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AC joint osteoarthritis: The role of genetics. An MRI evaluation of asymptomatic elderly twins

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Abstract

Purpose: The anatomy of the articular surfaces has historically identified as major responsible for acromioclavicular joint osteoarthritis (ACJO). On the other side, the almost 100% prevalence of ACJO in subjects over 50 years old seems to suggest a multifactorial etiology. We compared ACJO between asymptomatic elderly monozygotic (MZ) and dizygotic (DZ) twins to investigate the influence of genetics and environmental factors.

Materials and Methods: Thirty pairs of twins [15MZ-15DZ; mean age (SD): 63.70 (3.31); range: 53–72] were retrospectively enrolled. ACJO was evaluated on MRI through a 4-grade severity scale and ACJ configuration was assessed. Information regarding work activity were obtained. Heritability index was calculated.

Results: The intraclass correlation coefficient (ICC) value of 0.868 (95% CI; 0.798 to 0.917). An ICC values of 0.889 (95% CI; 0.798 to 0.944) and 0.843 (95% CI, 0.712 to 0.920) were found in the MZ and DZ groups, respectively. The polychoric correlation was 0.857 in the MZ twins and 0.757 in the DZ twins. The calculated heritability index was 0.20 (20%), and the contribution of the shared environment (c2) and unique environment (e2) was 0.66 (66%) and 0.14 (14%), respectively. No relationship between job types and ACJO in both the total cohort ($r = 0.089$; $p = 0.499$) and in the monozygotic ($r = 0.247$; $p = 0.187$) and the dizygotic twin groups ($r = -0.084$; $p = 0.658$) was found.

Conclusions: The role of genetics on ACJO accounts for only 20%; a specific anatomical configuration of the articular surfaces only partially acts on the development of joint osteoarthritis. Environmental factors have the greatest impact.

Level of Evidence: IV.

KEYWORDS

AC joint configuration, AC joint orientation, AC joint osteoarthritis, AC joint osteoarthritis etiology, anatomical predisposition of osteoarthritis, De Palma classification of AC joint, genetic role on AC osteoarthritis

1 | INTRODUCTION

The AC joint is a planar diarthrodial joint connecting the anteromedial acromion and the lateral clavicle. Despite the small articular surface area, the AC joint withstands significant forces (Mall et al., 2013; Ogata & Uhthoff, 1990); a fibrocartilaginous disk cushions the joint, corrects for incongruencies, and acts in a load-bearing fashion.

Evidence of morphological variation of the AC joint was firstly described by De Palma (1957); in a group of 66 cadavers, three types of acromioclavicular joints were identified based on the joint torsion with the Type I AC joint (average angulation of 16°) more prone to pathology due to the increased shearing force on the articular surface. In the following years, many authors (Colegate-Stone et al., 2010; Pennington et al., 2008; Petersson, 1983; Sahara et al., 2007; Seifarth & Roemer, 2015; Shubin Stein et al., 2006) investigated the AC morphology in both cadaveric and radiological analysis and confirmed previous findings giving to orientation and incongruencies of the articular surfaces, the responsibility for AC osteoarthritis development.

However, AC joint osteoarthritis is a constant finding during a clinical and instrumental examination of the shoulder; in fact, in their series, Shubin Stein et al. (2001) and Tauber et al. (2016), documented that degenerative changes of AC joint were present in 93% of subjects over 30 years and almost 100% in the over fifties. These data seem to suggest a multifactorial etiology of AC osteoarthritis.

To the best of our knowledge literature lacks investigations on the real influence of anatomy, intended as genetic predisposition, on the development of AC joint osteoarthritis. For this reason, we compared AC joint degenerative changes, evaluated by MRI, between asymptomatic elderly monozygotic and dizygotic twins with the aim to separate the contributions of genetic influences from shared and unique environments.

2 | MATERIALS AND METHODS

The study sample was enrolled from the National Twin Registry (NTR). The NTR research activities have been approved by the Ethical Committee of the National Institute of Health. All twins signed an informed consent.

From this database, 50 pairs of twins aged between 50 and 75 years were identified.

Exclusion criteria were: a history of shoulder girdle fractures, rheumatoid diseases or other autoimmune diseases, acromio-clavicular instability, adhesive capsulitis. Unlike-sex dizygotic twin pairs were not included. Zygosity was ascertained comparing the genotypes of nine tetranucleotide multiallelic markers between twins of each pair (accuracy 99.98%).

Acromio clavicular joint osteoarthritis of the dominant side was assessed by MRI (3 T; Siemens Magnetom Avanto Medical 76 × 32). Oblique coronal, oblique sagittal, and axial T2-weighted spin-echo MRIs (repetition time, 3,200 ms; echo time, 85 ms) images were obtained.

Acromioclavicular joint osteoarthritis was assessed according to five parameters (Veen et al., 2018):

- Subchondral bone marrow edema of the distal clavicle (1 point if present).
- Subchondral bone marrow edema of the medial acromion (1 point if present); both evaluated as hyperintense signal from cranial to caudal on fat-saturated T2-weighted images and hypointense signal on T1-weighted images.
- Acromioclavicular osteolysis: lytic bone lesion with cortical destruction of the distal clavicle (1 point if present).
- AC capsule distension: distal protrusion of the AC joint for a minimum 3 mm (measured from a horizontal line on the original under surface of the clavicle on sagittal or coronal images (1 point if present).
- AC joint inferior osteophytes on sagittal T1 or proton density sequences (1 point: no fat between AC joint and supraspinatus; 2 points: no fat plus indentation on the supraspinatus).

According to the obtained score, a 4-grade severity scale of AC joint osteoarthritis was introduced: Type 0: normal joint (score 0); Type I: mild (score: 1–2); Type II: medium (score: 3–4); Type III: severe (score: 5–6).

The evaluation was performed on every subject by three different physicians to assess interobserver reliability. Physicians performed their evaluation blinded to others, and their assessments were 1 to 24 hours apart.

On the coronal plane, the AC joint orientation was classified according to Colegate-Stone and colleagues (Colegate-Stone et al., 2010) into three types: Flat, oblique and curved.

One of the authors obtained information regarding the type and duration of participant employment. Three occupation groups were identified: group A (cleaners, laborers, craft workers, transportation, and operators), group B (administrative workers, technicians, housewife); group C (professionals and managers).

A flowchart of enrolled participants is shown in Figure 1.

2.1 | Statistical analysis

The Statistical Package for Social Sciences (SPSS) ver. 25 (SPSS IBM) has been used for calculations, and data were analyzed by a single researcher. Calculated p values were 2-sided, $p < 0.05$ has been considered significant, and all results have been reported with a 95% confidence interval (CI) when appropriate. For categorical variables Fisher's Exact Test have been conducted instead of chi-square test due to the low number of patients, and $p < 0.05$ was used as the significance threshold. Twin pairs were divided into two groups: (a) "mixed" whether the couple presents different AC joint configuration (flat, curve or oblique) or AC joint osteoarthritis status (Type 0, I, II, III); (b) “unique” category whether the

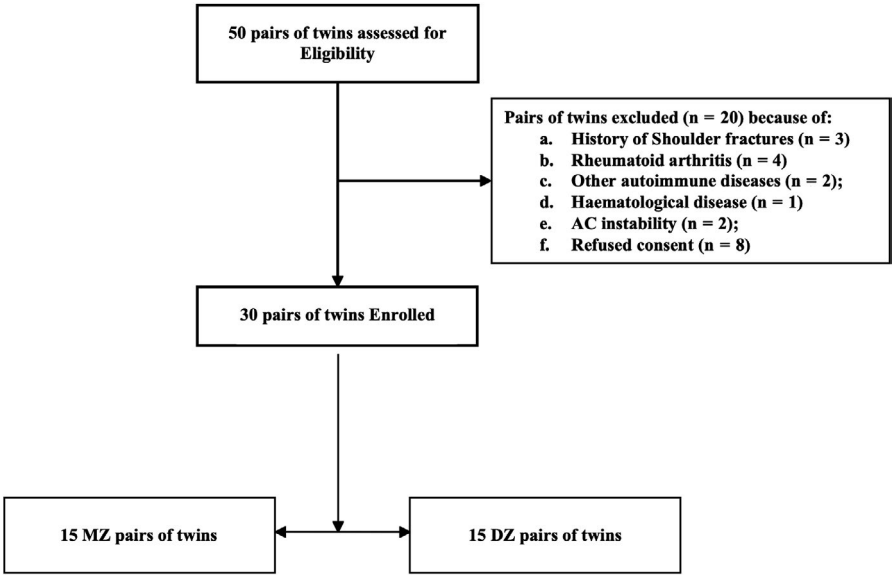

FIGURE 1 Flow chart of participants through the trial. MZ, monozygotic; DZ, dizygotic

couple presented the same configuration and AC joint osteoarthritis status.

Intraclass correlation coefficient (ICC) was calculated to assess reproducibility and it has been estimated with the 95% CI. The ICC can range from 0 to 1; 0.00 to 0.25 indicates little or no correlation, 0.26 to 0.49 indicates low correlation, 0.50 to 0.69 indicates moderate correlation, 0.70 to 0.89 indicates high correlation, 0.90 to 0.99 indicates very high correlation, and 1 indicates perfect correlation. SPSS HETCOR extension command (version 1.3.7) has been used to evaluate the polychoric correlation for the degrees of AC joint osteoarthritis (Type 0, I, II, III). Heritability (h2) has been calculated as twice the difference between the ICC (*r*) for monozygotic pairs (MZ) and that for dizygotic pairs (DZ): h2 = 2(*r*[MZ] 2 *r*[DZ]). The shared environmental influence (c2) has been estimated as the difference between the MZ ICC and the h2 index: [c2 = rMZ − h2]. The unique environmental influence (e2) has been calculated as the difference between 1 and the MZ ICC: [e2 = 1 − rMZ]. The Spearman rank-order correlation has been used to estimate differences among the three job types, both in the total cohort and within the monozygotic and dizygotic twin groups.

3 | RESULTS

Thirty pairs of twins were enrolled [15 MZ and 15 DZ; mean age (±standard deviation): 63.70 years ± 3.31, range: 53–72 years]. The mean age of MZ and DZ twins was 63.73 ± 4.42 years (range: 53–72 years), and 63.67 ± 1.65 years (range: 61–66 years), respectively. Baseline characteristics of all twins are reported in Table 1. Distribution of AC degeneration status is shown in Table 2. A Type 0 severity (normal joint) was never found. Fisher's Exact Test shows no significant correlation between MZ/DZ classification and AC joint osteoarthritis status ($p = 0.473$).

TABLE 1 Baseline characteristics of the enrolled twins

	MZ	DZ
Age ± SD (range)	63.73 ± 4.42 (53 to 72)	63.67 ± 1.65 (61 to 66)
Female (n)	10	18
Age ± SD (range)	62.60 ± 6.35 (53 to 72)	63.79 ± 1.78 (61 to 66)
Male (n)	20	12
Age ± SD (range)	64.30 ± 3.11 (60 to 72)	63.45 ± 1.44 (61 to 65)
Heavy manual workers	7 (23.3%)	6 (20%)
Administrative support workers	13 (43.3%)	15 (50%)
Professional workers	10 (33.3%)	9 (30%)

A flat, oblique and curve configuration of the AC joint was present in 21, 23, and 17 twins, respectively. Only four couple of twins (1 MZ and 3 DZ) had the same configuration of the joint: 1 MZ and 2 DZ pairs had oblique configuration, 1 DZ pair had flat ones. Fisher's Exact Test shows no significant correlation between MZ/DZ classification and AC joint configuration ($p = 0.597$). In addition, comparing "unique" or "mixed" AC morphology distribution and AC joint osteoarthritis presentation between twin pairs, no statistical correlation was found ($p = 0.598$).

The interobserver reproducibility was high, with an ICC value of 0.868 (95% CI, 0.798–0.917). An ICC values of 0.889 (95% CI, 0.798–0.944) and 0.843 (95% CI, 0.712–0.920) were found in the MZ and DZ groups, respectively. The polychoric correlation was 0.857 in the MZ twins and 0.757 in the DZ twins. The difference in correlation between MZ and DZ twins suggested a small genetic influence on AC joint OA. By that result, the calculated heritability index was 0.20 (20%), and the contribution of the shared environment (c2) and unique environment (e2) was 0.66 (66%) and 0.14 (14%), respectively.

TABLE 2 Distribution of AC joint osteoarthritis severity in the studied group

AC joint osteoarthritis severity	MZ		DZ		Total	
	Freq	%	Freq	%	Freq	%
Type 0	0	0.0%	0	0.0%	0	0.0%
Type 1	11	16.7%	5	20.0%	6	18.3%
Type 2	25	33.3%	10	50.0%	15	41.7%
Type 3	24	50.0%	15	30.0%	9	40.0%

The Spearman rank-order correlation showed no significant relationship between job types and the used classification in both the total cohort ($r = 0.089$; $p = 0.499$), and in the monozygotic ($r = 0.247$; $p = 0.187$) and dizygotic twin groups ($r = -0.084$; $p = 0.658$).

4 | DISCUSSION

The main purpose of our study was to assess the role of genetics on the etiology of AC joint osteoarthritis. We conducted a retrospective MRI analysis on elderly monozygotic and dizygotic twins; in fact, studies on twins are the only valuable tool to evaluate the contribution of both intrinsic and extrinsic factors to a disease or trait of interest (Snieder et al., 2010).

AC joint osteoarthritis is a common condition in subjects over 50 years of age. Its etiology is unclear; however, several causes have been identified as responsible for the development of AC joint osteoarthritis in order to explain such a high prevalence in subjects over 50 years of age (Tauber, 2016): age related degeneration of the intra-articular disk, posttraumatic conditions, distal clavicle osteolysis, inflammatory arthropathy, septic arthritis, joint instability, repetitive microtrauma.

Since the first cadaveric studies (De Palma, 1957) a genetic influence and an anatomical basis have been suggested as the main etiological factors for AC osteoarthritis. In fact, any movement that occurs at the acromioclavicular joint would be affected by its shape, and that repetitive movement, along with variations of the joint morphology, might contribute to differing degrees of damage. Evidence of morphological variation of the acromioclavicular joint was provided by De Palma (1957). In a cadaveric study on 66 joints, varying angles of torsion of the joint were found. The AC joint was classified according to its infero-medially angulated plane: type 1 (average angulation of 16°), type 2 (average angulation of 26°) and type 3 (average angulation of 36°). An association between acromioclavicular joint pathology and type 1 joints was also supposed. In the recent years, Colegate-Stone et al. (2010) performed a cadaveric and radiological analysis on 79 joints and demonstrated three main morphological groups namely flat, oblique and curved. As previously done, the authors hypothesized an association between the more asymmetrical shape, more prone to a skewed distribution of forces, and the development of AC joint disease.

Ac joint osteoarthritis was assessed on MRI as previously described by Veen et al. (2018). The MRI evaluation allows a complete evaluation of all the aspects that characterize osteoarthritis. A severity-scale of AC joint osteoarthritis was introduced in order to perform the detailed statistical analysis as a twin study design needed. Furthermore, AC joint configuration was evaluated and classified according to Colegate-Stone (Colegate-Stone et al., 2010).

The heritability index showed that genetic factors have only a slight influence on the development of AC joint osteoarthritis. In particular, the role of genetics on AC joint osteoarthritis accounts for only 20%.

It is plausible that the small articular joint area, together with the high loads experienced with repetitive microtrauma proper of everyday activity (Flatow, 1993; Kibler et al., 2012) results in high stresses within the AC joint leading to the development of osteoarthritis in the almost totality of subjects over 50 years of age, regardless of the specific anatomical configuration of the joint. Our study was the first to resize the association between a specific joint configuration and the development of ACJO. It is plausible that the oblique and asymmetrical orientation of the joint together with the incongruencies of the articular surfaces and the age-related disk degeneration are all factors that worsen the stresses on a joint biomechanically predisposed to osteoarthritis, as the calculated heritability index demonstrated. On the other side, our results revealed that both shared and unique environmental factors (working, sports activity, comorbidities, wrong habits) play a more significant role in influencing ACJ osteoarthritis, representing together 80% of the total heritability. Further studies have to be conduct in order to evaluate the associations between intrinsic factors, included comorbidities and wrong habits, and the development of ACJ osteoarthritis.

The relatively low number of twin pairs is a limit of our study since it did not allow us to apply quantitative genetic models (Snieder et al., 2010) to estimate the heritability by taking into account individual differences in age, sex. However, our study cohort, composed by elderly asymptomatic MZ and DZ twins, is free of bias for the application of the twin design analysis. It is an MRI evaluation and so AC joint osteoarthritis might be overestimated.

5 | CONCLUSION

Our study resizes the role of genetic on AC joint osteoarthritis; a specific anatomical configuration of the articular surfaces, such as the oblique one, only partially works on the development of joint osteoarthritis. Environmental factors have the greatest impact.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Candela V contributed to concept/design, drafting of the manuscript. Villani C and Scacchi M contributed to concept/design. Preziosi Standoli J contributed to data analysis/interpretation, drafting of the manuscript. Gumina S contributed to concept/design, drafting of the manuscript, critical revision of the manuscript.

ETHICAL APPROVAL

This article obtained the IRB approval.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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