Rheumatology 2003;42:258–262
doi:10.1093/rheumatology/keg073, available online at www.rheumatology.oupjournals.org

Factors affecting knee cartilage volume in healthy men

F. M. Cicuttini, A. Wluka, M. Bailey, R. O'Sullivan[1], C. Poon[2], S. Yeung[2] and P. R. Ebeling[2]

Objectives. **To understand the factors that influence joint cartilage in health and disease as they are important for the prevention and management of osteoarthritis.**
Methods. **We conducted a cross-sectional study to determine factors influencing knee cartilage volume in 45 males aged (mean $\pm$ S.D.) 52.5 $\pm$ 13.2 yr.**
Results. **Total and medial tibial volumes were inversely associated with age, body mass index (BMI) and amount of physical activity and positively associated with total bone content. BMI explained the largest amount of the variation in tibial cartilage volume (18.7%). There were similar findings at the lateral tibial cartilage, but for age and total bone content this did not reach statistical significance. There was a positive association with serum testosterone at all tibial cartilage sites, but this only reached statistical significance for medial tibial cartilage, where serum testosterone explained up to 8% of the variation in cartilage volume.**
Conclusions. **Modifiable risk factors of osteoarthritis also appear to be significant determinants of tibial cartilage volume. Serum testosterone may provide one possible explanation for gender differences in tibial cartilage volume and prevalence of tibiofemoral osteoarthritis. The proposed link between osteoarthritis and knee cartilage volume and the effect of testosterone will need to be confirmed in longitudinal studies.**

KEY WORDS: Knee, Cartilage, Risk factors, Men.

Understanding factors that influence joint cartilage in health and disease is important in the prevention and management of osteoarthritis (OA). We have recently shown that males have more knee cartilage than females, independent of body mass index (BMI) and bone size, in both healthy adults [1] and children [2] and that there is more knee cartilage in the lateral compartment than the medial compartment in healthy individuals [2]. Given that OA of the knee is 4–10 times more common in women than in men [3] and 4 times more common in the medial compared with the lateral compartment [4], low 'peak' cartilage volume may be a risk factor for knee OA.

Recent data have suggested a role for hormonal factors on knee cartilage volume. We have recently shown that women on long-term hormone replacement therapy (HRT) have 10% more knee cartilage than age-matched women not on HRT [5]. Gender differences in knee cartilage volume cannot be explained by differences in body size alone [1, 2] or level of physical activity [2], suggesting a role for hormonal factors. There are no studies relating hormones to knee cartilage volume in men. Marked gender differences in knee cartilage have been shown [1, 6–8].

A number of factors have been shown to impact on the risk of developing OA. We postulated that these factors might also affect knee cartilage volume. If so, perhaps knee cartilage volume may be used as a potential interim endpoint in studies of OA. We therefore conducted a cross-sectional study to determine what factors, including hormonal factors, affect knee cartilage in male adults.

Department of Epidemiology and Preventive Medicine, Monash University Medical School, Alfred Hospital, Prahran 3181, [1]MRI Unit, Mayne Health Diagnositc Imaging Group, Epworth Hospital, Richmond 3121 and [2]Department of Diabetes and Endocrinology, Royal Melbourne Hospital, Parkville 3050, Australia.

Submitted 12 November 2001; revised version accepted 15 July 2002.

Correspondence to: F. Cicuttini, Department of Epidemiology and Preventive Medicine, Alfred Hospital, Prahran, Victoria, 3181, Australia. E-mail: flaria.cicultini@med.monash.edu.au

Patients and methods

Forty-five, healthy Caucasian males aged (mean ± S.D.) 52.5 ± 13.2 yr were recruited through advertising in newspapers, through sporting clubs and through the staff association. Exclusion criteria included previous significant knee injury requiring non-weight-bearing treatment for >24 h or surgery (including arthroscopy), and contraindication to MRI. The study was approved by the ethics committee of the Royal Melbourne Hospital, Victoria, Australia. Weight was measured to the nearest 0.1 kg (shoes and bulky clothing removed) using a single pair of electronic scales. Height was measured to the nearest 0.1 cm (shoes removed) using a stadiometer. BMI [weight/height^2 (kg/m^2)] was calculated. Current total activity was a composite score of total amount of walking (0–4) + activity at home (0–4) + sporting activity (0–4) [9]. Each subject had an MRI performed on their dominant knee, defined as the lower limb from which they step off when walking.

Knees were imaged in the sagittal plane on a 1.5-T whole-body magnetic resonance unit (Signa Advantage Echospeed, GE Medical Systems, Milwaukee, WI, USA) using a commercial transmit-receive extremity coil. Knee cartilage volume was measured by two independent observers by means of image processing on an independent work station using the software program Osiris as previously described [1, 2]. The coefficients of variation for total, medial and lateral cartilage volume measures were 2.6, 3.3 and 2.0%, respectively. Medial and lateral tibial plateau areas were determined by creating an isotropic volume from the input images. This was reformatted in the axial plane. The areas were directly measured from these images [2]. Coefficients of variation were 2.3% for medial and 2.4% for lateral tibial plateau areas [2]. MRI scans were examined for features of OA as previously described [10].

Early morning blood samples were taken from all subjects. Serum specimens were stored at −20°C. Total testosterone was measured by radioimmunoassay (DPC Coat-A-Count® Total Testosterone kit). Free testosterone in picomoles (pM) was calculated using the Sodergard equation [11]. The intra- and interassay coefficients of variation were 9.8 and 15.6%, respectively. Sex hormone-binding globulin (SHBG) was measured by immunoradiometric assay (Orion® SHBG kit). The intra- and interassay coefficients of variation were 3.2 and 11.3%, respectively. Dehydroepiandrosterone sulphate (DHEAS) was measured by a DPC Immulite® autoanalyser. The intra- and interassay coefficients of variation were 9.5 and 13%, respectively. Oestradiol was measured by a DPC Immulite® autoanalyser. The intra- and interassay coefficients of variation were 4 and 5%, respectively. Luteinizing hormone (LH) was measured by Abbot AxSym® autoanalyser. The intra- and interassay coefficients of variation were 5.1 and 7.7%, respectively. Total body bone mineral content was measured by dual energy x-ray absorptiometry using a Hologic QDR 1000 W densitometer. The laboratory results were analysed blind to the clinical data.

Statistical analysis

Linear regression was used to examine the effect of age, sex, BMI, physical activity and total bone mineral content on total (medial + lateral) tibial cartilage, medial and lateral tibial cartilage volumes in univariate analyses and in a multivariate model. Cartilage volume is expressed in ml/cm^2 to adjust for the significant effect of bone size on cartilage volume, providing an average cartilage thickness over the bone area to enable comparison between individuals. Results are presented as regression coefficients that represent differences in cartilage volume per unit change in the relevant explanatory factor, while other factors are held constant (i.e. controlled for). Tibial, medial and lateral cartilage volumes per cm^2 were regressed against various serum hormone levels. Multivariate regression models were then constructed adjusting for known demographic predictors, namely age, BMI, physical activity and total bone mineral content. A P value <0.05 was considered to be statistically significant. Statistical analysis was performed using SAS Version 8.0 (SAS Institute Inc., Cary, NC, USA).

Results

Forty-five men aged 52.5 ± 13.2 yr with a BMI of 25.6 ± 3.5 kg/m^2 were examined in this study. Total knee, medial and lateral cartilage volume were inversely associated with age, BMI and amount of physical activity, but positively associated with total bone content on univariate analysis (Table 1). Each of these factors

TABLE 1. Factors affecting cartilage volume in men

	Univariate analysis regression coefficient[b]	Multivariate analysis regression coefficient[c]	95% CI (multivariate analysis)	P value (multivariate analysis)
Total tibial cartilage[a]				
Age	−0.009	−0.01	(−0.02, −0.003)	0.01
BMI	−0.02	−0.04	(−0.11, −0.02)	0.004
Physical activity	−0.08	−0.10	(−0.16, −0.03)	0.007
Total body bone mineral content	0.0001	0.0004	(0.000, 0.001)	0.03
Medial tibial cartilage[a]				
Age	−0.08	−0.01	(−0.02, −0.003)	0.004
BMI	−0.07	−0.05	(−0.09, −0.018)	0.005
Physical activity	−0.06	−0.07	(−0.013, −0.014)	0.017
Total body bone mineral content	0.0002	0.0004	(0.000, 0.001)	0.006
Lateral tibial cartilage[a]				
Age	−0.007	−0.01	(−0.03, 0.004)	0.15
BMI	−0.02	−0.07	(−0.13, −0.01)	0.02
Physical activity	−0.116	−0.14	(−0.23, −0.04)	0.000
Total body bone mineral content	0.0005	0.0004	(0.000, 0.001)	0.167

[a]Cartilage volume expressed as ml/cm^2 of tibial plateau area.
[b]Change in cartilage per unit increase in corresponding variable.
[c]Multivariate analysis with age, BMI, physical activity and bone mineral content in regression equation.

remained a significant determinant of both total knee cartilage and medial tibial cartilage when they were all examined in a multivariate model (Table 1). For total tibial cartilage, variation in cartilage volume could be explained 18.7% by BMI, 16% by physical activity, 12.8% by age and 10.4% by total body bone mineral content. Although the trend was for similar findings at the lateral tibial cartilage, only BMI and physical activity were statistically significant in the multivariate model.

In this population the mean hormone levels were: free testosterone 371 ± 147 pM/l, sex hormone-binding globulin 34.3 ± 15.1 nM/l, oestradiol 62.1 ± 31.8 pM/l, DHEAS 4.4 ± 2.1 μM/l and LH 4.8 ± 2.1 IU/l. Testosterone, DHEAS and LH appeared to relate to total, medial and lateral tibial cartilage volume on univariate analysis (Table 2). However, after adjustment for age, BMI, tibial bone size, total bone mineral content and physical activity, only testosterone was associated with total tibial cartilage and medial tibial cartilage volume (regression coefficient = 0.0008, $P = 0.08$ for total tibial cartilage) (Table 1). Overall, testosterone accounted for 8% (partial r^2) of the variation in medial and total tibial cartilage volume. This did not change significantly when oestradiol was added to the equation (7%). Three subjects had osteophytes on MRI. Repeating our analyses excluding those with OA did not change the results.

Discussion

In this study we have shown that total and medial tibial volumes were inversely associated with age, BMI and amount of physical activity and positively associated with total bone content. There were similar findings at the lateral tibial cartilage, but for age and total bone content this did not reach statistical significance. There was a positive association with serum testosterone at all tibial cartilage sites but this only reached statistical significance for medial tibial cartilage.

Age is a well known risk factor for knee OA [12]. There is evidence for a negative association between age and knee cartilage volumes in post-menopausal women, a mixed gender group of 52 subjects with OA and 40 subjects without OA, and in a study of men only [5, 7, 13]. An autopsy study of joint cartilage found similar results [14]. In our study of men, we demonstrated a significant inverse association between age and total tibial cartilage and medial tibial cartilage. At the lateral tibial cartilage there was an inverse, although not statistically significant, association with age. It may be that the effect of age is not as strong at this site in men.

Although elevated BMI is an established risk factor for knee OA, little is known about its relationship to knee cartilage volume [15–17]. We found increased BMI was associated with a reduction in tibial cartilage volume at all sites. In post-menopausal women, BMI contributes significantly to the variation in lateral and total tibial cartilage volume [5]. Consistent with our findings relating to cartilage volume, a previous study in a mixed gender group showed that body weight was inversely related to cartilage thickness in the hip [18].

The effect of physical activity on the risk of OA is unclear, although a number of studies suggest that previous and current high levels of physical activity are associated with knee OA [9, 19]. In this study, higher current levels of physical activity were associated with a reduction in tibial cartilage volume. In contrast, in children we have shown a positive association between physical activity and tibial cartilage volume [2]. It may be that there are age-related differences in the effect of physical activity on knee cartilage. Total bone mineral content was associated with total tibial and medial

TABLE 2. Relationship between tibial cartilage volume (ml/cm^2)[a] and sex hormones

	Univariate analysis regression coefficient[b]	Multivariate analysis regression coefficient[c]	95% CI (multivariate analysis)	*P* value (multivariate analysis)
Total tibial cartilage[a]				
Free testosterone	0.008	0.0008	(0.00, 0.002)	0.08
Sex hormone-binding globulin	−0.004	0.004	(−0.01, 0.01)	0.51
Oestrogen	0.0001	0.0008	(−0.003, 0.005)	0.69
Dehydroepiandrosterone sulphate	0.04	0.01	(−0.23, 0.25)	0.80
Luteinizing hormone	−0.02	−0.008	(−0.04, 0.06)	0.77
Medial tibial cartilage[a]				
Free testosterone	0.0008	0.0008	(0.000, 0.02)	0.04
Sex hormone-binding globulin	−0.005	0.001	(−0.009, 0.011)	0.84
Oestrogen	0.0006	0.0002	(−0.003, 0.002)	0.37
Dehydroepiandrosterone sulphate	0.03	0.005	(−0.06, 0.07)	0.87
Luteinizing hormone	−0.02	−0.001	(−0.05, 0.05)	0.97
Lateral tibial cartilage[a]				
Free testosterone	0.0008	0.0008	(0.000, 0.002)	0.19
Sex hormone-binding globulin	0.001	0.009	(−0.006, 0.025)	0.22
Oestrogen	0.001	0.0002	(−0.006, 0.006)	0.96
Dehydroepiandrosterone sulphate	0.04	0.009	(−0.102, 0.120)	0.87
Luteinizing hormone	−0.02	−0.002	(−0.099, 0.065)	0.68

[a]Cartilage volume expressed as ml/cm^2 of tibial plateau area.
[b]Change in cartilage per unit increase in corresponding variable.
[c]Multivariate analysis with age, BMI, physical activity and bone mineral content in regression equation.

cartilage volume. This has not previously been examined, although a number of studies have suggested an inverse relationship between osteoarthritis and osteoporosis [15–17]. However, these studies have mainly been in women rather than men. The Baltimore Longitudinal Study on ageing showed that the adjusted mean bone mineral content and radial width were increased in men with knee OA [20].

In this study we showed a positive association between medial tibial cartilage and serum testosterone levels. A similar, but non-significant, effect was observed for total tibial cartilage and lateral tibial cartilage. Few data are available on the effect of testosterone on joint cartilage or OA, despite its effects on other musculoskeletal tissues being better characterized [21, 22]. Decreasing testosterone level was found to be significantly associated with increasing hand OA scores in 573 women aged 24–45 yr participating in the Michigan Bone Health Study [23]. Testosterone receptors have been shown to be present in cartilage in humans [20]. As with the effect of other sex hormones on cartilage, the effect of testosterone may differ according to the developmental age of the organism, and sometimes differs according to gender [24–26].

There are a number of potential limitations in using MRI for cartilage volume estimates. The accurate delineation of articular cartilage depends on high contrast relative to adjacent tissues. We used a previously validated fat-suppressed gradient echo sequence [1, 2]. Furthermore, as has previously been recommended [27] in order to improve in-plane resolution we used a matrix of 512×192 pixels, resulting in an in-plane resolution of 0.31×0.83 mm. The reproducibility of our measurements was comparable with previously reported work [28]. In this study we have used tibial cartilage as the measure of joint cartilage at the tibiofemoral joint. We have shown strong correlation between the tibial and femoral cartilage in the medial and lateral tibiofemoral joint compartments [29]. The femoral cartilage articulates the medial and lateral tibiofemoral and the patellofemoral joints; it is difficult to identify the relevant component of femoral cartilage when assessing the respective tibiofemoral joints. In contrast, each of the tibial cartilages only forms part of one joint. Another limitation of our study is that we only included men. Our findings cannot be generalized to women since the associations may be gender specific. Few subjects had knee osteoarthritis. Repeating our analyses excluding these men did not change the magnitude or direction of our findings. There may also be important interactions between sex hormones in their effect on tibial cartilage; however our sample size was too small to examine this, particularly since there is large between-subject variability in cartilage volume [30].

Although we used calculated free testosterone values derived from total testosterone and SHBG, we found similar relationships between total testosterone and tibial cartilage volumes. Despite there being a relatively weak association with free testosterone, no such association existed between cartilage volumes and oestrogen. This suggests that testosterone may have more important effects on tibial cartilage than oestrogen, while the reverse is true for bone where about two-thirds of the bone resorption rate is accounted for by oestrogen [31].

Our data suggest that the modifiable risk factors of OA also appear to be significant determinants of tibial cartilage volume in men. If so, perhaps knee cartilage volume may be used as a potential interim endpoint in studies of OA. However, the proposed link between OA and knee cartilage volume will need to be confirmed in longitudinal studies directly relating these variables.

Acknowledgements

This study was supported by the Arthritis Foundation of Australia and the National Health and Medical Research Council. Thanks to Ms Judy Hankin for co-ordinating the recruitment of participants for this study. We give special thanks to the study participants who made this study possible.

References

1. Cicuttini F, Forbes A, Morris K, Darling S, Bailey M, Stuckey S. Gender differences in knee cartilage volume as measured by magnetic resonance imaging. Osteoarthritis Cartilage 1999;7:265–71.
2. Jones G, Glisson M, Hynes K, Cicuttini F. Sex and site differences in cartilage development: a possible explanation for variations in knee osteoarthritis in later life. Arthritis Rheum 2000;43:2543–9.
3. Felson DT, Naimark A, Anderson J, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly. The Framingham Osteoarthritis Study. Arthritis Rheum 1987;30:914–8.
4. Ledingham J, Regan M, Jones A, Doherty M. Radiographic patterns of osteoarthritis of the knee in patients referred to hospital. Ann Rheum Dis 1993;52:520–6.
5. Wluka AE, Davis SR, Bailey M, Stuckey SL, Cicuttini FM. Users of oestrogen replacement therapy have more knee cartilage than non-users. Ann Rheum Dis 2001;60:332–3.
6. Dupuy DE, Spillane RM, Rosol MS, Rosenthal I, Palmer WE, Burke DW *et al*. Quantification of articular cartilage in the knee with three-dimensional MR imaging. Acad Radiol 1996;3:919–24.
7. Cova M, Frezza F, Shariat-Razavi I, Ukmar M, Mucelli RS, Dalla Palma L. Magnetic resonance assessment of knee joint hyaline according to age, sex, and body weight. Radiol Med 1996;92:171–9.
8. Waterton JC, Solloway S, Foster JE, Keen MC, Gandy S, Middleton BJ *et al*. Diurnal variation in the femoral articular cartilage of the knee in young adult humans. Magn Reson Med 2000;43:126–32.
9. Spector TD, Harris PA, Hart DJ, Cicuttini FM, Nandra D, Etherington J *et al*. Risk of osteoarthritis associated with long-term weight-bearing sports: a radiologic survey of the hips and knees in female ex-athletes and population controls. Arthritis Rheum 1996;39:988–95.
10. McAlindon T, Watt I, McCrae F, Goddard P, Dieppe PA. Magnetic resonance imaging in osteoarthritis of the knee: correlation with radiographic and scintigraphic findings. Ann Rheum Dis 1991;50:14–9.

11. Sodergard R, Backstron T, Shanbhag B, Carstensen H. Calculation of free and bound fractions of testosterone and estradiol-17 beta to human plasma proteins at body temperature. J Steroid Biochem 1982;16:801–10.
12. Felson DT. The epidemiology of knee osteoarthritis: results from the Framingham Osteoarthritis Study. Semin Arthritis Rheum 1990;20(Suppl. 1):42–50.
13. Karvonen RL, Negendank WG, Teitge RA, Reed AH, Miller PR, Fernandez-Madrid F. Factors affecting articular cartilage thickness in osteoarthritis and aging. J Rheumatol 1994;21:1310–8.
14. Meachim G, Bentley G, Baker R. Effect of age on thickness of adult patellar articular cartilage. Ann Rheum Dis 1977;36:563–8.
15. Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham Study. Ann Intern Med 1988;109:18–24.
16. Davis MA, Ettinger WH, Neuhaus JM, Hauck WW. Sex differences in osteoarthritis of the knee: The role of obesity. Am J Epidemiol 1988;127:1019–30.
17. Hart DJ, Spector TD. The relationship of obesity, fat distribution and osteoarthritis in women in the general population: The Chingford Study. J Rheumatol 1993; 20:331–5.
18. Moore RJ, Fazzalari NL, Manthey BA, Vernon-Roberts B. The relationship between head-neck-shaft angle, calcar width, articular cartilage thickness and bone volume in arthrosis of the hip. Br J Rheumatol 1994;33:432–6.
19. McAlindon TE, Wilson PWF, Aliabadi P, Weissman B, Felson DT. Level of physical activity and the risk of radiographic and symptomatic knee osteoarthritis in the elderly: The Framingham Study. Am J Med 1999; 106:151–7.
20. Hochberg MC, Lethbridge-Cejku M, Scott WW, Reichle R, Plato CC, Tobin JD. Upper extremity bone mass and osteoarthritis of the knees: data from the Baltimore Longitudinal Study of Aging. J Bone Miner Res 1995;10:432–8.
21. Hannan MT, Anderson JJ, Zhang Y, Levy D, Felson DT. Bone mineral density and knee osteoarthritis in elderly men and women. The Framingham Study. Arthritis Rheum 1993;36:1671–80.
22. Sowers MF, Hochberg M, Crabbe JP, Muhich A, Crutchfield M, Updike S. Association of bone mineral density and sex hormone levels with osteoarthritis of the hand and knee in premenopausal women. Am J Epidemiol 1996;143:38–47.
23. Ben-Hur H, Thole HH, Mashiah A, Insler V, Berman V, Shezen E *et al.* Estrogen, progesterone and testosterone receptors in human fetal cartilaginous tissue: immunohistochemical studies. Calcif Tissue Int 1997;60:520–6.
24. Colman RJ, Lane MA, Binkley N, Wegner FH, Kemnitz JW. Skeletal effects of aging in male rhesus monkeys. Bone 1999;24:17–23.
25. Davis S, McCloud P, Strauss B, Burger H. Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. Maturitas 1995;21:227–36.
26. Amin S, Zhang Y, Sawin CT, Evans SR, Hannan MT, Kiel DP *et al.* Association of hypogonadism and estradiol levels with bone mineral density in elderly men from the Framingham study. Ann Intern Med 2000;133:951–63.
27. Ornoy A, Giron S, Aner R, Goldstein M, Boyan BD, Schwartz Z. Gender dependent effects of testosterone and 17 beta-estradiol on bone growth and modelling in young mice. Bone Miner 1994;24:43–58.
28. Schwartz Z, Nasatzky E, Ornoy A, Brooks BP, Soskolne WA, Boyan BD. Gender-specific, maturation-dependent effects of testosterone on chondrocytes in culture. Endocrinology 1994;134:1640–7.
29. Cicuttini F, Wluka A, Stuckey S. Tibial and femoral cartilage changes in knee osteoarthritis. Ann Rheum Dis 2001;60:977–80.
30. Eckstein F, Winzheimer M, Hohe J, Englmeier KH, Reiser M. Interindividual variability and correlation among morphological parameters of knee joint cartilage plates: analysis with three-dimensional MR imaging. Osteoarthritis Cartilage 2001;9:101–11.
31. Carlson CS, Loeser RF, Jayo MJ, Weaver DS, Adams MR, Jerome CP. Osteoarthritis in cynomolgus macaques: a primate model of naturally occurring disease. J Orthop Res 1994;12:331–9.