness (cm). For analysis, the average of three repeated measurements was used. Physical activity and functional assessments were evaluated using multiple standardized questionnaires. The International Physical Activity Questionnaire (IPAQ) was utilized in its 7-item short form, which is self-administered. This version provides information on time spent walking, performing moderate-intensity and vigorous activities, and sitting time as a separate measure. The total score was calculated by summing the duration (minutes) and frequency (days) of these activities. The Upper Extremity Functional Index (UEFI) consisted of 15 questions rated on a 5-point Likert scale. The questionnaire, which has been adapted into Turkish, provided scores ranging from 0 to 80, with higher scores indicating better functional ability. The raw scores were converted into final scores using a reference table provided in the appendix. Similarly, the Lower Extremity Functional Index (LEFI) included 20 questions on a 5-point Likert scale, also adapted into Turkish, with scoring ranging from 0 to 80. Although ceiling effects have been reported, UEFI and LEFI were chosen because they are short, freely available, validated for adult OI, routinely collected at our centre since 2018, and recommended for cross-study comparison in international rare-bone registries.

The SARC-F questionnaire was used as a screening tool for sarcopenia. All items were interviewer-administered by a trained physiotherapist during the clinic visit; no self-completed forms were employed. The instrument comprises five questions that assess (1) muscle strength, (2) need for assistance while walking, (3) difficulty rising from a chair, (4) ability to climb stairs and (5) history of falls. Each item is scored from 0 to 2, giving a total score between 0 and 10. A score  $\geq 4$  is considered indicative of probable sarcopenia. We followed the EWGSOP2 algorithm and adopted a probabilistic screening approach. Accordingly, we defined probable sarcopenia as either SARC-F  $\geq 4$  points, or Handgrip strength  $< 27$  kg (men) /  $< 16$  kg (women).

The grip-strength thresholds are taken directly from EWGSOP2, while the SARC-F  $\geq 4$  threshold is supported by its original validation study<sup>12</sup> and by the first large community confirmation<sup>13</sup>. In adult OI patients, routine DXA is often avoided because of radiation exposure, and lower-limb deformities can distort appendicular lean-mass indices. In the remainder of this study, the term 'sarcopenia' is used to denote 'probable sarcopenia' as defined by EWGSOP2

**Table 1.** Comparison of Demographic and Anthropometric Characteristics Between OI Patients and Controls. (Median values with interquartile range (IQR) or mean  $\pm$  SD where applicable).

Parameter	Patients	Control Group	P-value
Median Age(min-max)	31 (18-63)	31 (18-60)	0.973
Sex Distribution (%)	Female 8 (47.1%), Male: 9 (52.9%)	Female 8 (47.1%), Male: 9 (52.9%)	1.0
Median Height (cm)	160 (133-176)	161 (146-182)	0.708
Median Weight (kg)	66 (40-104)	64 (45-97)	0.838
Mean BMI (kg/m <sup>2</sup> )	26.7 $\pm$ 6.5	25.3 $\pm$ 4.8	0.469

criteria, given the absence of gait-speed and muscle-mass data in this retrospective cohort.

Blood biomarkers were also analyzed to assess various physiological parameters. Serum levels of calcium, phosphorus, albumin, alkaline phosphatase (ALP), 25(OH)D, osteocalcin, parathyroid hormone (PTH), TSH, free T4, LDL, triglycerides, and HbA1c were measured. Blood samples were collected after an overnight fast and analyzed using automated biochemistry analyzers. The choice of blood-biomarker panel was guided by the retrospective study design and by our center's standard adult osteogenesis imperfecta surveillance protocol. Since 2019, albumin, total cholesterol, calcium, phosphorus, 25-hydroxy-vitamin D [25(OH)D], thyroid-stimulating hormone (TSH) and free thyroxine (fT4) have been measured annually as part of routine care, with results automatically archived in the hospital information system. All seven biomarkers were available within  $\pm$  3 months of the muscle-strength assessment in 17 patients, who therefore constituted the analytical cohort. By contrast, 11 contemporaneous patients were excluded because at least one of these core analytes (e.g. albumin or 25(OH)D) had never been obtained. Creatinine and creatine kinase (CK) were ordered only when trauma, acute myalgia or renal impairment was suspected; consequently, values within  $\pm$  3 months of strength testing existed for just 6 patients. Including these markers would have reduced the sample from  $n = 17$  to  $n = 6$  and introduced substantial selection bias. Moreover, the literature indicates that creatinine-based GFR equations can underestimate true renal function in individuals with low muscle mass; this may likewise apply to patients with osteogenesis imperfecta<sup>14</sup>. Because habitual activity levels are chronically low in osteogenesis imperfecta, serum creatine-kinase is often within the normal range and thus lacks the sensitivity needed to detect subclinical myopathic damage—unlike its well-established diagnostic value in inflammatory myopathies<sup>15</sup>. Accordingly, we focused on biomarkers that are universally available in the routine panel, entail minimal missing data, and are supported by literature links—direct or indirect—to skeletal-muscle performance. The limitation posed by missing creatinine

and CK data is acknowledged in the discussion; and future prospective studies should incorporate an expanded panel (e.g. CK isoenzymes, lactate, cytokines) to address this gap.

#### *Bias and Sample Size Considerations*

To minimize selection bias, controls were strictly matched for key demographic and physical characteristics. Due to the rarity of OI, sample size was limited, but a comprehensive matching strategy and detailed functional assessments were used to enhance statistical power.

#### **Statistical Analysis**

Statistical analyses were performed using IBM® SPSS Statistics v27.0. The normality of the data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For group comparisons, Student's t-test was applied to normally distributed continuous variables, while the Mann-Whitney U test was used for non-normally distributed continuous variables. Categorical variables were analyzed using the Chi-square ( $\chi^2$ ) test or Fisher's exact test, depending on the data distribution. Correlation analysis was conducted using Spearman's rank correlation for non-parametric continuous data. A p-value of less than 0.05 was considered statistically significant.

Two participants had free T4 values above our laboratory's reference range, yet neither exhibited clinical signs or symptoms of hyperthyroidism. Isolated, asymptomatic elevations of fT4 are occasionally reported in healthy adults and are generally attributed to assay variability or transient changes in binding proteins. Consequently, we treated these two cases as physiological outliers.

#### **Results**

As shown in Table 1, the study included a total of 17 patients (8 women and 9 men), with a median age of 31 years (range 18-63), a median height of 160 cm (133-176 cm), and a median body weight of 66 kg (40-104 kg). The mean BMI was calculated as 26.7 $\pm$ 6.5 kg/m<sup>2</sup>. When

**Table 2.** Comparison of Leg Ultrasound Findings Between OI Patients and Controls. (Data are presented as mean  $\pm$  SD. p-values indicate statistical significance between groups).

Characteristics (mean $\pm$ SD)	Patients (n=17)	Controls (n=17)	p-value
Right Leg			
Skin thickness (cm)	0.20 $\pm$ 0.03	0.22 $\pm$ 0.03	0.072
Fat tissue thickness (cm)	0.56 $\pm$ 0.33	0.50 $\pm$ 0.18	0.568
Gastrocnemius thickness (cm)	2.21 $\pm$ 0.43	2.37 $\pm$ 0.38	0.259
Gastrocnemius pennation angle	35.7 $\pm$ 5.5	37.2 $\pm$ 3.7	0.350
Left Leg			
Skin thickness (cm)	0.21 $\pm$ 0.02	0.22 $\pm$ 0.04	0.343
Fat tissue thickness (cm)	0.58 $\pm$ 0.27	0.54 $\pm$ 0.17	0.627
Gastrocnemius thickness (cm)	2.27 $\pm$ 0.50	2.36 $\pm$ 0.45	0.596
Gastrocnemius pennation angle	36.0 $\pm$ 4.4	37.5 $\pm$ 3.6	0.279

**Table 3.** Muscle Strength and Functional Assessment Scores in OI Patients and Controls. (Handgrip strength is reported in kg. Functional indices include UEFI, LEFI, and SARC-F scores).

Parameters	Patient (n=17)	Control (n=17)	p-value
Right handgrip strength, kg	24.2 $\pm$ 5.0	26.6 $\pm$ 4.2	0.139
Left handgrip strength, kg	21.8 $\pm$ 4.9	25.3 $\pm$ 4.2	0.034
IPAQ (short form), n (%)			
Inactive	4 (23.5)	1 (5.9)	0.324
Minimally active	9 (52.9)	10 (58.8)	
Highly active	4 (23.5)	6 (35.3)	
UEFI, median (min-max)	100 (36-100)	100 (59-100)	0.245
UEFI, mean $\pm$ standard deviation	83.9 $\pm$ 24.2	95.3 $\pm$ 13.4	
Ceiling effect for UEFI	11 / 17 patients (64.7 %) reached the maximal UEFI score (100)	15 / 17 patients (88.2 %) reached 100	
LEFI, median (min-max)	80 (10-80)	80 (35-80)	0.259
LEFI, mean $\pm$ standard deviation	64.6 $\pm$ 24.4	70.4 $\pm$ 12.2	
Ceiling effect for LEFI	0 / 17 (58.8 %) reached the maximal LEFI score (80)	12 / 17 (70.6 %) reached 80	
SARC-F, median (min-max)	0 (0-9)	0 (0-1)	0.114
<4, n (%)	14 (82.4)	17 (100)	0.227
>4, n (%)	3 (17.6)	0 (0)	
Use of walking aid or wheelchair, n (%)	4 (23.5)	0 (0)	0.103

comparing the patient and control groups, no statistically significant differences were observed in terms of median age ( $p = 0.973$ ), sex distribution ( $p = 1.000$ ), median height ( $p = 0.708$ ), median body weight ( $p = 0.838$ ), or mean BMI ( $p = 0.469$ ).

At the time of enrollment, patients provided details about their fracture histories, the number of surgeries they had

undergone, and any ongoing treatments. However, many patients were unable to recall their exact fracture histories or the number of surgeries they had undergone, resulting in incomplete data for some variables.

Of the 17 patients, 5 of the 8 women (62.5%) reported more than five fractures in their lifetime, while 3 (37.5%) had between 10 and 20 fractures. Among the 9 men, 4

**Table 4.** Laboratory Findings of OI Patients. (Values are expressed as median (min-max). Normal reference ranges are provided).

Parameters, median (min-max)	Findings	Normal Range
TSH, mIU/L	1.1 (0.8-3.2)	0.4 - 5.3
Free T4, pmol/L	11.2 (8.8-16.5)	7.9 - 14.4
HbA1C, %	5.5 (5.1-6.8)	3.5 - 5.6
Calcium, mg/dL	9.6 (9.1-10.1)	8.8 - 10.6
Phosphorus, mg/dL	3.2 (2.1-3.9)	2.5 - 4.5
Albumin, g/dL	4.5 (3.9-4.9)	3.5 - 5.2
Alkaline phosphatase, IU/L	68 (37-170)	30 - 120
Osteocalcin, ng/mL	6.4 (3.7-14.3)	2 - 12
25(OH)D vitamin, ng/mL	26.4 (20.4-36.1)	20 - 40
Parathyroid hormone, pg/mL	40.8 (22.9-80.4)	12 - 88
LDL cholesterol, mg/dL	124 (72-159)	< 130
Triglycerides, mg/dL	75 (64-298)	< 150

**Table 5.** Correlation Between Handgrip Strength and Demographic & Clinical Parameters in OI Patients. (Spearman correlation coefficients (r) and corresponding p-values are reported).

Parameters	Right Handgrip	Left Handgrip
Age	r = -0.634 p = 0.006	r = -0.642 p = 0.005
BMI	r = -0.368 p = 0.146	r = -0.298 p = 0.245
UEFI	r = 0.536 p = 0.026	r = 0.523 p = 0.031
LEFI	r = 0.442 p = 0.076	r = 0.428 p = 0.086
SARC-F	r = -0.416 p = 0.097	r = -0.404 p = 0.107

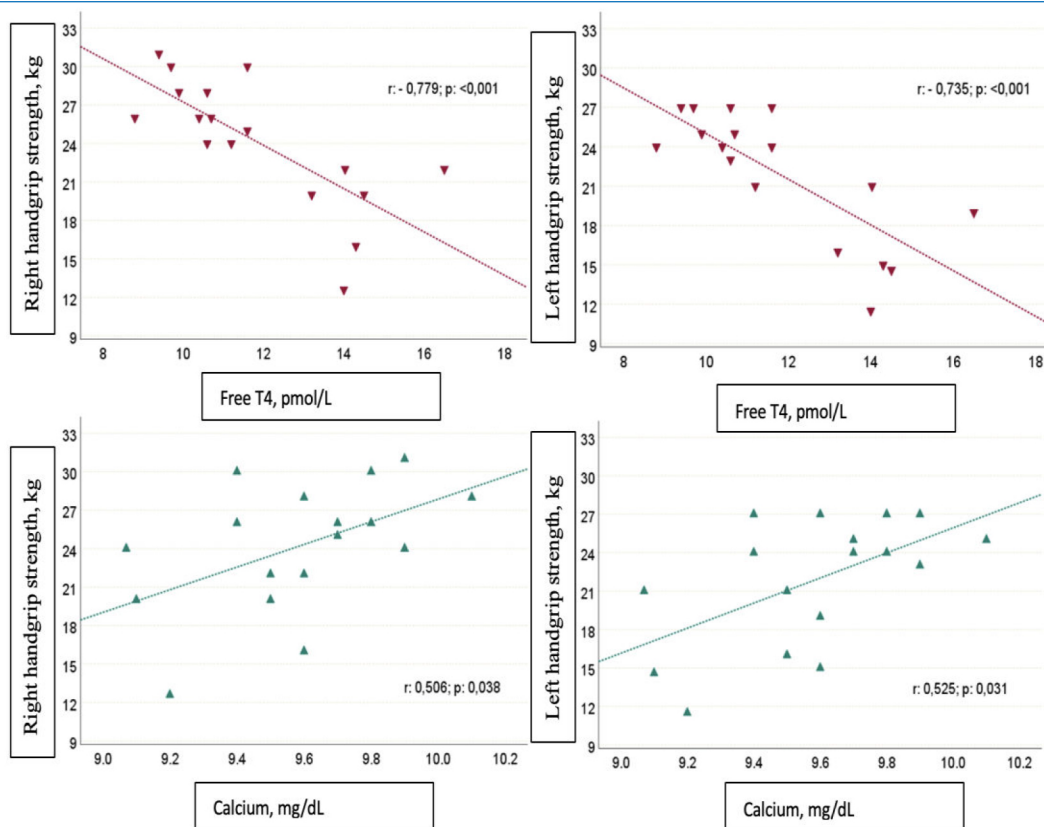
**Table 6.** Correlation Between Handgrip Strength and Biochemical Parameters in OI Patients. (Significant correlations (p<0.05) are indicated in bold).

Parameters	Right Handgrip	Left Handgrip
TSH	r = 0.199 p = 0.445	r = 0.143 p = 0.583
Free T4	r = -0.779 p = <0.001	r = -0.735 p = <0.001
HbA1C	r = 0.092 p = 0.726	r = 0.024 p = 0.928
Calcium	r = 0.506 p = 0.033	r = 0.525 p = 0.031
Phosphorus	r = -0.156 p = 0.549	r = -0.098 p = 0.708
Albumin	r = 0.571 p = 0.017	r = 0.604 p = 0.010
Alkaline phosphatase	r = 0.112 p = 0.668	r = 0.089 p = 0.734
Osteocalcin	r = -0.115 p = 0.682	r = -0.155 p = 0.581
25(OH)D vitamin	r = 0.144 p = 0.581	r = 0.175 p = 0.503
Parathyroid hormone	r = -0.367 p = 0.147	r = -0.343 p = 0.178
LDL cholesterol	r = -0.194 p = 0.457	r = -0.227 p = 0.382
Triglycerides	r = 0.508 p = 0.037	r = 0.511 p = 0.036

(44.44%) had fewer than five fractures, while 5 (55.56%) had a lifetime total of more than five fractures. Six patients (35.29%) had undergone more than five surgeries related to fractures throughout their lives. Due to limited recall, especially for surgeries performed in childhood, the specific types of surgeries could not be clarified for most patients.

Treatment status varied. Five patients (29.41%) were not receiving any treatment for their condition at the time of enrollment, while twelve (70.59%) were undergoing either vitamin D or alendronate therapy. Only one of the three patients receiving alendronate had been treated within the past year. There were no patients receiving both vitamin D and alendronate simultaneously.

As presented in Table 2, right-leg ultrasound



**Figure 1.** Correlation Between Free T4 Levels and Handgrip Strength in OI Patients. (A significant negative correlation was observed between free T4 levels and handgrip strength ( $r = -0.779$ ,  $p < 0.001$ , right hand;  $r = -0.735$ ,  $p < 0.001$ , left hand)).

measurements revealed lower mean skin thickness, gastrocnemius thickness, and pennation angle in individuals with OI compared to healthy controls, although these differences did not reach statistical significance ( $p = 0.072$ ,  $p = 0.259$ , and  $p = 0.350$ , respectively). OI patients showed a trend towards higher mean right-leg fat thickness than the control group ( $0.56 \pm 0.33$  cm vs.  $0.50 \pm 0.18$  cm,  $p = 0.568$ ). Left-leg measurements were consistent with those of the right leg.

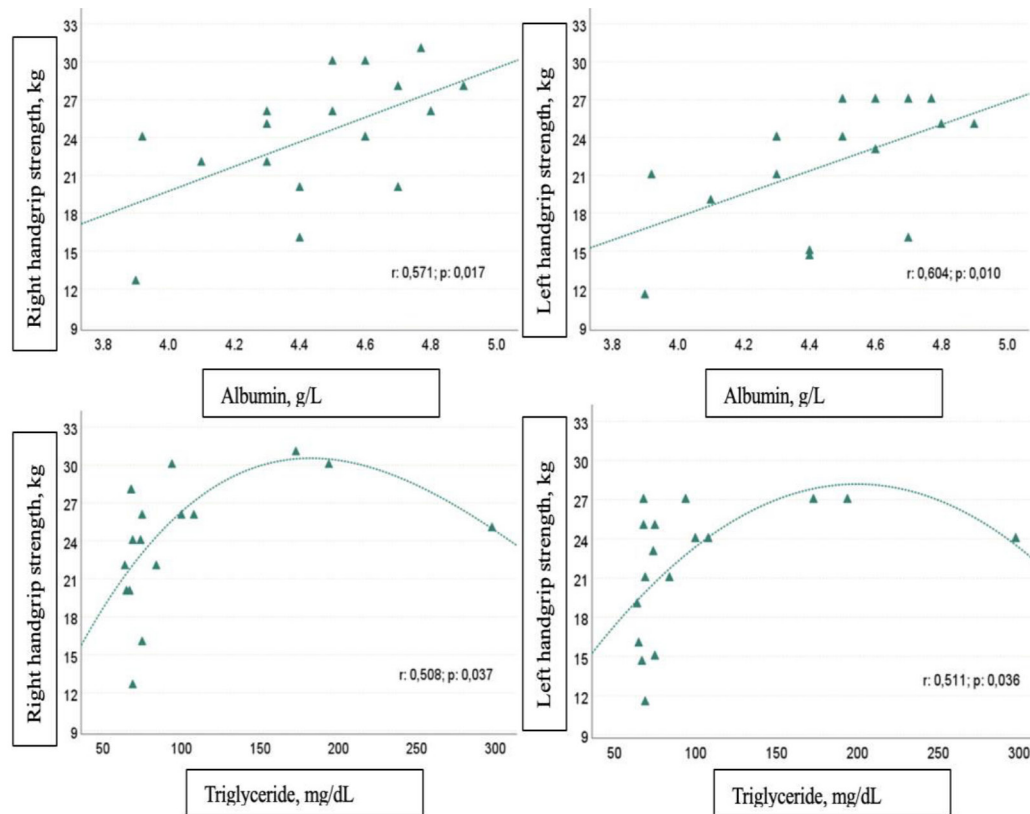
As shown in Table 3, all participants were right-hand dominant. In the patient group, the mean right-handgrip strength was  $24.2 \pm 5.0$  kg, compared to  $26.6 \pm 4.2$  kg in the control group ( $p = 0.139$ ). Left-handgrip strength was significantly lower in patients with OI compared to healthy controls. According to the International Physical Activity Questionnaire (IPAQ), 4 patients (23.5%) were inactive, 9 (52.9%) were minimally active, and 4 (23.5%) were highly active. In the control group, only 1 participant (5.9%) was inactive, 10 (58.8%) were minimally active, and 6 (35.3%) were highly active. No statistically significant differences in activity levels were found between the groups.

In patients with Osteogenesis Imperfecta (OI), the median TSH level was 1.1 mIU/L, and the median free T4 level was 11.2 pmol/L (7.9 – 14.4 pmol/L), with 11.8% of patients having elevated free T4. The median HbA1C was 5.5%, calcium 9.6 mg/dL, phosphorus 3.2 mg/dL, and albumin 4.5 g/dL. Median ALP and osteocalcin levels were 68 IU/L and 6.4 ng/mL, respectively, with elevated levels observed in 11.8% and 5.9% of patients. The median 25(OH)D vitamin level was 26.4 ng/mL, parathyroid hormone 40.8 pg/mL, LDL 124 mg/dL, and triglycerides 75 mg/dL.

As shown in Table 4, biochemical parameters varied among patients, with some showing elevated free T4, ALP, and osteocalcin levels.

A negative correlation was observed between handgrip strength and UEFI; however, it did not reach statistical significance (Right hand:  $r = -0.442$ ,  $p = 0.076$ ; Left hand:  $r = -0.428$ ,  $p = 0.086$ ). Additionally, although not statistically significant, a negative correlation between handgrip strength, BMI, and SARC-F score was notable.

As presented in Table 5, the relationship between handgrip strength and functional parameters showed a



**Figure 2.** Correlation Between Serum Albumin, Triglycerides, and Handgrip Strength in OI Patients. (Handgrip strength showed a positive correlation with serum albumin ( $r = 0.571$ ,  $p = 0.017$ ) and triglyceride levels ( $r = 0.508$ ,  $p = 0.037$ )).

negative trend, though statistical significance was not reached.

No significant correlation was found between handgrip strength and serum TSH, HbA1C, phosphorus, ALP, osteocalcin, 25(OH)D vitamin, parathyroid hormone, or LDL cholesterol levels.

As shown in Table 6, there was no statistically significant relationship between handgrip strength and biochemical parameters.

The use of walking aids or wheelchairs was observed in 23.5% of patients, while no control participants reported such usage ( $p = 0.103$ ). Functional indices showed no statistically significant differences between groups in upper extremity functional index (UEFI), lower extremity functional index (LEFI), or SARC-F scores ( $p = 0.245$ ,  $p = 0.259$ , and  $p = 0.114$ , respectively). However, closer inspection of SARC-F scores revealed that three patients (17.65%) scored above 4, whereas no individuals in the control group did. All control group members scored below 4.

As illustrated in Figure 1 and Figure 2, a strong negative correlation was found between handgrip strength and

serum free T4 levels in the patients. Two participants had free T4 values above our laboratory's reference range (14.5 pmol/L and 16.5 pmol/L), yet neither exhibited clinical signs or symptoms of hyperthyroidism. Isolated, asymptomatic elevations of fT4 are occasionally reported in healthy adults and are generally attributed to assay variability or transient changes in binding proteins. Consequently, we treated these two cases as physiological outliers.

Handgrip strength was shown to be positively associated with serum calcium levels. Similarly, a positive correlation was observed between handgrip strength and serum albumin levels. Handgrip strength in both hands was found to be associated with serum triglyceride levels.

## Discussion

This study demonstrates that adults with OI exhibit significantly reduced muscle strength, particularly in the non-dominant (left) hand, compared to healthy controls. All participants reported right-hand dominance, and grip

strength was accordingly higher on the right—an expected physiological “dominant-hand advantage” documented in healthy adults. In patients with osteogenesis imperfecta, this normal asymmetry may be magnified by repeated fractures, casting or surgery on the dominant limb. The present difference therefore likely reflects both habitual dominance and unilateral OI-related loading history.

Additionally, we observed strong correlations between handgrip strength and key biochemical markers, including serum calcium, albumin, and triglyceride levels, while an inverse correlation was found with free T4 levels. These findings suggest that muscle function impairment in OI extends beyond mechanical disuse and may involve metabolic and endocrine factors.

Our findings are consistent with previous studies that have reported muscle weakness and altered muscle-bone interactions in individuals with OI. Coussens et al. (2022) demonstrated that individuals with OI Type I exhibited lower muscle cross-sectional area, decreased bone mineral density, and reduced physical activity levels compared to healthy controls<sup>11</sup>. Similarly, Coussens et al. (2024) reported that OI patients with low physical activity levels performed poorly in functional tests. In line with these findings, our study identified lower muscle strength and potential sarcopenia prevalence in adult OI patients<sup>16</sup>. However, while their study examined a broader range of muscle parameters and identified differences between various OI subtypes, our study primarily focused on muscle strength and its associations with metabolic factors. These results support the notion that OI is not merely a bone disorder but a systemic disease affecting musculoskeletal function.

In our cohort, 17.6 % of adults with osteogenesis imperfecta exceeded the SARC-F cut-off of  $\geq 4$ , indicating probable sarcopenia. In community-dwelling adults of comparable age, a Hong Kong-based study by Woo et al. (2014) found that only about 5–6 % exceeded the SARC-F threshold of  $\geq 4$ <sup>13</sup>. Thus, the burden in OI appears to be about three-fold higher, a result that remains clinically relevant despite the lack of statistical significance ( $p > 0.05$ ) and the Type II error risk linked to our small sample. Because diminished muscle strength can compound fall and fracture risk in OI, routine SARC-F screening and timely interventions—such as resistance-exercise programmes, nutritional optimisation, and vitamin D supplementation—should be considered for patients who score  $\geq 4$ .

These exploratory findings warrant confirmation in larger, adequately powered studies.

Another mechanism that may contribute to muscle weakness is collagen dysfunction. Pre-clinical evidence shows that type I collagen mutations can weaken the muscle-tendon unit even in the absence of unloading. In *Crtap*<sup>-/-</sup> mice—a recessive OI model—the Achilles and patellar tendons are markedly thinner and mechanically weaker, and fore-limb grip strength is reduced despite normal activity levels<sup>19</sup>. Similarly, *Col1a1*<sup>ΔJrt/+</sup> mice carrying a dominant collagen defect display smaller tendon cross-sectional

areas and impaired force transmission, again independent of disuse<sup>17</sup>. These findings indicate that defective collagen compromises the myotendinous junction and intramuscular connective tissue, reducing the efficiency with which muscle fibres convey force to bone. Such intrinsic matrix weakness provides a mechanistic basis for OI-related muscle deficits that cannot be explained by reduced physical activity alone.

The observed association between elevated free T4 levels and reduced handgrip strength suggests a thyroid-mediated mechanism underlying muscle dysfunction in OI<sup>18</sup>. Several converging pathophysiological factors may explain why the fT4–muscle link is stronger in osteogenesis imperfecta than in the general population. First, defective type I collagen triggers continuous micro-fracture repair, raising resting energy expenditure by  $\approx 10$ – $20$  %; even modest fT4 fluctuations therefore accelerate oxidative phosphorylation, deplete ATP more rapidly, and amplify fatigue-related strength loss<sup>15,19</sup>. Second, the endomysial-perimysial network of skeletal muscle is rich in type I collagen; impaired cross-linking reduces lateral force transmission, and the fT4-driven increase in protein turnover further weakens this fragile matrix, exaggerating power loss during tetanic contraction<sup>15</sup>. Third, fT4 stimulates osteoclastic bone resorption; because baseline amino-acid and phosphate demand is already high in OI, additional diversion of these substrates to bone limits their availability for myofibrillar synthesis<sup>20</sup>. Fourth, fear of fracture often leads to a sedentary lifestyle, with atrophy of fast-twitch (type II) fibres and predominance of slow-twitch (type I) fibres; since thyroid hormones predominantly enhance glycolytic, type II-dependent pathways, this fibre-type shift blunts the usual performance benefits of fT4<sup>21</sup>. Finally, animal and cell-culture studies indicate that mutant collagen amplifies thyroid-hormone-dependent oxidative-stress signalling, creating molecular cross-talk that further depresses contractility<sup>15</sup>.

Previous research has linked hyperthyroidism to reduced muscle strength, showing that elevated thyroid-hormone levels can drive sarcopenia through increased protein catabolism and muscle atrophy<sup>18</sup>. Although OI is not traditionally associated with thyroid dysfunction, our findings underscore the importance of incorporating comprehensive endocrine evaluation into the clinical follow-up of OI patients.

Moreover, the presence of a significant negative correlation between free T4 and handgrip strength—even though only about 12 % of patients had elevated free T4—can be accounted for by several factors. Recent mechanistic research indicates that even modest, high-normal elevations of thyroxine accelerate skeletal-muscle protein catabolism by boosting mitochondrial turnover, stimulating autophagy and activating the ubiquitin–proteasome system<sup>22</sup>. Notably, both patients with elevated free T4 had low handgrip strength (at the lower end of the cohort distribution), consistent with the observed inverse fT4–muscle strength association.

Complementary in-vitro work shows that increasing free

T4 by as little as ~20 % within the physiological range is sufficient to trigger a measurable net loss of myofibrillar protein in cultured human myotubes<sup>23</sup>.

Together, these findings offer a biologically plausible explanation for the inverse FT4–handgrip strength association observed in our cohort, even though most participants' thyroid-hormone levels remained within the reference interval.

The pronounced ceiling effect seen for both the UEFI and LEFI likely reflects the relatively high functional status of our participants, the majority of whom had mild (Sillence type I) OI. Because these instruments have a limited dynamic range, subtle functional differences between groups may have been masked. Future studies should therefore incorporate more granular tools—such as the adaptive PROMIS-Physical Function scale or the OI-specific OBS-P—within a multi-layered assessment framework to minimise ceiling effects and capture potential group disparities with greater sensitivity.

Dominant gastrocnemius thickness averaged  $2.21 \pm 0.43$  cm in the OI group and  $2.37 \pm 0.38$  cm in controls. Although the difference did not reach statistical significance, the downward trend parallels the reduction in handgrip strength and may signal distal muscle loss that could compromise balance and elevate fracture risk.

Pennation angle—the angle formed between muscle fascicles and the tendon axis—is a key architectural determinant of physiological cross-sectional area and, by extension, maximal isometric force. In our study, the pennation angle of the dominant gastrocnemius averaged  $35.7 \pm 5.5^\circ$  in the OI cohort versus  $37.2 \pm 3.7^\circ$  in controls, a nominal difference of  $\sim 1.5^\circ$  that did not reach statistical significance. Several OI-specific mechanisms could nevertheless underlie this modest downward trend:

Impaired collagen quality may lower the tensile stiffness of the endomysial and perimysial matrix, allowing fascicles to realign more parallel to the tendon axis; the resulting decrease in pennation angle shortens the muscle's moment arm and reduces peak force output.

Chronic activity restriction and fear of micro-fracture can induce selective atrophy of fast-twitch (type II) fibres, which ordinarily exhibit larger pennation angles than type I fibres; a fibre-type shift toward type I would therefore depress the overall angle.

During adaptive remodelling, tendinous tissue may remain relatively intact while intrafascicular connective tissue slackens, causing the fascicle bundle to adopt a more “stretched” geometry aligned with the tendon pull.

From a clinical standpoint, even a 1–2° reduction in pennation angle can lower plantar-flexor force-transmission efficiency, weakening push-off during gait, stair ascent, and other balance-critical tasks, thereby indirectly increasing fall and fracture risk in individuals already prone to skeletal fragility.

Despite these novel insights, our study has four principal limitations. First, the small sample size and single-centre design restrict the generalisability of the findings. The small

sample size and absence of a formal power calculation increase the likelihood of both type-I (false-positive) and type-II (false-negative) errors, particularly given the number of correlations tested. Consequently, the results should be viewed as hypothesis-generating only; replication in larger, adequately powered studies—using appropriate corrections for multiple comparisons—is required before definitive clinical conclusions can be drawn.

Second, muscle status was assessed only with handgrip dynamometry and gastrocnemius ultrasound; muscle mass was not measured by DXA, pQCT, or BIA, gait speed was not recorded, and the ultrasound metrics could not be normalised to body-size indices such as BMI or calf circumference. Consequently, sarcopenia could be classified only as “probable sarcopenia” under the EWGSOP2 framework, and its prevalence may have been either under- or over-estimated. Third, a pronounced ceiling effect in the UEFI and LEFI likely reflects the high functional status of our predominantly mild Sillence type I cohort and may have obscured subtle between-group differences; moreover, because IPAQ-derived physical-activity levels differed between groups and were not adjusted for, residual confounding of handgrip strength cannot be entirely ruled out. Finally, the absence of genetic subtyping limits extrapolation across the heterogeneous molecular spectrum of OI.

Future work should adopt larger, multicentre designs, incorporate genotype stratification, and employ low-dose advanced imaging modalities (e.g., pQCT, DXA-HSA) to characterise muscle and bone more comprehensively. In addition, adaptive functional instruments such as PROMIS-Physical Function or the OI-specific OBS-P are recommended to minimise ceiling effects and detect group differences with greater sensitivity.

#### Ethics Approval

*This study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (Approval ID: SBA 24/448).*

#### Consent to Participate

*Written informed consent was obtained from all participants prior to their inclusion in the study.*

#### Authors' Contributions

*Fatma Güntülü Değirmenci Karaahmetoğlu: Study design, data collection, statistical analysis, manuscript writing. Banu Ertürk: Study supervision, manuscript revision. Alp Çetin: Ultrasonographic evaluations, data interpretation. Ömer Alper Gürlek: Study concept, methodology, manuscript review. All authors read and approved the final version of the manuscript.*

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