

Isokinetic Profile of Knee Extensor and Flexor Muscles in Patellofemoral Pain Syndrome Patients

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Abstract

Original Research Article

Purpose: The aim of the present investigation was to determine the influence of patellofemoral pain syndrome (PFPS) on knee extensors and flexors. **Methods:** 58 subjects diagnosed with PFPS underwent an isokinetic concentric examination at 60°/s and at 180°/s. Data were analyzed through descriptive and correlative statistics with a significance level of 0.05. **Results:** Patients showed lower extension peak torques compared to body weight and lower muscle peak torques on the involved knee compared to the healthy one, but a normal flexors to extensors ratio. Difference between genders concerned peak torques and total work. Relationships between anthropometric and isokinetic data existed only in females. Pain levels were not correlated to isokinetic measurements. A bigger male sample size and eccentric testing might be necessary to expose other correlations. **Conclusion:** Our results suggest that strengthening both knee extensors and flexors must be considered in the treatment and prevention of PFPS.

Keywords: Anterior knee pain - concentric - isokinetic - knee - patellofemoral pain syndrome.

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INTRODUCTION

Patellofemoral pain syndrome (PFPS) is a very common cause of anterior knee pain, often encountered in young individuals, due to repetitive flexion stress and poor patellar kinetics. In the absence of degenerative lesions or bad patella centering, the problem is frequently attributed to a strength imbalance between knee flexors and extensors muscles.

Isokinetic testing has become an increasingly popular modality during the last decades and the Cybex HUMAC NORM® isokinetic dynamometer has been widely used in clinical testing to objectively assess factors of muscle performance that would otherwise be difficult to obtain.

It would be interesting to gather knee flexion and extension isokinetic parameters in PPS subjects to create an isokinetic profile that can be used later on as reference for clinical and research purposes.

MATERIALS & METHODS

Our study was conducted for a 2 years period, between January 2018 and January 2020.

Participants

58 subjects took part in this study. The group consisted of 39 women and 19 men, their age ranging from 22 to 68 years with a mean of 35.8 years for women and 34.3 years for men.

Criteria for inclusion were:

- A minimum of three months duration of PFPS with a mild to severe retro or peripatellar pain, especially during walking, jogging, using stairs and/or inclined surfaces, squatting, prolonged sitting with flexed knees ;
- Blockage or giving way episodes ;
- Positive signs of patellofemoral compression: pain on direct compression of the patella, tenderness on palpation of the posterior surface of the patella, pain on resisted knee extension, Zohlen sign.

In addition, negative findings in the examination of knee ligaments, menisci, bursae, synovial plicae, Hoffa's fat pad, iliotibial band, and the hamstrings, quadriceps and patellar tendons and their insertions; plus the absence of other knee pathologies (inflammatory or orthopedic afflictions);

and of former knee surgery; were also necessary in order to include the subjects in the PFPS study.

All PFPS subjects underwent a detailed physical examination including parameters relating to

muscle build, range of motion, limb alignment and patellar orientation. In addition, a series of X-ray and/or CT scans and or MRI were performed. The characteristics of the individuals are presented in Table-1.

Table-1: Anthropometric and clinical characteristics of the PFPS patients

Characteristics	Males	Females	p value
AGE (years)*	34.31±7.86	35.82±11.9	0.6193
BMI (Kg/m2)*	25.58±2.89	26.14±4.26	0.6092
Pain on VAS*	3.84±1.25	4.10±1.61	0.5407
SIDE OF INJURY	Unilat dom: 6 Unilat non dom: 7 Bilat: 6	Unilat dom: 3 Unilat non dom: 8 Bilat: 28	
LOWER EXTREMITY MALALIGNMENT	10.52%	12.8%	
FLAT FEET	10.52%	7.68%	
ZOHLEN TEST +	47.34%	61.92%	
PATELLAR MALPOSITION	36.82%	33.28%	

*Values are presented as mean ± standard deviation

Procedures

Clinical examination has noted the anthropometric data: weight, height and BMI. Prior to knee joint testing, the subjects undertook a warm-up consisting of 10 to 15 min on an ergocycle. Then the principle of testing was thoroughly explained, followed up by a familiarization trial on the machine consisting of four submaximal concentric contraction cycles at a submaximal effort. The isokinetic testing was done using the Cybex HUMAC NORM® dynamometer.

Subjects were tested in the sitting position at 85° hip flexion, with a support for the lower back, a fixation girdle around the thigh, shoulders and abdomen, arms holding at two stabilization bars. The center of motion of the lever arm was aligned as accurately as possible with the flexion-extension axis of the knee joint and the resistance pad was placed at two digits above the external malleolus. The knee was tested

from full extension to 120 of flexion. The effect of shank gravity was systematically withdrawn. Following familiarization sets, the actual examination began. The isokinetic evaluation was carried out using the concentric mode. Subjects were instructed to perform repetitive flexion and extension cycles as fast as possible with maximum effort. Protocol comprised a set of 5 repetitions at 60°/sec angular velocity, a set of 15 repetitions at 180°/sec, then a last set of 30 repetitions at 180°/sec (Table-2). Between each set, a pause of 1 minute was observed. The same protocol was then applied to the other knee. All subjects were encouraged both verbally by the examiner, and visually by following the visual feedback displayed in real time on the computer screen.

An example of parameters recorded in the isokinetic report is presented in Figure-1.

Table-2: Overview of isokinetic testing protocol

Speed	Sessions	Mode	Resting Time Between Each Session
60°/sec 180°/sec	5 repetitions 15 repetitions 30 repetitions	Concentric	1 minute

Data Collection & Analysis

Visual analogue scale was used to assess pain that patients experienced during daily activities.

The following variables were studied: extensors’ and flexors’ peak torques at 60°/s, and 180°/s, extension peak torque to bodyweight, flexors’ to extensors’ Ratio, Total work at 180°/s in flexion and extension and Right/Left extension deficit at 60°/s.

The data collected from the Cybex® isokinetic recordings was analyzed using Excel software and STHDA online tool. Descriptive statistics included the mean, median, minimum, maximum, and standard

deviation. Quadriceps to Hamstring ratios considered were those at 60°/s. In cases of bilateral dysfunction, the limb with lower ratio was considered.

Force-Range of Motion curves were searched for a “break” produced by torque alteration along a particular ROM segment. A torque curve was judged to be irregular when the tracing was accompanied by one or multiple deflections, as illustrated in Figure 2.

For comparisons between groups, regarding the quantitative variables, was considered the Student t-test for independent samples. For intragroup

comparisons, regarding the quantitative variables, were considered the Student t-test for paired samples.

Pearson chi-squared test was used to evaluate whether or not a linear dependence exists between

anthropometric data and isokinetic parameters.

The statistical significance was set at $p \leq 0.05$ and the confidence intervals at 95%.

Isocinétique CON/CON		Extenseurs (CON)		Flechisseurs (CON)			Ratio
Vitesse 60/60 d/s 5 Mouvements	Moyenne	Coef Var	Couple/Poids	Moyenne	Coef Var	Couple/Poids	
Pic de couple (Newton-Mètre - Meilleure répétition)							
Droit	237	0.11	316	103	0.05	137	43
Gauche	161	0.05	215	113	0.06	149	70
Déficit	32			8			
Travail par répétition (Newton-Mètre - Meilleure répétition)							
Droit	254	0.04	337	144	0.05	191	57
Gauche	195	0.09	259	161	0.07	215	83
Déficit	23			11			
Amplitude angulaire (Degrés)							
Droit	1	0.67		119	0.00		
Gauche	0	0.43		123	0.00		
Isocinétique CON/CON		Extenseurs (CON)		Flechisseurs (CON)			Ratio
Vitesse 180/180 d/s 15 Mouvements	Moyenne	Coef Var	Couple/Poids	Moyenne	Coef Var	Couple/Poids	
Pic de couple (Newton-Mètre - Meilleure répétition)							
Droit	156	0.22	209	68	0.21	89	43
Gauche	114	0.20	152	85	0.24	113	75
Déficit	27			21			
Indice de fatigue							
Droit	-48	0.00		12	0.00		
Gauche	-9	0.00		5	0.00		
Travail total effectué (Newton-Mètre)							
Droit	2397	0.00	3195	757	0.00	1007	32
Gauche	1733	0.00	2310	1215	0.00	1618	70
Déficit	28			38			
Isocinétique CON/CON		Extenseurs (CON)		Flechisseurs (CON)			Ratio
Vitesse 180/180 d/s 30 Mouvements	Moyenne	Coef Var	Couple/Poids	Moyenne	Coef Var	Couple/Poids	
Pic de couple (Newton-Mètre - Meilleure répétition)							
Droit	146	0.29	194	68	0.42	89	46
Gauche	115	0.19	155	69	0.63	92	60
Déficit	21			2			
Indice de fatigue							
Droit	57	0.00		67	0.00		
Gauche	27	0.00		86	0.00		
Travail total effectué (Newton-Mètre)							
Droit	3828	0.00	5099	1424	0.00	1895	37
Gauche	3408	0.00	4539	1253	0.00	1669	37
Déficit	11			12			
MaxGET	Droit 19/06/2018 26			Gauche 19/06/2018 23			

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Fig-1: Isokinetic report example

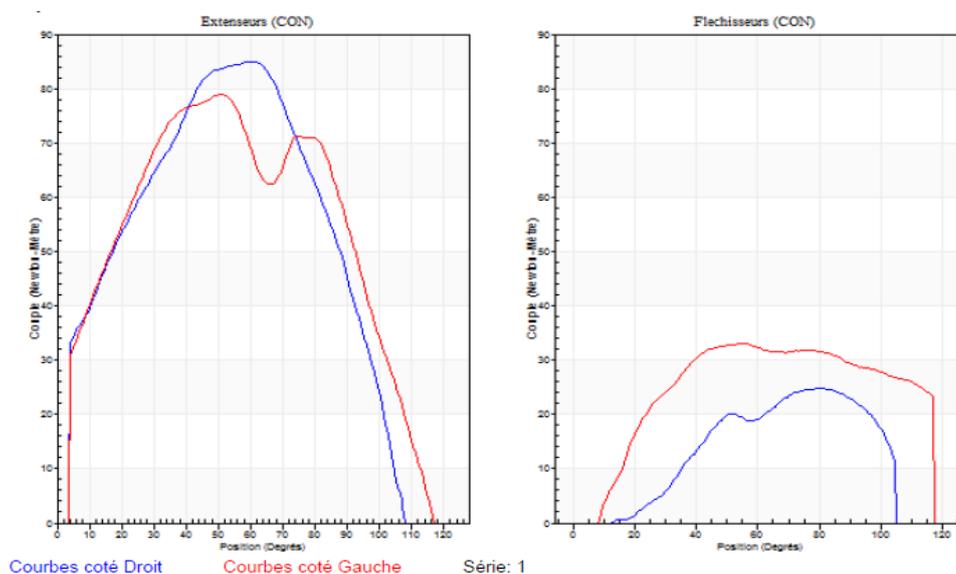


Fig-2: Example of an isokinetic torque curve with a break in the left extensors curve.

RESULTS

Among participants, there was a female predominance: 67.24%. 58.62% of patients complained of bilateral symptoms. 43.10% of subjects had a normal BMI, 32.75% were overweight, 6.89% were moderately obese and 3.45% were severely obese.

12% of patients had genu valgum axis deformation. 10.34% of patients had flat feet. 48.27% of patients had a 2 cm circumference difference between the involved thigh and the healthy one. The Zohlen sign was present in 72 % of cases.

34.48% of patients had a patellar malposition (alta or tilt) showing on tangential view X-ray imaging. MRI revealed chondromalacia in 6.9% of patients.

The isokinetic evaluation objectified a lower relative peak extension torque compared to body weight in 87.9% of patients. There was a significant difference

between male's and female's extensors and flexors peak torques at both velocities.

There was also a significant difference between male's and female's total concentric work of extensors and flexors at 180°/s.

The flexors' to extensors' ratio was normal in 72.41%, low in 24.14% of patients, and high in 3.45% of patients. The average H/Q ratio was 50.21% in men and 46.71% in women. No significant difference was found between male's and female's groups ($p=0.5319$).

Morphological anomalies in the form of a "break" were present in 44.8% of cases. 66.67% of women and 63.15% of men presented a right/left extensors deficit; while 76.9% of women 78.9% of men presented a right/left flexors deficit. Yet, no significant difference was found between genders.

All the data related to isokinetic variables is depicted on Table-3.

Table-3: Isokinetic variables in male and female groups

	Male group MEAN \pm SD n = 19	Female group MEAN \pm SD n = 39	Total MEAN \pm SD n = 58	P value
Ratio f/e 60°/s conc	50.2105 \pm 16.0471	46.7179 \pm 21.4095	48.4642 \pm 18.72845	0.5319
Ext peak torque 60°/s conc	158.3684 \pm 47.3289	89.0513 \pm 22.3747	123.70985 \pm 34.8518	3.385e-10
Flex peak torque 60°/s conc	78.3684 \pm 28.204	46.359 \pm 23.1238	62.3637 \pm 25.6639	2.458e-05
Ext peak torque 180°/s conc	114 \pm 40.2892	55.9487 \pm 14.8571	89.97435 \pm 27.57315	7.528e-11
Flex peak torque 180°/s conc	57.0526 \pm 24.9677	32.1538 \pm 17.8082	44.6032 \pm 21.38795	5.518e-05
Total work 180°/s ext conc	1631.1053 \pm 489.2959	847.8462 \pm 285.5915	1239.47575 \pm 387.42525	2.441e-10
Total work 180°/s flex conc	746.8421 \pm 357.6375	378.2051 \pm 233.7431	562.5236 \pm 295.6903	1.662e-05
R/L ext deficit 60°/s conc	20.2105 \pm 16.4235	18.0526 \pm 14.4446	19.13155 \pm 15.43405	0.6135
R/L flex deficit 60°/s conc	22.9474 \pm 16.3893	21.2368 \pm 13.1096	22.0921 \pm 14.74945	0.6712

PT = Peak Torque, conc. = concentric, flex = flexors, ext = extensors, SD = standard deviation

In patients with unilateral affliction, men made up the majority with a percentage of 54.16%, and the impaired knee was predominantly the non-dominant one (62.5%).

In those patients, concentric peak torques of both quadriceps and hamstring muscles were lower on the involved side compared to the uninvolved side at 60°/s and at 180°/s; as was the case for flexors' to extensors' ratios (Table 4). However, no significant difference was observed.

Table-4: Mean peak torques and F/E ratios in unilaterally injured patients.

Speed	Variable	Mean \pm SD Involved Side	Mean \pm SD Uninvolved Side	P Value
60°/s	Quadriceps PT (Nm)	121.33 \pm 44.97	129.67 \pm 56.39	0.5741
	Hamstrings PT(Nm)	58 \pm 27.86	62.46 \pm 26.87	0.5753
	F/E ratio	47.29 \pm 15.55	48.71 \pm 9.80	0.7075
180°/s	Quadriceps PT (Nm)	82 \pm 31.95	83.42 \pm 31.84	0.8784
	Hamstrings PT(Nm)	42.5 \pm 22.44	45.04 \pm 23.71	0.7046
	F/E ratio	48.42 \pm 13.6	51.62 \pm 11.91	0.3891

PT = Peak Torque, F = flexors, E = extensors, SD = standard deviation

The relationships between different anthropometric variables and isokinetic measurements were examined within the female group and the male group as summarized in Tables 5, 6 and 7.

Negative correlations were found between extension peak torque and Age on one hand ($r = -0,5781$), and extension peak torque and BMI on the

other hand ($r = -0,36$), but concerned exclusively the group of women.

No correlation was found between level of pain and the isokinetic parameters studied, in neither group.

No correlation was found between Flexors to extensors Ratio N and the anthropometric nor the isokinetic parameters studied.

Table-5: PEARSON correlations between different anthropometric and isokinetic variables in men

Men	Age		BMI		VAS		F/E ratio 60	
	r	p	r	p	r	p	r	p
Conc Ext peak torque at 60°/s	-0.1574	0.5198	0.1874	0.4425	0.002	0.9936		
F/E Ratio at 60°/s	-0.2269	0.3501	0.167	0.4943	0.2795	0.2465		
Total work of Ext at 180°/s	-0.029	0.9061	0.0751	0.76	0.2397	0.323	0.2495	0.303

*Data in bold indicate significant correlation ($p < \text{or} = 0.05$).

Table-6: PEARSON correlations between different anthropometric and isokinetic variables in women

Women	Age		BMI		VAS		F/E ratio 60	
	r	p	r	p	r	p	r	p
Conc Ext peak torque at 60°/s	-0.5781	0.0001159	-0.36	0.02438	0.0267	0.8717		
F/E Ratio at 60°/s	0.2341	0.1514	0.1103	0.5037	-0.0295	0.8584		
Total work of Ext at 180°/s	-0.1881	0.2516	-0.0196	0.9058	0.0493	0.7658	0.0859	0.6029

*Data in bold indicate significant correlation ($p < \text{or} = 0.05$).

Table-7: PEARSON correlations between different anthropometric and isokinetic variables in total

Total	Age		BMI		VAS		F/E ratio 60	
	r	p	r	p	r	p	r	p
Conc Ext peak torque at 60°/s	-0.2935	0.02534	-0.1324	0.3218	-0.0486	0.7172		
F/E Ratio at 60°/s	0.1399	0.2948	0.1148	0.3909	0.0302	0.8219		
Total work of Ext at 180°/s	-0.1312	0.3264	-0.0403	0.7639	0.0207	0.8776	0.155	0.2454

*Data in bold indicate significant correlation ($p < \text{or} = 0.05$).

Data was visually represented and analyzed with linear regression curves as presented in Figure 3 and 4. As the cloud of dots can attest, the correlations found are weak.

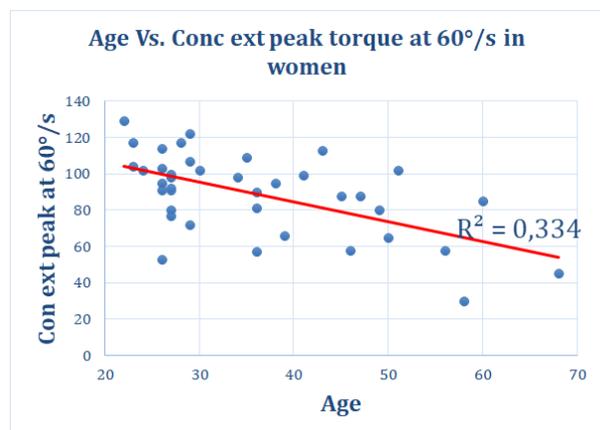


Fig-3: Age Vs. concentric extension peak torque at 60°/s in women

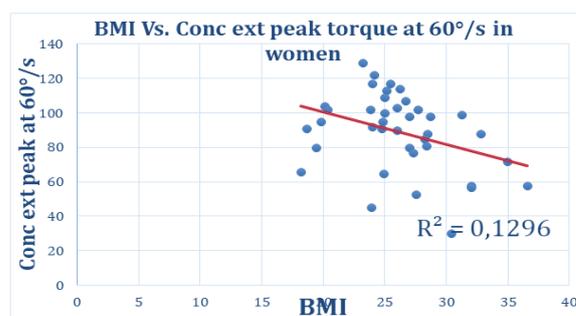


Fig-4: BMI Vs. concentric extension peak torque at 60°/s in women

DISCUSSION

Patellofemoral pain syndrome (PFPS) is a common knee condition characterized by a diffuse anterior knee pain with an insidious onset and a slow progression.

Its incidence is higher in physically active populations, such as teenagers and young adults, especially females, within whom it creates great physical and psychological morbidity by impairing

functional incapacities, thus compromising daily life activities.

The pathophysiology names multiple factors but the most accepted hypothesis is poor patellar alignment [1]. Hypothetically, other factors contribute to the onset or worsening of PFPS, such as chondromalacia, quadriceps weakness, abnormal neuromuscular control of the vastus medialis obliquus and vastus lateralis [2], alterations in the lower extremity postural alignment, especially related to hindfoot and Q angles [3] and abnormalities in the biomechanics of the feet and legs, such as subtalar excessive eversion [4] smaller angle of knee flexion, weak hip muscles [5] in addition to excessive hip adduction and internal rotation [6]. The muscular aspects of PFPS have been the subject of a number of scientific papers.

Isokinetic evaluation is often used to accurately measure muscle function at various modes and speeds, it is then a suitable tool for PFPS analysis.

Many studies have been performed in order to evaluate the torque of knee flexors and extensors using isokinetic dynamometry.

One parameter stood out frequently and has been suggested as a potential cause of PFPS: decreased quadriceps concentric peak torque, which is due to the atrophy or rather the inhibition of quadriceps to prevent pain during knee extension [7]. However, whether decreased torque is, truly, a cause or an effect of PFPS, remains unknown.

In our sample, 87.9% of patients showed a low peak extension torque. Duffey *et al.*, [8] noted, in a retrospective study, significantly weaker knee extensors peak torque measurements in PFPS patients compared to controls.

A similar result was found in Van Tiggelen *et al.*, study, where absolute and relative peak torques of knee extensors to body weight at 60°/s differed significantly between injured and control groups ($p=0.005$) [9].

Ott *et al.*, [10] attributed lower knee extensors torque in individuals with PFPS to the inhibition of this muscle because of the pain, especially during functional activities, in the same manner that Powers *et al.*, [11], did by considering this muscle's deficiency a result of strategies adopted to avoid the pain.

On the other hand, Callaghan and Oldham [7] proclaim that lower torque peak in individuals with PFPS cannot be explained by muscle atrophy, considering that they did not find a correlation between the extensors' peak torque and the quadriceps transversal section area, which leads to think that there

are more subtle mechanisms, such as modifications in neuromuscular control strategies that eventually limit quadriceps functioning.

It has been documented that men generally have double the muscular strength as that of women. Our study didn't make the exception; indeed, a significant difference was stated between male's and female's both extensors and flexors concentric peak torques at 60°/s as well at 180°/s.

However, many studies advocated that male and female significant variation in muscular strength is related to a culturally enhanced sense of competitiveness in men and higher social pressure to achieve physical prowess [12].

Another important parameter in isokinetic testing is the hamstrings to quadriceps peak torque ratio. Extensors peak torques are documented to be greater than those of the flexors. Though there is no particular ratio that is appropriate for all categories of people, some studies have set a conventional interval between 40% and 90% in healthy subjects [12]. That ratio may vary depending on the type of population tested, measuring equipment, test position and angular velocity utilized. But the typical reference landmark is 60%, first suggested by Steindler and then supported by further isokinetic dynamometers investigations making it the optimal proportion for preventing knee injury [13].

This ratio clearly reflects the agonist-antagonist knee muscle balance, which means that a weakened quadriceps muscle results in a higher ratio as it is the case in PFPS patients [14].

Our findings didn't quite go in line with those predictions, as 72.41% of our patients had a normal ratio, 24.14% had a low one, while only 3.45% demonstrated a high ratio. This was probably the effect of even lower hamstrings peak torques.

No significant difference was observed when comparing those ratios between gender groups.

The normal shape of the quadriceps torque curve at low velocity isokinetic concentric testing depicts a smooth 'inverted-U'. Variations in this curve associated with malfunctioning muscle-joint systems were described as early as the eighties [15] and are characterized as sudden and considerable reductions in the torque output later termed 'breaks'.

Hart *et al.*, established that the magnitude of these breaks should be greater than the 5 Nm to distinguish them from the small oscillations of the normal curve [16] while Dvir *et al.*, suggested 10% as the critical value [17].

A retrospective study by Hsieh *et al.*, [18] demonstrated that PFPS patients had the highest rate of abnormal torque curves during isokinetic concentric exercise compared to healthy subjects, and occurred at 60°/s, the lowest velocity used in their protocol. However, Elton *et al.*, [19] studied the same type of patients at a high speed 180°/s and didn't find this kind of torque curve abnormalities. In fact, low angular speeds of 30 or 60°/s are believed to increase compressive forces in the patellofemoral joint.

Our subjects, who underwent concentric testing at 60°/s and 180°/s, such breaks on extensor force curves were present in 44.8% of cases.

The break phenomenon has been attributed to a possible reflex inhibition aimed at joint load release to prevent overstressing the articular facets of the patella by compressive or shear load forces [20].

In Dvir *et al.*, study, breaks occurred exclusively during eccentric isokinetic activity [17].

Lastly, our paper took an interest in examining existing differences between the healthy and pathological knees in the same individual.

The results showed a lower concentric quadriceps and hamstring peak torques on the involved side compared to the uninvolved side at 60°/s and 180°/s. But the difference was not significant.

In Kaux *et al.*, study [21], the isokinetic results demonstrated significantly lower quadriceps and hamstrings 60°/s peak torques in the pathological limb (respectively 170.5 ± 44.6 and 97.2 ± 21.9) compared to the healthy one (respectively 193.4 ± 35.6 and 103.6 ± 22.8).

Besides, there was a significant difference in VAS between the pathological and the contralateral limb in the range of 3.43 ± 2.80 .

It had been reported that individuals attain peak muscle strength in the third decade of life (between the ages of 20 and 30 years) after which the strength begins to decline gradually so that the strength of a person of 65 years is approximately 80% of that attained between the ages of 20 and 30 years [22].

This decline in strength with advancing age has been attributed to a reduction in the number of motor neurons and therefore a decline in muscle mass [23].

Our study demonstrated an inverse relationship between quadriceps concentric extension peak torque at 60°/s and age ($r=-0.5781$) on female patients; this is in agreement with previous reports stating that age affects muscle strength.

One research paper [12] showed that in healthy subjects between 21 and 40 years old, body weight presents a fairly negative correlation with quadriceps muscle strength in male subjects (-0.643) and a poor positive one in male subjects between 41 and 60 years old (0.443). Height was fairly to poorly correlated with quadriceps muscle strength (0.176 to 0.447) depending on age group. The relationship between each of weight and height and the H:Q ratio is generally poor (0.066-0.472). Correlations were poor to non-existent as regard to female subjects.

Those results are conflicting with ours, mostly as regards to gender implication. In fact, all correlations observed in our case concerned women, only. We can presume that it is a matter of sample size, which was small concerning our male patients.

Moreover, we noted inverse relationships between extensors peak torques and age and BMI. This may be an effect of musculoskeletal and cardiovascular deconditioning resulting from aging and/or a sedentary lifestyle.

At the same time, no correlation was found between H:Q Ratio and anthropometric data, which corresponds well with findings in literature.

The peculiar observation though, was that pain levels were not correlated with isokinetic measurements.

Theoretically, we would have expected quadriceps peak torques to decrease according to increasing levels of pain. The limitation, in our experiment, may be that pain level was determined based on the patient's recalling of pain experienced during daily functional activities. It might have been more suited to evaluate it during actual isokinetic testing.

However, Guney *et al.*, [24] reported significant negative correlations between level of pain during stair ascending and prolonged sitting and concentric quadriceps peak torque on the one hand, and between pain level during stair descending and squatting and prolonged sitting and concentric hamstrings peak torque on the other hand.

In any way, we should bear in mind that pain felt is not necessarily reflective of tissue damage.

One could also argue that our isokinetic examination must have included eccentric testing so as to find a relationship with pain ratings and eccentric outputs, in the manner it had been carried out in Dvir *et al.*, studies [25]. The reason being that eccentric activity produces significantly greater pain than concentric activity. Then again, patellofemoral pain should, ideally, be assessed during functional activities.

CONCLUSION

Literature is relatively poor when it comes to a detailed isokinetic PFPS investigation. The main objective of our study was to assess an isokinetic profile in subjects with PFPS by quantifying different parameters and looking for a trend in muscle weakness and muscular unbalance according to age, gender and anthropometric data.

Impairment by PFPS was mainly represented by lower relative peak extension torques compared to body weight, and lower extensors' peak torques in the involved side compared to the healthy side.

Other research protocols including slower velocities, fatigue protocols and eccentric contractions might bring new insight, but these preliminary observations can already help physicians improve PFPS treatment since the examined variables are good indicators of the patient's condition until full recovery.

Conflict of Interest: All authors have no conflicts of interest with respect to the data collected and procedures used within this study. Authors declare that they have no sponsor in the study design, in the collection, analysis and interpretation of data, in writing of the manuscript, and in the decision to submit the manuscript for publication.

Ethical Statement

The authors confirm that this research paper conforms to the International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.

The authors confirm that this research has the approval of the Ethics Committee of the University Hospital Mohammed VI and was conducted according to the Ethical Principles for medical research involving human subjects of the World Medical Association Declaration of Helsinki and that participants provided informed verbal consent to participate in this study.

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