

# Bilateral Symmetries and Conventional Torque Hamstrings: Quadriceps (H:Q) in Different Sports

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## DOI:

10.32098/mltj.04.2024.08

## LEVEL OF EVIDENCE: 2

## SUMMARY

**Background.** Isokinetic dynamometer is a widely used and valid method to evaluate bilateral torque symmetries and agonist-antagonist muscular ratios that may be implicated in injury risk. Therefore, this study aimed to evaluate the inter-limb strength asymmetries and the conventional hamstring:quadriceps ratio (H:Q) of dominant and non-dominant limbs at two angular velocities (60 and 300°/s) in athletes of basketball (BA), American football (AF), futsal (FT) and running (RU).

**Methods.** Fifty-seven athletes participated in the study. All athletes underwent body composition assessments and, subsequently, were tested in an isokinetic dynamometer. After warming up, all athletes performed two maximal voluntary isometric contraction of knee extension-flexion during five seconds each. The subjects also performed five repetitions of concentric knee extension-flexion in two angular velocities (60 and 300°/s). All analysis used a significance level of  $\alpha = 0.05$ .

**Results.** There was no imbalance (higher than 15%) between limbs in any of the evaluated athletes. None of the evaluated groups showed imbalances in conventional H:Q ratio during high angular speed. AF, FT and RU demonstrated conventional H:Q asymmetries in low angular velocity. The BA group was the only one that showed a balanced conventional H:Q ratio in both limbs and in both angular velocities evaluated.

**Conclusions.** None of the evaluated groups had inter-limb strength limb asymmetry. The BA group was the only one fully balanced in both angular velocities while AF, FT and RU were imbalanced only for concentric H:Q ratio in low angular velocity.

## KEY WORDS

*Bilateral symmetries; concentric torque; hamstring:quadriceps ratio torque; hamstrings injury risk; sports.*

## INTRODUCTION

Success in team sports performance is multimodal, and depends on physical, technical, and tactical factors. Physical demands, such as muscle strength, is one of the main components for fitness evolution of athletes or rehabilitation in different populations (1-4). However, potential muscular force or torque asymmetries in a specific joint can increase risks for musculoskeletal injuries (1, 5, 6). Thus, the assessment of muscular asymmetries through torque ratios performed using the isokinetic dynamometry technique can assist various healthcare professionals in supporting muscle and musculoskeletal training and rehabilitation routines (2, 7-10).

Different training routines can induce structural changes that may lead to an increased risk of hamstring injuries, which are one of the most common muscle injuries among athletes in various sports (11-13). Hamstring injuries often occur during high-speed movements of running due to the high eccentric load on the hamstrings during deceleration in the late swing phase (14-16). Among the various risk factors for hamstring injuries, the capacity of muscle force generation is an important variable that should be regularly assessed, recognizing that hamstring injuries have a multifactorial nature (17, 18). Bilateral muscle strength asymmetries can be a significant risk factor for hamstring injuries. Muscle imbalances of 8 to 15% between lower limbs can be classified as an increased risk of hamstring injuries in athletes involved in track and field, soccer and american football (AF) (19). However, some studies (20, 21) did not find a predictive relationship between muscle imbalances and increased risk of hamstring injuries. Despite this discrepancy among studies, bilateral hamstring strength asymmetries can lead to an increased risk of injuries in this muscle group, as reported in a cohort study of athletes (10, 22-24). The increased risk of hamstring injuries due to bilateral asymmetries may be associated with load distribution during the terminal swing phase of running, resulting in biomechanical alterations during running (19). Muscular imbalances between hamstrings-to-quadriceps (H:Q) are also a significant factor in the increase of hamstring injuries. The H:Q torque ratio in athletes can vary based on factors such as the sport they are involved, position and training regimen. However, athletes aim for a balanced torque ratio between the H:Q to optimize performance and reduce the risk of injuries (1, 17). Nevertheless, there is ongoing discussion about the utility of the H:Q ratio as a predictive tool for injury screening (1, 25), considering the multifactorial nature of injury risk for hamstrings strains and/or anterior cruciate ligament (ACL) tears (26, 27) and the lack of cutoff normative values in the literature (28-30). When introducing the H:Q ratios, Steindler *et al.* (31) suggested that the H:Q torque ratios should be of

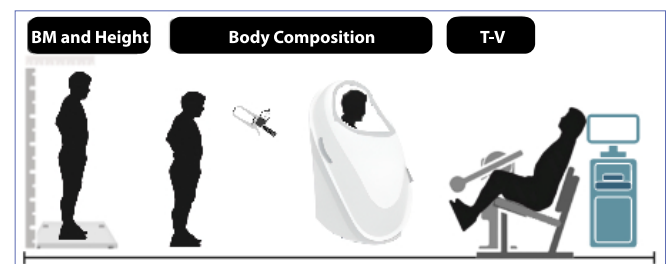
magnitude 66% for joint balance. More recent studies have reported that normal H:Q ratios assessed at low concentric speed (60°/s) should be close to 60% (32, 33) and at high concentric speeds (*e.g.*, 300°/s) increase to 70-80% (33), reducing the risk of injuries in athletes (17, 33). However, imbalance between H:Q ratios did not show an association with the risk of hamstrings and ACL injuries (1).

There is still controversy in the literature regarding the assessment of muscle imbalances between limbs and among antagonist muscle groups (*e.g.*, H:Q) and their implications for the risk of hamstrings and ACL injuries in different sports disciplines. Therefore, aim of this study is to assess the torque ratios between lower limbs for knee extensor and flexor muscles in four different sports (AF, basketball - BA, futsal - FT and endurance running - RU). Additionally, the conventional H:Q torque ratios at two concentric angular speeds (60 and 300°/s) in athletes from different sports will be compared. The first hypothesis is that acyclic sports may exhibit knee torque imbalances (higher 15%) between lower limbs. Furthermore, our second hypothesis is that all sports disciplines will demonstrate imbalances in H:Q torque ratios, indicating hamstring weakness when compared to the quadriceps.

## MATERIALS AND METHODS

### Experimental design

This study is characterized as a cross-sectional study. All participants were informed about the aims of the study, potential risks, and benefits of their participation in our study, and they gave their informed written consent to the experimental procedure, complying with the rules of the local scientific board. The study was approved by the Local Research Ethics Committee of Federal University of Santa Maria in October 12, 2022 (Number: 5.698.140), and all procedures were in accordance with the Declaration of Helsinki. The experimental design is shown in **figure 1**. Each athlete visited the laboratory on one occasion. Initial-



**Figure 1.** Experimental study design.

BM: Body mass; T-V: Torque-velocity of knee extension-flexion.

ly, anthropometry was assessed and after that, each athlete was positioned on an isokinetic dynamometer to assess the maximum torque of knee extensors and flexors muscles of both lower limbs.

### Participants

Fifty-seven trained male athletes of four different sports discipline (AF: 17 athletes; BA: 11 athletes; FT: 15 athletes; RU: 14 athletes), with at least two years of competitive experience, and specific training volume of 2-3 times per week in the respective sports disciplines, having regularly participated in regional competition events, were evaluated. Athletes with any medical restriction to maximal tests performance, any recent history of lower limb pain, musculoskeletal injury, metabolic disorders, chronic diseases, surgical procedures, physical, cognitive, and/or psychological limitations to the execution and understanding of the tests were excluded. All athletes were instructed to not engage in any vigorous physical activity for 24 hours before the tests.

### Data collection

Athletes' body mass was accessed by digital scale (Marte® LS200A, Santa Rita do Sapucaí, MG, Brazil), with a resolution of 0.1 kg and maximal capacity of 180 kg. The height was accessed using an anthropometry tape (Cescorf®, Porto Alegre, RS, Brazil), with 0.1 cm resolution. The body composition was accessed using a scientific adipometer TopTec 2 (Cescorf®, Porto Alegre, RS, Brazil), with 0.01 mm resolution, and a Plethysmography Cabinet BOD POD® (COSMED, Concord, CA, USA). Before each measurement, the BOD POD® was calibrated according to recommendations. Before the tests athletes answered the Waterloo questionnaire for lower dominant limb preference.

After that, data were collected on an isokinetic dynamometer (Biodex, System 4 Pro™, Biodex Medical Systems, New York, NY, USA) which was calibrated according to the manufacturer's instructions. Subjects were positioned on the isokinetic dynamometer seated with the hip joint at 85° of flexion and attached to the chair with velcro straps in order to provide stability during maximal knee extensors and flexors movements. The rotation axis of the dynamometer was aligned with the rotation axis of the tested knee joint (lateral femoral condyle). The lever arm was positioned in lower limb length, and a fixed length pad was positioned 1 cm above the lateral malleolus.

Two researchers were responsible for the guidelines and verbal encouragement. After a warm-up, consisting of 20 concentric knee extension-flexion repetitions at an angular velocity of 120°/s with a submaximal effort level, athletes performed isometric and concentric maximal tests. First, athletes performed two maximum voluntary isomet-

ric contractions (MVIC) with five-second duration each on knee extensors and flexors muscle, keeping the knee joint at 70° of flexion (0° = full extension). Then, athletes performed five consecutive maximum concentric contractions of knee extensor and flexor muscles, executed in the concentric-concentric mode. Movements were performed at two angular velocities (60°/s and 300°/s), and a range of motion of 80° (10°-90° of knee flexion), with total knee extension being considered as 0° of flexion. There was a two-minute resting period between each MVIC and between each concentric trial. All tests were stimulated with verbal encouragement by two researchers aiming to achieve the real maximum effort. All procedures were performed in both (dominant and non-dominant) limbs.

### Data analysis

Body fat percentage was obtained by BOD POD® Gold Standard, which calculates the body volume and density by measuring the air displaced in a closed chamber. Weight (kg) was also obtained with a high-precision scale coupled to the equipment. After weighing on the scale, two sequential measurements of body volume were obtained. The subject used tight fitting shorts, as well as a swim cap to compress the hair. In addition to weight and body volume, the equipment provides estimates of total fat mass and fat-free mass percentages using Siri's equation (34).

Knee extensor and flexor torque signals were recorded after gravity correction and sampled at 100 Hz using the dynamometer's software (Biodex, System 4 Pro™, Biodex Medical Systems, New York, NY, USA). The highest peak torque of each muscle MVIC and concentric contractions at 60 and 300°/s trials were used for further analysis. Peak torque of each maximal concentric contraction was normalized by MVIC in both muscle groups. The conventional H:Q ratio during two angular velocities of 60°/s and 300°/s (35) was calculated from equation 1:

$$H:Q \text{ ratio} = (\text{Hamstrings Concentric Torque}) / (\text{Quadriceps Concentric Torque})$$

Where:

H = hamstrings

Q = quadriceps

The side-to-side torque asymmetry was determined according to the Chavett *et al.* (36) following equation 2:

$$\text{Asymmetry}\% = (DO-ND) / DO \times 100$$

Where:

DO = dominant

ND = non-dominant limb

### Statistical analysis

All data are presented as mean and standard deviation since data normality and homogeneity was evaluated using the

Shapiro-Wilk and Levene tests, respectively. Normalized peak torque of knee extensors and flexors in both angular velocities (60 and 300°/s) and conventional H:Q ratio was compared between modalities (AF, BA, FT and RU), using the one-way ANOVA with a Bonferroni post-hoc test to identify the main effects. All statistical tests were performed using the Statistical Package for Social Science - SPSS® (IBM SPSS 22.0, Chicago, IL, USA), using a significance level of  $\alpha = 0.05$ .

## RESULTS

**Table I** provides an overview of the descriptive characteristics of each modality. The BA group was younger than AF and RU groups ( $p < 0.05$ ), however when compared with FT group no significant age difference was observed ( $p > 0.05$ ), and FT group was younger than RU group ( $p < 0.05$ ). The only difference ( $p < 0.05$ ) in body mass was found between AF and RU group, which was higher in the AF group. There were no significant height differences between groups ( $p > 0.05$ ). Body fat was greater for the AF group when compared with BA and RU groups ( $p < 0.05$ ). In contrast, fat-free body mass was higher for BA and RU groups compared with the AF group ( $p < 0.05$ ). Differences in muscle mass were only found for the RU group which was higher than the AF group ( $p < 0.05$ ). The FT group had more experience time than the AF group ( $p < 0.05$ ), without other differences between any groups.

**Table II** demonstrates peak torque values and torque symmetries of knee extensors and flexors of the preferred and non-preferred limb at 60°/s and 300°/s normalized by the MIVC. There were no significant differences ( $p > 0.05$ )

in knee extension torque at 60°/s and 300°/s, as well as knee flexion torque at 300°/s for both limbs between groups. However, knee flexion torque (60°/s) at the dominant limb in the BA group was 13.2% higher than AF group and 11.7% higher than FT ( $p < 0.05$ ).

Inter-limb asymmetries (15% or higher) were not identified within or between sports modalities (**table II** – lower table). The BA was the only sport that had symmetry (H:Q ratio  $> 0.60$ ) at 60°/s for both the dominant and non-dominant limbs. Notably, BA H:Q ratio at 60°/s in the dominant limb was greater when compared to all other modalities ( $p < 0.05$ ). However, the conventional H:Q ratio at 60°/s for the non-dominant limb in the BA was higher ( $p < 0.05$ ) only compared with the AF. In contrast, AF (DO: 0.54; ND: 0.51), FT (DO: 0.54; ND: 0.56), and RU (DO: 0.58; ND: 0.57), demonstrated asymmetry in the conventional H:Q ratio at 60°/s for both limbs, without significant differences between them ( $p > 0.05$ ).

All groups presented a balance of conventional H:Q ratios at 300°/s (0.70 to 0.95). Notably, the BA group exhibited higher values of conventional H:Q ratio in dominant (~0.95) and non-dominant (~0.90) limbs compared to all other groups ( $p < 0.05$ ). No significant differences were observed in conventional H:Q ratio at 300°/s between the AF, FT, and RU groups in any limbs ( $p > 0.05$ ).

## DISCUSSION

This study aimed to compare the torque asymmetries between lower limbs in knee extensors and flexors, besides the conventional H:Q ratio in two concentric angular velocities (60°/s and 300°/s) among athletes of different sports

**Table I.** Anthropometric characteristics of basketball (BA), American football (AF), futsal (FT), running (RU).

Sports Modalities	Age (years)	Body Mass (kg)	Height (cm)	BF (%)	FFBM (%)	MM (%)	Experience (years)
BA	17.0 ± 0.8	86.4 ± 31.9	174.3 ± 31.8	8.4 ± 5.8	91.6 ± 5.8	35.9 ± 2.1	6.0 ± 2.9
AF	27.2 ± 8.0	97.7 ± 24.0	182.5 ± 4.6	21.7 ± 12.4	78.3 ± 12.4	33.2 ± 5.0	3.9 ± 4.1
FT	22.3 ± 5.3	80.9 ± 15.5	178.1 ± 6.5	16.6 ± 9.4	83.4 ± 9.4	34.0 ± 3.9	11.0 ± 5.8
RU	30.6 ± 12.3	69.2 ± 4.4	174.0 ± 5.0	10.8 ± 4.6	89.2 ± 4.6	37.3 ± 2.2	7.0 ± 5.0
Comparison	P-value	P-value	P-value	P-value	P-value	P-value	P-value
BA × AF	<b>0.010</b>	1.000	0.934	<b>0.002</b>	<b>0.002</b>	0.445	1.000
BA × FT	0.598	1.000	1.000	0.151	1.151	1.000	0.069
BA × RU	<b>0.001</b>	0.277	1.000	1.000	1.000	1.000	1.000
AF × FT	0.541	0.161	1.000	0.703	0.703	1.000	<b>0.001</b>
AF × RU	1.000	<b>0.002</b>	0.697	<b>0.009</b>	<b>0.009</b>	<b>0.020</b>	0.438
FT × RU	<b>0.037</b>	0.835	1.000	0.531	0.531	0.111	0.172

BF: body fat; FFBM: fat free body mass; MM: muscle mass. Significant differences between sports modalities ( $p < 0.05$ ).

**Table II.** Comparison between modalities.

Sports modalities	Dominant limb				Non-dominant limb			
	Knee extensor		Knee flexor		Knee extensor		Knee flexor	
	60°/s (%MVIC)	300°/s (%MVIC)	60°/s (%MVIC)	300°/s (%MVIC)	60°/s (%MVIC)	300°/s (%MVIC)	60°/s (%MVIC)	300°/s (%MVIC)
BA	87.5 ± 12.0	51.5 ± 10.9	109.9 ± 10.3	86.7 ± 15.7	85.7 ± 13.5	49.9 ± 8.8	103.9 ± 14.9	83.5 ± 18.0
AF	84.7 ± 9.7	50.6 ± 8.0	95.3 ± 9.3	76.9 ± 9.3	83.9 ± 10.7	50.5 ± 8.0	99.4 ± 10.4	81.3 ± 12.6
FT	81.9 ± 10.0	48.0 ± 6.2	97.0 ± 14.3	78.6 ± 15.3	81.2 ± 9.7	49.6 ± 5.9	94.5 ± 12.7	76.3 ± 10.9
RU	81.5 ± 7.3	48.7 ± 5.8	97.3 ± 12.2	79.9 ± 10.2	77.4 ± 7.1	49.6 ± 8.9	93.3 ± 3.5	76.3 ± 10.5
Comparison	P-value	P-value	P-value	P-value	P-value	P-value	P-value	P-value
BA × AF	1	1.000	<b>0.013</b>	0.295	1.000	1.000	1.000	1.000
BA × FT	0.956	1.000	<b>0.047</b>	0.662	1.000	1.000	0.220	0.997
BA × RU	0.832	1.000	0.059	1.000	0.310	1.000	0.124	1.000
AF × FT	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
AF × RU	1.000	1.000	1.000	1.000	0.534	1.000	0.774	1.000
FT × RU	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Sports modalities	Inter-limb asymmetry (%)		Inter-limb asymmetry (%)		Dominant H:Q ratio		Non-dominant H:Q ratio	
	60°/s	300°/s	60°/s	300°/s	60°/s	300°/s	60°/s	300°/s
BA	1.2 ± 9.7	1.7 ± 5.7	8.8 ± 5.6	6.2 ± 13.0	0.71 ± 0.12	0.95 ± 0.14	0.65 ± 0.6	0.90 ± 0.17
AF	1.1 ± 11.2	0.7 ± 9.0	6.5 ± 12.8	5.8 ± 11.8	<b>0.54 ± 0.08</b>	0.70 ± 0.11	<b>0.51 ± 0.08</b>	0.70 ± 0.10
FT	5.8 ± 10.0	1.5 ± 12.7	1.1 ± 15.2	0.9 ± 15.3	<b>0.54 ± 0.08</b>	0.74 ± 0.14	<b>0.56 ± 0.09</b>	0.74 ± 0.10
RU	4.1 ± 9.8	2.1 ± 10.9	5.4 ± 10.5	6.3 ± 13.1	<b>0.58 ± 0.09</b>	0.80 ± 0.09	<b>0.57 ± 0.07</b>	0.74 ± 10
Comparison	P-value	P-value	P-value	P-value	P-value	P-value	P-value	P-value
BA × AF	1.000	1.000	1.000	1.000	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>	<b>&lt; 0.001</b>
BA × FT	1.000	1.000	0.7	1.000	<b>&lt; 0.001</b>	<b>0.001</b>	0.068	<b>0.008</b>
BA × RU	1.000	1.000	1.000	1.000	<b>0.013</b>	<b>0.033</b>	0.164	<b>0.008</b>
AF × FT	1.000	1.000	1.000	1.000	1.000	1.000	0.535	1.000
AF × RU	1.000	1.000	1.000	1.000	1.000	0.177	0.271	1.000
FT × RU	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Basketball: BA; American football: AF; futsal: FT; running: RU. The upper table shows results of concentric torque in two velocities (60°/s and 300°/s) of the knee extensor and flexor muscle at dominant and non-dominant limbs. Lower table shows results of knee extensor and flexor inter-limb asymmetry and concentric Hamstrings:Quadriceps (H:Q) ratio. Significant differences between sports modalities (p < 0.05).

discipline (BA, AF, FT, and RU). None of the groups had torque asymmetries between limbs and the BA group was the only one that did not show H:Q ratio imbalance in low angular velocity. In high angular velocity, none of the groups presented ratio imbalances according to Baroni *et al.* (33). The use of isokinetic dynamometry provides substantial information about the torque profile as asymmetries between limbs or the torque relationship of antagonist muscles, such as conventional H:Q ratio (9, 37-38). The relative strength difference between limbs is known as “inter-limb strength

asymmetry” (39), and the size of those asymmetries may provide useful information about injury risk and performance (19, 37). Differences of 10-15% between limbs are classified as asymmetries, and verifying the size of these asymmetries is useful in restoring normal function through strength programs (40). In the present study, none of the groups had strength asymmetries higher than 8.8% when comparing dominant with non-dominant limb, which may be a protection against sports injuries.



Assessing the inter-limb strength asymmetry is commonly used in different sports discipline when trying to verify hamstring injury risk (10, 23, 32, 41, 42). Ochard *et al.* (23) stated that knee flexors strength asymmetry between limbs higher than 8% may be a risk for hamstring injury in AF, which agrees with Heiser *et al.* (32) who found that 10% hamstring strength asymmetry could be a risk factor in AF players. Fousekis *et al.* (43) and Dauty *et al.* (44) suggest asymmetries equal or higher than 15% for hamstring is a risk factor among Soccer players. In addition, Croisier *et al.* (10) found that hamstring strength asymmetries higher than 15% could increase four times the chances of hamstring injury. Noteworthy, a few researches did not find strength limb asymmetry as a hamstring injury risk factor; however, these findings might be influenced by the imbalance absence in injury and non-injury players in the cited studies (6, 30, 45).

H:Q ratio is another well recognized isokinetic variable used among different sports discipline. A lower conventional H:Q ratio can be interpreted as insufficient hamstring capacity to slow down the quadriceps knee extension in the late swing phase during the running motion, the phase of sprinting gait cycle most likely to cause hamstring strain injury (10, 14, 21, 32, 46). Moreover, when hamstrings have strength or activation deficits, knee ligaments are not fully protected (46). In this way, conventional H:Q asymmetries could be justified as an associated risk injury factor of hamstrings and ACL injury (47).

A cut off value of 0.6 for H:Q ratio at 60°/s was proposed by Heiser *et al.* (32), since hamstring injury among football players was significantly reduced after reaching this ratio. Moreover, Yeung *et al.* (21) using a Cox regression analysis also found that conventional H:Q ratio below 0.6 would increase the hamstrings injury risk seventeen times. This meets the primary findings of Ochard *et al.* (23) in which conventional H:Q ratio smaller than 0.61 in AF may put the athlete at an increased hamstring strain injury risk. It is noteworthy that both studies had a low number of subjects (44 and 37, respectively) to generalize this value. Nevertheless, muscle asymmetries such as conventional H:Q ratio were assessed in a great number of subjects (462 soccer players) by Croisier *et al.* (10) who observed that athletes with values below 0.47 had greater chances of suffering hamstring injuries and athletes who correct their asymmetries tend to reduce injury frequencies. Lee *et al.* (6) using a multivariable logistic regression also attributed conventional H:Q ratio lower than 50.5% as responsible for a three-fold increase in the risk of injuries.

Even with previous studies demonstrating some evidence and cut off points for H:Q ratios, one variable is not responsible for injury prediction (19). A recent systematic review

with meta-analyses showed that H:Q ratio data has limited evidence for predicting hamstring or ACL injuries (1). This information corroborates previous findings of Van Dyk *et al.* (27) and Dauty *et al.* (30, 45) showing no hamstring injury prediction power. The use of H:Q ratio as an injury prediction may not be useful when other variables are not accessed, due to the multifactor mechanism of hamstring injury occurrence (19).

### Limitations

This study has limitations such as the low number of subjects and the different number of subjects in each sports discipline. If the number of subjects in each group was the same, as well as age and training experience time, the results could be different. The low level of weekly training volume and no proportional experience in training time between each sports discipline might influence the results. Functional workload demands according to modalities specificity may influence the results of strength asymmetries and conventional H:Q ratio. The absence of functional H:Q ratio provides a deficiency of information on eccentric torque which means a lack of functional knee torque knowledge, and in those athletes, this information may be more reliable with their sports demands.

### Practical implications

Despite sports injuries being multifactorial, assessing strength asymmetry and conventional H:Q ratio still is a valid tool, since weakness is a risk factor identified within the injury puzzle. A higher frequency of this kind of evaluation could become data more reliable with injuries, one time injuries occurrence and evaluation have a considerable time difference.

## CONCLUSIONS

BA, AF, FT, and RU present symmetry of torque of knee extensors and flexors between the lower limbs (less than 15% difference between DO and ND limbs). However, three sports discipline (AF, FT, and RU) present asymmetries in conventional H:Q ratio in both lower limbs at 60°/s, without asymmetry at 300°/s. BA was the only group of athletes that presented symmetry in the conventional H:Q ratio in both angular velocities evaluated (60 and 300°/s).

## FUNDINGS

TDLN received scholarship from Fundo de Incentivo a Pesquisa (FIPE), Federal University of Santa Maria (UFSM-Brazil). Biomechanics laboratory received all

devices from Brazilian Ministry of Sports for performing presente study.

## DATA AVAILABILITY

Data are available under reasonable request to the corresponding author.

## CONTRIBUTIONS

TDLN, FJL: conceptualization, design, data analysis. TDLN, FJL, MFS, SCM, DLS: experiments conduction, writing – review & editing. TDLN: writing – original draft.

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## ACKNOWLEDGEMENTS

The authors acknowledge the athletes for their generous involvement in this study. They also thank the Brazilian Ministry of Sports for making it possible to purchase the equipment used in this project. They extend our acknowledgments to all Brazilian citizens who, through the payment of their taxes, allow many researchers to improve their scientific knowledge.

## CONFLICT OF INTERESTS

The authors declare that they have no conflict of interests.

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