


# Family Predisposition for Rotator Cuff Tear and Other Tendinopathies – A Case-Control Study\*

## *Predisposição familiar para rotura do manguito rotador e outras tendinopatias – Um estudo de caso-controle*

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### Abstract

**Objective** To evaluate the prevalence of family history of rotator cuff tear and the presence of tendinopathy in other joints in patients with rotator cuff tears and to compare them with paired controls. To estimate the odds ratio for rotator cuff tear for these two risk factors.

**Methods** We performed a case-control study comparing patients submitted to treatment for rotator cuff tear with asymptomatic controls. All cases and controls were evaluated by imaging exams and matched by age ( $\pm 2$  years) and gender. We conducted an interview using a standardized questionnaire, and collected data on various risk factors.

**Results** We evaluated 144 patients, 72 per group. Patients with rotator cuff tears reported a higher number of consanguineous relatives who underwent treatment for the same disease and tendon injuries in other joints compared to the controls ( $p = 0.005$  and  $p = 0.045$  respectively). Individuals with a family history of treatment for rotator cuff tear or with tendinopathies in other joints were more likely to present a rotator cuff tear, with odds ratios of 3.3 (95% confidence interval [95%CI] = 1.4–7.7) and 2.7 (95%CI = 1.1–6.9) respectively.

**Conclusions** Patients with rotator cuff tear have a higher prevalence of family members with the same disease and tendinopathies or tendon injuries in other joints. The presence of consanguineous relatives with treatment for rotator cuff and tendinopathies in other joints are risk factors for the presence of rotator cuff tears.

### Keywords

- ▶ rotator cuff
- ▶ genetics
- ▶ tendinopathy
- ▶ family history

### Resumo

**Objetivo** Avaliar as prevalências de antecedente familiar de rotura do manguito e de tendinopatia em outras articulações em pacientes com rotura do manguito rotador e

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compará-las com controles pareados. Estimar a razão de chances de uma rotura do manguito rotador para estes dois fatores de risco.

**Métodos** Realizamos um estudo de caso-controle comparando pacientes submetidos ao tratamento para rotura do manguito rotador com controles assintomáticos. Todos os casos e controles foram avaliados por exames de imagem e pareados por idade ( $\pm 2$  anos) e sexo. Realizamos uma entrevista utilizando um questionário padronizado, e coletamos dados referentes a vários fatores de risco.

**Resultados** Avaliamos 144 pacientes, 72 por grupo. Os pacientes com rotura do manguito rotador relataram, em maior número, a presença de familiares consanguíneos que realizaram tratamento para a mesma doença e de lesões tendíneas em outras articulações em relação aos indivíduos controles ( $p = 0,005$  e  $p = 0,045$ , respectivamente). Indivíduos com antecedente familiar de tratamento para rotura do manguito rotador ou com tendinopatias em outras articulações tiveram maior probabilidade de apresentar rotura do manguito rotador, com razões de chances de 3,3 (intervalo de confiança de 95% [IC95%] = 1,4–7,7) e 2,7 (IC95% = 1,1–6,9), respectivamente.

**Conclusões** Os pacientes com rotura do manguito rotador têm maior prevalência de familiares com a mesma doença e de tendinopatias ou lesões tendíneas em outras articulações. A presença de familiares consanguíneos com tratamento para rotura do manguito rotador e tendinopatias em outras articulações são fatores de risco para presença de roturas do manguito rotador.

#### Palavras-chave

- ▶ manguito rotador
- ▶ genética
- ▶ tendinopatia
- ▶ histórico familiar

## Introduction

Rotator cuff tendinopathy is the main cause of shoulder<sup>1</sup> pain, and tears of these tendons are prevalent in 20% of the population.<sup>2</sup> The number of patients undergoing surgical treatment for these lesions grows annually,<sup>3</sup> and the arthroscopic repair of the rotator cuff presents satisfactory clinical results in up to 93% of the patients.<sup>4–6</sup>

The etiology of rotator cuff tear is considered multifactorial.<sup>7</sup> Decreased tendinous vascularization, intrinsic degenerative alterations of the tendon, micro- and macrotraumas, impact syndrome and genetics are factors associated with the development of rotator cuff tear.<sup>8,9</sup>

Routinely in the clinical practice, physicians observe patients with tendinopathies or tendinous lesions in multiple sites, and there is a possible genetic component involved in the individual's susceptibility to tendinopathy.<sup>10</sup> However, few studies evaluate the familial predisposition or presence of lesion in others joints in patients with a rotator cuff tear.

Initial studies indicate that the presence of family members with rotator cuff tear<sup>11,12</sup> or the presence of tendinopathies in other joints<sup>13,14</sup> are risk factors for the development of a rotator cuff tear. However, most studies are epidemiological or use population and hospital databases,<sup>12,14,15</sup> with few case-control studies<sup>11,13</sup> to evaluate these risk factors. We also emphasize that the research of other risk factors as confounding variables and the pairing of the participants by gender and age are rarely employed in case-control studies on this topic.

The objectives of the present study were to evaluate the prevalence of tendinopathy in other joints and family history

of cuff tear in patients with rotator cuff tear, to compare them with paired controls, and to estimate the odds ratio of a rotator cuff tear for these two risk factors.

## Materials and Methods

### Study design, Participants and Eligibility

A case-control study was carried out. We evaluated patients aged between 40 and 65 years with complete rotator cuff tears. The control group consisted of patients treated at the same institution due to traumatic injuries not involving the scapular girdle, with no complaint of shoulder pain, and physical examination without the presence of rotator cuff tear signs. All patients and controls were submitted to an imaging examination (magnetic resonance or ultrasonography) to confirm the tear or the integrity of the rotator cuff. The patients and the controls were paired by age ( $\pm 2$  years) and gender.

The exclusion criteria were: rheumatic diseases, diabetes, previous shoulder surgeries, and previous or current infectious processes in the studied joint. Moreover, patients with traumatic rotator cuff tears were not included, as well as those with partial tears.

The present study was approved by the Ethics in Research Committee of our institution under the number 11186.

### Outcomes

#### Primary outcome

The odds ratio of individuals with a family history of rotator cuff tear to present the same disease was evaluated, as well

as the prevalence of relatives who underwent treatment for rotator cuff tear in the case and control groups.

### Secondary outcome

The prevalence of tendinopathy or tendinous lesions in other joints was evaluated in individuals with and without rotator cuff tear. We also evaluated the odds ratio of patients with tendinopathies in other joints to have a rotator cuff tear in relation to the control patients.

### Valuation Methods

We conducted an interview using a standardized questionnaire, and collected the following data from patients and controls: age, gender, ethnicity, smoking, diagnosis or treatment for systemic arterial hypertension, hypothyroidism, performance of sports with the upper limbs and professional activity with repetitive shoulder abduction movements ( $\geq$  two hours per day). We also asked some questions about the personal and family history of rotator cuff tears and other tendinopathies by means of a standardized questionnaire (**►Figure 1**).

### Statistical Analysis

#### Sample size

The sample calculation used a significance level of 5%, a power of 80%, and a case/control ratio of 1:1.

Using the prevalence rate of rotator cuff tear for the controls and family members of the patients with the same disease, which were obtained from the study by Harvie et al.<sup>11</sup> a total of 72 individuals in each group was required.

#### Data Analysis

We submitted the continuous variables to a normality assessment using the Kolmogorov-Smirnov test, and a homogeneity assessment through the Levene test. The continuous variables were presented as means and standard deviations, while the categorical variables were expressed as absolute values and percentages. Among the collected variables, age was considered a continuous variable, and the others were considered categorical variables.

The comparison between the cases and controls regarding the different variables was performed by Chi-squared or

Fisher exact tests for the categorical variables. For the continuous variables, the Student *t* test was used if the distribution of the data was parametric, and the Wilcoxon was used if the distribution of the data was non-parametric.

The difference in the prevalence of consanguineous relatives with history of treatment for rotator cuff tear, as well as the presence of tendinopathy and tendinous lesions in other joints in the individuals with rotator cuff tear and in the controls were evaluated by the Chi-squared test. The probability of association of these two risk factors with rotator cuff tears was also calculated as odds ratios, with a 95% confidence interval (95%CI).

For the data analysis, we used the Statistical Package for the Social Sciences (SPSS, IBM Corp., Armonk, NY, US) software, version 21.0, and a significance level of 5%.

## Results

We evaluated 144 patients, 72 with complete rotator cuff tear and 72 controls. The cases and controls had mean ages of  $53.6 \pm 6$  and  $53.2 \pm 6.1$  respectively ( $p = 0.592$ ). Both groups were composed of 48 (66.6%) women and 24 (33.3%) men. The groups did not differ statistically regarding ethnicity, smoking and the presence of systemic arterial hypertension ( $p = 0.825$ ;  $p = 0.673$ ; and  $p = 0.567$  respectively). The general characteristics of the sample can be observed in **►Table 1**.

Patients with rotator cuff tear reported the presence of consanguineous patients who underwent treatment for the same disease in a larger number than the control subjects ( $p = 0.005$ ). Individuals with family history of treatment for rotator cuff tear presented a higher chance of having the same disease, with an odds ratio of 3.3 (95%CI = 1.4–7.7) (**►Table 2**). Among the individuals with rotator cuff tear, 15 (20.8%) reported having at least 1 first-degree family member with the same disease, 7 (9.7%) had at least one second-degree family member with a diagnosis of rotator cuff tear, and 1 (1.4%) patient had first- and second-degree relatives with the same disease. In total, 5 (6.9%) controls reported having a first-degree family member who performed treatment for rotator cuff tear, and 4 (5.6%) had a second-degree family member with the same condition.

- 1. Do you currently have or you had any problem or disease in any tendon in your body? If yes, which tendon or joint?**
- 2. Have you ever any surgery in any tendon in your body other than the shoulder?**
- 3. Do you have any blood relative with problems or diseases in the shoulder tendons? If yes, which relative or relatives?**
- 4. Do you have any blood relative who has had surgery in the shoulder tendons? If yes, which relative or relatives?**

**Fig. 1** Questionnaire on personal and family history for rotator cuff tear and other tendinopathies.

**Table 1** General characteristics of the sample

	Cases	Controls	p-value
Age	53.6 ± 6	53.2 ± 6.1	0.592
Gender			
Male	24 (33.3%)	24 (33.3%)	> 0.999
Female	48 (66.6%)	48 (66.6%)	
Ethnicity			
White	48 (66.6%)	46 (63.9%)	0.825
Black	10 (13.9%)	9 (12.5%)	
Brown	14 (19.4%)	17 (23.6%)	
Smoking			
Yes	15 (20.8%)	13 (18.1%)	0.674
No	57 (79.2%)	59 (81.9%)	
Systemic arterial hypertension			
Yes	17 (23.6%)	20 (27.8%)	0.567
No	55 (76.4%)	52 (72.2%)	
Hypothyroidism			
Yes	3 (4.2%)	4 (5.6%)	0.698
No	69 (95.8%)	68 (94.4%)	
Repetitive work with shoulders			
Yes	33 (45.8%)	25 (34.7%)	0.174
No	39 (54.2%)	47 (65.3%)	
Sport with use of the upper limbs			
Yes	7 (9.7%)	9 (12.5%)	0.596
No	65 (90.3%)	63 (87.5%)	

Tendinopathies or tendon injuries in other joints were more prevalent among patients with rotator cuff tear ( $p = 0.045$ ). These patients were more likely to develop a rotator cuff tear, with an odds ratio of 2.7 (95%CI = 1.1–6.9) (► **Table 3**). Among the patients with rotator cuff tear, the most common tendinopathies or tendinous lesions were lateral epicondylitis and tendinopathy of the calcaneal tendon, which were present in 8 (11.1%) and 7 (9.7%) of the patients respectively.

**Discussion**

Our results show that patients with rotator cuff tear have a higher prevalence of family members with the same disease

**Table 2** Presence of consanguineous relatives who underwent rotator cuff tear treatment

	Cases	Controls	p-value	Odds ratio
	(n = 72)	(n = 72)		95% confidence interval
Relatives who underwent rotator cuff tear treatment				
Yes	23 (31.9%)	9 (12.5%)	0.005	3.3 (1.4–7.7)
No	49 (68.1%)	63 (87.5%)		

**Table 3** Presence of tendinopathy or tendinous lesions in other joints

	Cases	Controls	p-value	Odds ratio
	(n = 72)	(n = 72)		95% confidence interval
Presence of tendinopathy or lesions in other joints				
Yes	16 (22.2%)	7 (9.7%)	0.045	2.7 (1.1–6.9)
No	56 (77.8%)	65 (90.3%)		

(31.9%) in relation to the controls (12.5%). They also report in greater numbers the presence of tendinopathies or tendon injuries in other joints (22.2%) compared to individuals with intact rotator cuffs (9.7%). The presence of family members with rotator cuff tear and the presence of tendinopathy or tendon injuries in other joints were risk factors for rotator cuff tear, with odds ratios of 3.3 and 2.7 respectively.

Few studies have assessed the possibility of relatives of rotator cuff tear patients having increased risk of developing the same disease.<sup>11,12</sup> Harvie et al.<sup>11</sup> state that siblings of rotator cuff tear patients have 2.4 times more risk of presenting the same lesion, and almost 5 times more risk of having symptoms in relation to the control group. However, the authors of this study evaluated only first-degree relatives (siblings), and used the spouses as controls. Due to the close proximity between cases and controls, environmental and family factors may have interfered in the analysis.

Tashjian et al.<sup>12</sup> conducted a study evaluating a population database with health information from the state of Utah, United States, and observed that the family members of rotator cuff tear patients had a greater chance of having the same disease. Relatives with a degree of kinship up to the third degree had an increased risk of rotator cuff tear, especially those who had people in the family with this disease under the age of 40 years. The relative risk for rotator cuff tear among second-degree relatives was of 3.7, and, for the third-degree relatives it was of 1.8. This result and those found by us and by Harvie et al.<sup>11</sup> suggest a familial and genetic predisposition for rotator cuff tears.

For the association between risk factors and a disease, two measures of effect can be used: the relative risk and the odds ratio. The relative risk can be obtained in cohort studies, clinical trials and cross-sectional studies. And the odds ratio can only be obtained directly in case-control studies. The studies conducted by Harvie et al.<sup>11</sup> and Tashjian et al.<sup>12</sup> were retrospective cohorts, so they used the relative risk as a measure of effect. In turn, the present study was a case-control one, and we used the odds ratio. In general, when the prevalence of a disease in the population is lower than 10%, the odds ratio has a very similar value to that of the relative risk. In the study by Yamamoto et al.<sup>2</sup> the prevalence of rotator cuff tear in patients younger than 60 years of age was of 9%.

Patients with rotator cuff tear have a greater chance of presenting tendinopathies or tendon injuries in other joints.<sup>13,14</sup> Tashjian et al.<sup>13</sup> found that 38.7% of rotator cuff tear patients also report tendinopathies or tendon injuries in

other joints, while only 19.3% of the individuals in the control group report the same thing. We found a lower prevalence of tendinopathies in other joints in both groups, but, as the authors of the aforementioned study, we also observed a statistically significant difference between the two groups. Genetic and familial factors are probably involved in the development of tendinous lesions in multiple sites.<sup>13,15</sup>

Rotator cuff tear, as well as the development of other tendinous lesions, can be considered multifactorial.<sup>7</sup> A certain number of genes may be involved in the etiology of tendinous lesions, each one making a small contribution. The proteins encoded by the multiple genes and the environment participate concomitantly in the development of these injuries.<sup>16</sup> Polymorphisms in the receptor  $\beta$  gene related to estrogen have already been associated with rotator cuff tear<sup>17,18</sup> and tendinopathy of the posterior tibial tendon.<sup>18</sup> Genes regulating the expression of metalloproteinases and tenascin C, which are important enzymes in the tendinous homeostasis, present polymorphisms associated with rotator cuff tear,<sup>19,20</sup> tendinopathy of the Achilles tendon,<sup>21</sup> and the posterior tibial tendon.<sup>22,23</sup> However, the functions of these genes or their coded proteins in the pathophysiology of the tendinous lesions need to be better studied, and other candidate genes may be associated with tendinous lesions.

Our study has some limitations. We did not evaluate all known risk factors for rotator cuff tear, such as body mass index<sup>24</sup> and the patient's dominant upper limb.<sup>2</sup> These factors were not evaluated in our sample, and may act as confounding factors for the results found. We conducted an interview to collect data on the presence of consanguineous relatives with previous treatment for rotator cuff tear and on the current or previous treatment for tendinopathies and tendinous lesions in other joints. Rotator cuff tear patients should probably have better information about personal orthopedic diseases and their relatives, for the lack if it leads to a bias of memory. And as the information was reported by the patient, the diagnoses may also be inaccurate and may have increased the association between these risk factors and the rotator cuff tear. The sample with 144 individuals evaluated may be considered small. Studies with larger samples or among other populations must be performed to confirm the association of these risk factors with rotator cuff tear.

However, we can emphasize that our study performed a pairing of cases and controls by gender and age with a maximum difference of two years. We also evaluated other risk factors that could be confounding variables in our analysis. This methodological refinement was not employed in the few previous studies on the subject. We also performed imaging exams to evaluate the tear or the integrity of the rotator cuff in all study participants. Imaging examinations of the cases and controls were only employed in the study conducted by Harvie et al.<sup>11</sup> Other studies<sup>25,26</sup> show that up to 60% of patients with rotator cuff tear may be asymptomatic. We can also state that our findings collaborate for the identification of important risk factors for the development of rotator cuff tears and emphasize the need for further research to identify genetic markers for the development of tendinous lesions to enable the identification of susceptible individuals.

## Conclusions

Rotator cuff tear patients have a higher prevalence of family members with the same tendinopathies or tendinous lesions in other joints. The presence of consanguineous relatives with treatment for rotator cuff tear and tendinopathies in other joints are risk factors for the presence of rotator cuff tears.

### Conflict of Interests

The authors have none to declare.

## References

- Mitchell C, Adebajo A, Hay E, Carr A. Shoulder pain: diagnosis and management in primary care. *BMJ* 2005;331(7525):1124–1128
- Yamamoto A, Takagishi K, Osawa T, et al. Prevalence and risk factors of a rotator cuff tear in the general population. *J Shoulder Elbow Surg* 2010;19(01):116–120
- Malavolta EA, Assunção JH, Beraldo RA, Pinto GMR, Gracitelli MEC, Ferreira Neto AA. Rotator cuff repair in the Brazilian Unified Health System: Brazilian trends from 2003 to 2015. *Rev Bras Ortop* 2017;52(04):501–505
- Checchia SL, Doneux S, Miyazaki AN, et al. Avaliação dos resultados obtidos na reparação artroscópica das lesões do manguito rotador. *Rev Bras Ortop* 2005;40(05):229–238
- Godinho GG, França FO, Freitas JMA, et al. Avaliação da integridade anatômica por exame de ultrassom e funcional pelo índice de Constant & Murley do manguito rotador após reparo artroscópico. *Rev Bras Ortop* 2010;45(02):174–180
- Antonio M, Veado C, Afonso I, Filho A, Duarte RG, Leitão I. Avaliação funcional do reparo artroscópico das lesões completas do manguito rotador associado a acromioplastia. *Rev Bras Ortop* 2008;43(11/12):505–512
- Longo UG, Berton A, Khan WS, Maffulli N, Denaro V. Histopathology of rotator cuff tears. *Sports Med Arthrosc Rev* 2011;19(03):227–236
- Maffulli N, Longo UG, Berton A, Loppini M, Denaro V. Biological factors in the pathogenesis of rotator cuff tears. *Sports Med Arthrosc Rev* 2011;19(03):194–201
- DE Giorgi S, Saracino M, Castagna A. Degenerative disease in rotator cuff tears: what are the biochemical and histological changes? *Joints* 2014;2(01):26–28
- Magra M, Maffulli N. Genetic aspects of tendinopathy. *J Sci Med Sport* 2008;11(03):243–247
- Harvie P, Ostlere SJ, Teh J, et al. Genetic influences in the aetiology of tears of the rotator cuff. Sibling risk of a full-thickness tear. *J Bone Joint Surg Br* 2004;86(05):696–700
- Tashjian RZ, Farnham JM, Albright FS, Teerlink CC, Cannon-Albright LA. Evidence for an inherited predisposition contributing to the risk for rotator cuff disease. *J Bone Joint Surg Am* 2009;91(05):1136–1142
- Tashjian RZ, Saltzman EG, Granger EK, Hung M. Incidence of familial tendon dysfunction in patients with full-thickness rotator cuff tears. *Open Access J Sports Med* 2014;5:137–141
- Titchener AG, White JJ, Hinchliffe SR, Tambe AA, Hubbard RB, Clark DI. Comorbidities in rotator cuff disease: a case-control study. *J Shoulder Elbow Surg* 2014;23(09):1282–1288
- Tashjian RZ, Farnham JM, Granger EK, Teerlink CC, Cannon-Albright LA. Evidence for an Environmental and Inherited Predisposition Contributing to the Risk for Global Tendinopathies or Compression Neuropathies in Patients With Rotator Cuff Tears. *Orthop J Sports Med* 2016;4(04):2325967116642173
- September AV, Schweltnus MP, Collins M. Tendon and ligament injuries: the genetic component. *Br J Sports Med* 2007;41(04):241–246, discussion 246

- 17 Motta GdaR, Amaral MV, Rezende E, et al. Evidence of genetic variations associated with rotator cuff disease. *J Shoulder Elbow Surg* 2014;23(02):227–235
- 18 Teerlink CC, Cannon-Albright LA, Tashjian RZ. Significant association of full-thickness rotator cuff tears and estrogen-related receptor- $\beta$  (ESRRB). *J Shoulder Elbow Surg* 2015;24(02):e31–e35
- 19 Assunção JH, Godoy-Santos AL, Dos Santos MCLG, Malavolta EA, Gracitelli MEC, Ferreira Neto AA. Matrix Metalloproteases 1 and 3 Promoter Gene Polymorphism Is Associated With Rotator Cuff Tear. *Clin Orthop Relat Res* 2017;475(07):1904–1910
- 20 Kluger R, Burgstaller J, Vogl C, Brem G, Skultety M, Mueller S. Candidate gene approach identifies six SNPs in tenascin-C (TNC) associated with degenerative rotator cuff tears. *J Orthop Res* 2017; 35(04):894–901
- 21 Mokone GG, Gajjar M, September AV, et al. The guanine-thymine dinucleotide repeat polymorphism within the tenascin-C gene is associated with achilles tendon injuries. *Am J Sports Med* 2005; 33(07):1016–1021
- 22 Godoy-Santos A, Cunha MV, Ortiz RT, Fernandes TD, Mattar R Jr, dos Santos MCLG. MMP-1 promoter polymorphism is associated with primary tendinopathy of the posterior tibial tendon. *J Orthop Res* 2013;31(07):1103–1107
- 23 Saunders CJ, van der Merwe L, Posthumus M, et al. Investigation of variants within the COL27A1 and TNC genes and Achilles tendinopathy in two populations. *J Orthop Res* 2013;31(04):632–637
- 24 Gumina S, Candela V, Passaretti D, et al. The association between body fat and rotator cuff tear: the influence on rotator cuff tear sizes. *J Shoulder Elbow Surg* 2014;23(11):1669–1674
- 25 Yamamoto A, Takagishi K, Kobayashi T, Shitara H, Osawa T. Factors involved in the presence of symptoms associated with rotator cuff tears: a comparison of asymptomatic and symptomatic rotator cuff tears in the general population. *J Shoulder Elbow Surg* 2011; 20(07):1133–1137
- 26 Tempelhof S, Rupp S, Seil R. Age-related prevalence of rotator cuff tears in asymptomatic shoulders. *J Shoulder Elbow Surg* 1999;8 (04):296–299