

## Original article

**Does subclinical inflammation contribute to impairment of function of knee joints in aged individuals? High prevalence of ultrasound inflammatory findings**

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**Abstract**

**Objectives.** To investigate the prevalence of knee US findings of inflammation and structural damage in aged individuals ( $\geq 60$  years) of a long-term population-based cohort and to correlate these findings with demographic, clinical and laboratory parameters.

**Methods.** Cross-sectional clinical and US investigation of both knee joints during the 2010 follow-up of the prospective population-based Bruneck Study. Demographic variables, physical activity, comorbidities, medications, pain, and functional scales related to the knee joints were recorded. US-assessed parameters were synovial hypertrophy, power Doppler signal, joint effusion, cartilage abnormalities, osteophytes, enthesopathy and bursitis. Statistics included univariate and multivariate regression analysis.

**Results.** A total of 488 subjects (mean age 72.5 years; 53.5% females, 46.5% males) were examined by clinical assessment, and 433 of these underwent US examination of both knees. Both inflammatory and structural abnormalities were found in 296 (68.8%) subjects. Inflammatory abnormalities were significantly associated with age in years, male gender, diabetes and the presence of knee joint symptoms. In the multivariate analysis, age, male gender and knee swelling emerged as independent predictors of inflammation [odds ratio (OR) (95% CI) = 1.06 (1.03, 1.09), 2.55 (1.55, 4.21) and 5.92 (1.99, 17.58), respectively].

**Conclusion.** The present study showed a high prevalence of US inflammatory abnormalities in the knee joints of a normal aged population. These data suggest a substantial contribution of inflammation in progressive impairment of joint function with age.

**Key words:** arthritis, subclinical disease, imaging, ultrasound, age, diabetes.

**Rheumatology key messages**

- US-detected inflammatory lesions are present in the knee joints of the elderly population.
- US lesions increase the likelihood of developing symptomatic joint disease

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## Introduction

Western societies, and increasingly also developing countries, are characterized by profound demographic changes with progressive ageing of the population. The segment of the population older than 65 years accounts for ~20% of the entire population in Western societies and represents its fastest growing part [1, 2]. Decrease in cardiovascular mortality and better treatment for most forms of cancer have improved survival, with the consequence that the burden of musculoskeletal disease has become more important. Impaired musculoskeletal function during ageing is one of the major health problems associated with several complications, such as higher likelihood of falls, osteoporosis associated with fracture and increased susceptibility to infections.

The cause of the increasing musculoskeletal burden during ageing is not completely understood, although the wear-and-tear concept, suggesting decline of musculoskeletal function due to life-long mechanical stress, is a common theory. However, this concept is purely hypothetical, and one cannot exclude the possibility that other factors precipitate the deterioration of musculoskeletal function during ageing. Importantly, ageing is associated with substantial changes in body composition, with increase in adipose tissue at the expense of muscle tissue. Body fat is a major source of inflammatory cytokines and is associated with a generalized inflammatory state, indicated by elevated levels of acute-phase reactants in aged individuals [3–5]. It is well established that inflammation is deleterious to the musculoskeletal system in triggering arthritis, lowering the threshold for pain and inducing progressive bone loss.

Current knowledge about inflammatory changes in elderly people is based solely on the evaluation of clinical symptoms in this segment of the population with the highest musculoskeletal disease burden. Such data are mostly driven by either patient-oriented questionnaires or the prevalence of arthroplasty. In contrast, detailed data on structural changes in the joints of people aged over 60 years are scarce. Among weight-bearing joints, affection of the knee often leads to profound impairment in joint function. Knee involvement is usually evaluated by conventional radiography, which allows detection of only rather advanced structural changes, with no or only limited information on inflammatory changes. On the other hand, modern imaging techniques such as MRI or US permit simultaneous detection of both inflammatory and structural joint changes [6–9].

In order to evaluate the prevalence and severity of inflammation and structural joint changes in the knee joints of the elderly population, we performed a detailed clinical and US examination of women and men aged over 60 years from a well-defined population-based cohort (Bruneck study) [10–14]. We also evaluated potential association between US lesions and demographic, clinical and laboratory characteristics of the patients.

## Methods

### Population

The Bruneck Study is a prospective population-based cohort study on the epidemiology and pathogenesis of atherosclerosis and disorders of the brain and joints [15–17]. The population was recruited in 1990 (baseline) as a random sample of all inhabitants of Bruneck (Italy) from the fifth to the eighth decades of age. This population is characterized by homogeneous access to a single public health care structure (Bruneck Hospital), in which all the medical records of each individual have been collected and made completely accessible in one location. The study protocol of the Bruneck cohort was approved by the local ethics committees (Comitato Etico del Comprensorio sanitario di Bolzano), and all study subjects gave their written informed consent. At baseline, in 1990, a total of 927 men and women were enrolled, and complete clinical and laboratory examinations were conducted at baseline and every 5 years thereafter. Population mobility within the Bruneck area was low (0.2% per year), and migration to outside communities was a rare event ( $n=4$  during the 20 years of follow-up). Our study was reviewed and approved by the ethics committee of the Medical University of Innsbruck.

### Clinical examination

During the fourth follow-up, in September 2010, all subjects alive and agreeing to participate underwent a general physical examination that included evaluation of the knee joints. The presence of joint swelling and pain, information about physical activity (i.e. spare time spent in performing sport activities, walking and cycling), functional scales related to knee impairment (i.e. WOMAC), and performance in daily living and mobility activities (Barthel Index), as well as current medications (i.e. NSAIDs, glucocorticoids, analgesic drugs) for musculoskeletal complaints, were recorded.

Comorbidities such as diabetes mellitus, and clinical characteristics such as BMI, were also recorded. Conventional radiography was performed in cases of painful joint (according to clinical judgement) during each follow-up visit.

### Ultrasonographic assessment

US was performed on both knees by an expert ultrasonographer who was unaware of clinical and laboratory data, using a MyLab25 machine (ESAOTE, Genova, Italy) equipped with a 4- to 13-MHz linear probe. In addition, power Doppler was used (Doppler frequency 6.7 MHz; PRF 750 Hz, gain 40–50 dB) for detecting vascular flow at synovial membrane and tendon level. The examination was performed according to internationally practised guidelines and definitions for US pathology [8, 9]. The knees were examined, modifying the joint flexion according to the different structures being evaluated. Both transverse and longitudinal scans of the supra- and infrapatellar regions, the lateral, medial and posterior

compartments, as well as the parapatellar recesses were performed.

Inflammatory abnormalities were defined by the presence of hypoechoic synovial hypertrophy (SH), intrasynovial power Doppler signal, and joint effusion in the supra- and parapatellar recesses. Structural lesions were defined as cartilage abnormalities of the femoral condyles (i.e. loss of the anechoic structure or of its sharpness on at least one margin, the presence of irregularities of the superficial margin and thinning of the layer) and femoral and tibial osteophytes. In addition, US signs of quadriceps and patellar (proximal and distal) enthesopathy, as well as the presence of bursitis of the patellar ligament (superficial and deep) and of the posterior compartment (i.e. Baker's cyst), were recorded. All US features were scored dichotomously (presence/absence), except for SH, joint effusion, power Doppler signal, and the combination of SH and power Doppler, which were also scored using a semi-quantitative scale (0 = normal; 1 = mild change; 2 = moderate change; 3 = severe change) [18].

### Statistical analysis

Continuous variables were described by mean s.d. or median (interquartile range), whereas ordinal and nominal data were described by percentages. Comparisons between groups were performed by means of the Kruskal-Wallis non-parametric test for continuous or ordinal data, and by the Chi-square test for nominal data. Variables that showed an association with inflammatory lesions in univariate analysis at  $P < 0.2$  were introduced in multivariate analysis. The latter analysis was performed using a logistic regression model. The main interactions were tested, and goodness of fit was assessed.  $P < 0.05$  was considered statistically significant. All analyses were carried out with the R statistical language (R Foundation for Statistical Computing, Vienna, Austria. <http://www.R-project.org>).

## Results

### Population characteristics

Of the 576 participants in the Bruneck Study still alive in 2010, 488 participated in the follow-up investigation. Of these, 16 had a diagnosis of inflammatory arthritis (4 of RA, 1 of PsA and 10 of CPDD); 15 subjects had knee arthroplasty (7 right, 6 left and 1 bilateral total knee replacement, respectively). The mean age was 72.57 years (s.d. 8.53) [median 71 years (range 60–98)], and 261 (53.5%) were females. The population was rather lean, with a mean BMI of 26.33 (s.d. 4.06) (median 25.86, range 16.81–41.98), and low prevalence of comorbidities such as type 2 diabetes mellitus (59 cases). In accordance, most individuals were still very active; 80.3% ( $n = 392$ ) performed  $>2$  h per week of sports activities and 58.8% ( $n = 287$ ), performed  $>30$  min of walking per day. Furthermore, the Barthel index, a measure of the functional capacity of the individual, showed complete

autonomy in daily life activities [mean 95.1 (s.d. 14.33)] in the majority of the subjects.

### Prevalence of clinical symptoms in the knee joint

Regarding clinical symptoms in the knee joints, 31.6% of the patients ( $n = 109$ ) experienced referred knee pain, mostly after physical activity, but only 14.0% ( $n = 47$ ) presented joint swelling at clinical examination. Knee radiographs were available for 85 out of the 109 patients. Among these, 82 subjects presented a Kellgren and Lawrence radiographic score of  $\geq 2$ . The evaluation of clinical symptoms using the total WOMAC score showed a low severity score [mean of 91.73 (s.d. 12.69), theoretical range 0–100, where 100 is the absence of impairment]. We did not observe any statistically significant difference in the prevalence of these parameters according to gender, age ( $>$  or  $\leq 70$  years), BMI or type 2 diabetes mellitus.

### Prevalence of US inflammatory abnormalities in the knee joints

US was performed in 443 out of 488 examined subjects (886 knees in total). No exclusion was made in relation to inflammatory disease or knee replacement. Among these, only five individuals (1.1%) did not present any sign of inflammatory or structural abnormalities. With respect to US changes linked to inflammation, joint effusion was the most frequently detected abnormality (60% of the subjects) (Table 1). Importantly, however, SH associated with a positive power Doppler signal (considered the most stringent US sign for inflammatory joint disease) was detected in 53.1% of the population. All inflammatory abnormalities were mild in the majority of cases, and grade 1 was the most frequent severity score recorded for abnormalities (grade 1: SH 27.9%, effusion 41%, power Doppler signal 15.4%, SH and power Doppler signal 26.8%; grade 2: SH 12.1%, effusion 13.3%, power Doppler signal 6.6%, SH and power Doppler signal 12.9%; grade 3: SH 3.9%, effusion 6.1%, power Doppler signal 0.6%, SH and power Doppler signal 4.1%). Furthermore, Baker's cyst was prevalent in this population [attributed to 144 subjects (32.5%)].

### Factors associated with US knee inflammation

We next searched for demographic and clinical characteristics associated with the presence of US inflammatory abnormalities (i.e. SH without PD, and joint effusion). Comparisons between subjects with and without US inflammatory lesions are reported in Table 2. The presence of US inflammation was significantly associated with age ( $>70$  years;  $P < 0.001$ ), male gender ( $P = 0.004$ ) and diabetes ( $P = 0.01$ ). In addition, there was a significant association with structural abnormalities (both cartilage lesions and osteophytes) ( $P < 0.001$  each) as well as clinical symptoms such as knee swelling ( $P < 0.001$ ) and knee pain, whereby association with the latter was close to significance ( $P = 0.065$ ) (Table 1). In order to identify symptomatic subjects we grouped knee pain, knee swelling and NSAID intake to create three composite indices:

**TABLE 1** US findings in the knee joints of the population aged over 60 years

US finding	n (%)
Inflammation (n = 443) <sup>a</sup>	
No	138 (31.4)
Yes	301 (68.6)
Synovial hypertrophy	
Absent	229 (46.9)
Grade 1	136 (27.9)
Grade 2	59 (12.1)
Grade 3	19 (3.9)
Effusion	
Absent	148 (30.3)
Grade 1	200 (41)
Grade 2	65 (13.3)
Grade 3	30 (6.1)
Power Doppler signal	
Absent	333 (68.2)
Grade 1	75 (15.4)
Grade 2	32 (6.6)
Grade 3	3 (0.6)
Synovial hypertrophy and power Doppler signal	
Absent	229 (46.9)
Grade 1	131 (26.8)
Grade 2	63 (12.9)
Grade 3	20 (4.1)
Structural damage (n = 443) <sup>a</sup>	
No	10 (2.3)
Yes	433 (97.7)
Cartilage abnormalities	
No	69 (15.6)
Yes	374 (84.4)
Osteophytes <sup>b</sup>	
No	16 (3.6)
Yes	426 (96.4)
Enthesopathy <sup>a,c</sup>	
No	51 (11.5)
Yes	391 (88.5)
Baker's cyst <sup>a</sup>	
No	294 (67.1)
Yes	144 (32.9)
Bursitis <sup>a,d</sup>	
No	435 (98)
Yes	9 (2)

Missing data (maximum 45). <sup>a</sup>Right and left knee evaluation; <sup>b</sup>osteophytes detected in both medial and lateral compartments; <sup>c</sup>enthesopathy of quadriceps tendon insertion on the patella and of proximal and distal patellar ligament insertions on the apex of the patella and on the tibial tuberosity respectively; <sup>d</sup>patellar bursitis (superficial and deep).

subjects with knee pain and swelling (index 1); subjects using NSAIDs for knee pain or knee swelling (index 2); and NSAID intake associated with knee pain and swelling (index 3). Only index 1 was statistically significantly different in the two groups ( $P < 0.001$ ). Table 3 reports the results of comparisons between the three groups of individuals obtained by combining the presence/absence of US inflammatory (i.e. SH with or without PD, and/or joint

effusion) signs and symptoms for the three composite indices. It is of note that the presence of symptoms and inflammatory signs at US was statistically significantly associated with higher age, male gender, higher BMI, the presence of diabetes and a more severe WOMAC score.

#### Link between inflammatory and structural changes at US

Structural abnormalities such as osteophytes or cartilage lesions were observed in 433 (97.7%) subjects; among them osteophytes were detected in 426 (87.3%) individuals and cartilage abnormalities in 374 (76.6%) (Table 1). Structural abnormalities were mostly detected in association with inflammatory findings. Thus, 296 (68.8%) of the subjects showed structural abnormalities in conjunction with inflammation, whereas only 133 (30%) individuals showed structural abnormalities in the absence of signs of inflammation, suggesting a strong link between inflammatory and structural changes in the knee joint. Fig. 1A–D shows some example of inflammatory and structural findings detected by US in the population. The global distribution of each inflammatory sign (i.e. effusion, SH and power Doppler signal) and of each structural abnormality (i.e. cartilage lesions and osteophytes) is shown in Fig. 2A and 2B).

#### Predictors for symptomatic inflammatory lesions in the knee joint

Using a multivariate analysis of the whole cohort, only age in years, male gender and the presence of knee joint swelling were independent predictors of the presence of inflammatory signs at US [OR 1.06 (95% CI 1.03, 1.09) per year, 2.55 (95% CI 1.55, 4.21) and 5.92 (95% CI 1.99, 17.58), respectively]. Similar results were observed for SH and joint effusion taken alone (data not shown). Interestingly, the isolated presence of a power Doppler signal was predicted only by knee swelling and cartilage abnormalities [OR 3.61 (95% CI 1.82, 7.15) and 3.35 (95% CI 1.14, 9.84), respectively]. Among the three composite indices for symptomatic knee joint involvement, only index 1 (i.e. knee pain and swelling) was found to be an independent predictive factor for US inflammation [OR 7.34 (95% CI 1.66, 32.33),  $P = 0.0085$ ], along with age and sex.

#### Discussion

Musculoskeletal symptoms progressively increase with age and impair physical function, particularly over the age of 60 years. In this study we showed that the prevalence of any type of structural alteration of the knee joints in this segment of the population is very high and is mostly underestimated by clinical findings. The Bruneck Study, which is based on a randomly selected sample of the general population followed over 20 years, represents the ideal instrument for evaluating the burden of joint impairment in the normal aged population. The health status of the Bruneck Study's subjects has been longitudinally characterized in great detail, facilitating the assessment of

**TABLE 2** Comparison between individuals with and without ultrasound inflammatory changes

	Inflammation yes 301	Inflammation no 138	P-value	Multivariate OR (95% CI), P-value
<b>Demographic characteristics</b>				
Age, mean (s.d.), years	73.3 (8.2)	70.2 (7.7)	<0.001	1.06 (1.02, 1.09), 0.0003
Male sex, <i>n</i> (%)	164 (54.5)	54 (39.1)	0.004	2.55 (1.55, 4.21), 0.0002
<b>Clinical characteristics</b>				
BMI, median (IQR)	25.6 (23.8–28.4)	25.9 (23.8–28.8)	0.522	
Presence of diabetes, <i>n</i> (%)	39 (13.0)	6 (4.3)	0.01	
WOMAC, median (IQR)	96.9 (87.8–100)	97.9 (91.2–100)	0.146	
Barthel Index, median (IQR)	100 (100–100)	100 (100–100)	0.332	
Physical activity, <sup>a</sup> <i>n</i> (%)			0.218	
1	19 (6.3)	13 (9.4)		
2	35 (11.6)	10 (7.2)		
3	247 (82.1)	115 (83.3)		
Walking <sup>b</sup>				
1	53 (17.6)	26 (18.8)		
2	29 (9.6)	15 (10.9)		
3	43 (14.3)	12 (8.7)		
4	47 (15.6)	23 (16.7)		
5	129 (42.9)	62 (44.9)		
Cycling <sup>c</sup>				
1	147 (48.8)	69 (50)		
2	53 (17.6)	24 (17.4)		
3	47 (15.6)	27 (19.6)		
4	20 (6.6)	7 (5.1)		
5	34 (11.3)	11 (8)		
Knee pain, <sup>d</sup> <i>n</i> (%)	76 (34.7)	27 (24.1)	0.065	
Knee swelling, <sup>d</sup> <i>n</i> (%)	40 (18.2)	4 (3.4)	<0.001	5.92 (1.99, 17.58), 0.0014
NSAIDs, <i>n</i> (%)	50 (16.6)	23 (16.7)	0.988	
Glucocorticoids, <i>n</i> (%)	1 (0.3)	3 (2.2)	0.102	
<b>Composite indices</b>				
Index 1: pain and swelling, <sup>d</sup> <i>n</i> (%)	29 (13.2)	2 (1.8)	0.001	
Index 2: NSAID use and (pain or swelling), <sup>d</sup> <i>n</i> (%)	18 (6.4)	4 (3.0)	0.16	
Index 3: NSAID use and pain and swelling, <sup>d</sup> <i>n</i> (%)	8 (2.8)	1 (0.8)	0.207	
<b>Structural changes (US)</b>				
Presence of osteophytes, <sup>d</sup> <i>n</i> (%)	296 (98.3)	133 (96.4)	0.027	
Presence of cartilage damage, <sup>d</sup> <i>n</i> (%)	259 (86)	111 (80.4)	0.174	

<sup>a</sup>Physical activity: sports activity in spare time (1: 0 h/week; 2: ≤2 h/week; 3: >2 h/week); <sup>b</sup>walking during spare time (1: <5 min; 2: 5–15 min; 3: 15–20 min; 4: 30–45 min; 5: >45 min); <sup>c</sup>cycling during spare time (1: <5 min; 2: 5–15 min; 3: 15–20 min; 4: 30–45 min; 5: >45 min); <sup>d</sup>both uni- and bilateral.

risk-predicting factors for cardiovascular disease, diabetes, fractures and joint diseases such as OA [10–15]. In our cross-sectional evaluation, we have concentrated our investigations on the knee joint, as it represents a weight-bearing joint of central importance for locomotion, which is exposed to lifelong mechanical load.

The increase in degenerative joint abnormalities with age could have been expected; however, the observation of a high prevalence of inflammatory signs in the knee joint, even if mild in most cases, and the relative absence of clinical findings was astonishing. Thus, more than half of the individuals showed signs of inflammation such as SH or increased vascularity measured by power Doppler signal. These data suggest that subclinical inflammation may have a prominent role in the decrease in locomotor function during ageing, and that joint involvement, in the

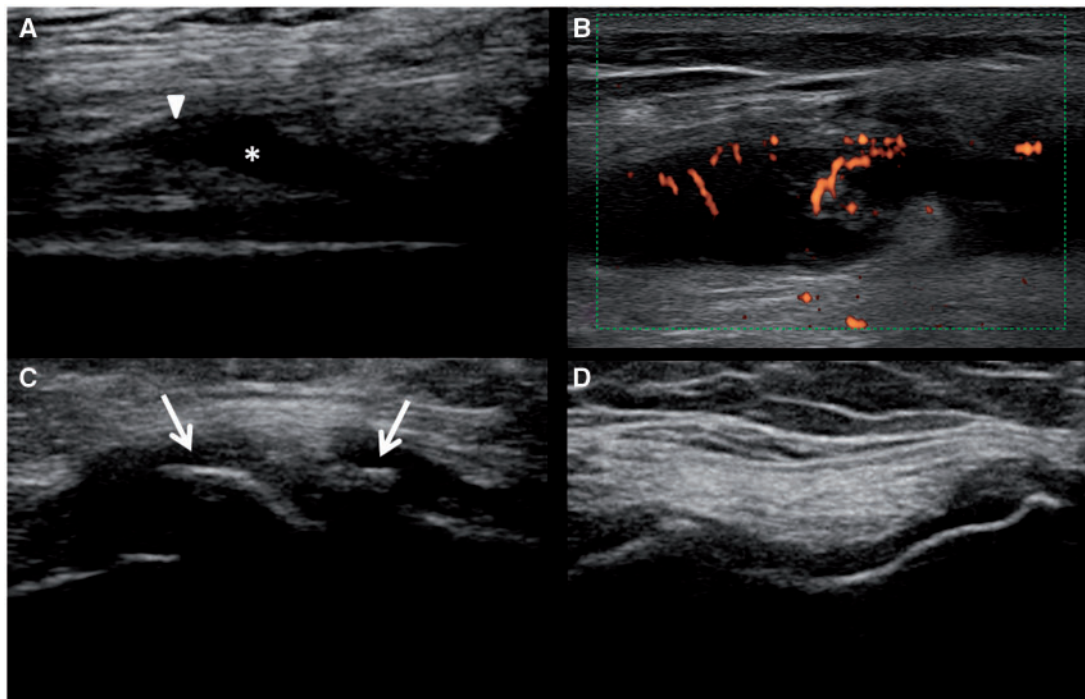
absence of overt clinical symptoms, is underestimated and undervalued in the general population.

The strong association between inflammatory abnormalities in the US and clinical symptoms, such as swelling and pain, confirms that these US lesions are clinically meaningful because they increase the likelihood of developing symptomatic joint disease. It was interesting to observe that increased age, male gender and the presence of diabetes, but not physical activity, were associated with the presence of inflammatory lesions at US. The association between age and US inflammation may suggest that the higher rate of joint disease in aged individuals could result from a higher inflammatory burden. Indeed, systemic markers of inflammation increase during ageing, which exposes the aged joint to an inflammatory milieu. An alternative explanation is that

**TABLE 3** Comparisons of patients with and without clinical symptoms and with or without inflammatory US findings

	Group 1 Inflammation (no) Symptoms (no)	Group 2 Inflammation (yes) Symptoms (no)	Group 3 Inflammation (yes) Symptoms (yes)	P-value
<i>n</i>	112	191	29	
Age, mean (s.d.), years	69.96 (7.71)	73.38 (8.6)	73.31 (7.2)	0.002
Females, <i>n</i> (%)	68 (60.7)	82 (42.9)	18 (62.1)	0.005
BMI, median (IQR)	26.2 (24.0–28.9)	25.1 (23.7–27.9)	28.7 (24.8–31.2)	0.006
Diabetes, <i>n</i> (%)	6 (5.4)	25 (13.1)	6 (20.7)	0.028
WOMAC, median (IQR)	97.9 (91.7–100)	97.3 (91.7–100)	79.2 (64.6–88.8)	<1.0 × 10 <sup>-6</sup>
Barthel Index, median (IQR)	100 (100–100)	100 (100–100)	100 (95–100)	0.074
NSAIDs, <i>n</i> (%)	17 (15.2)	24 (12.6)	8 (27.6)	0.103
Glucocorticoids, <i>n</i> (%)	2 (1.8)	1 (0.5)	0 (0)	0.12
Presence of osteophytes, <i>n</i> (%)	106 (94.6)	189 (99.0)	28 (96.6)	0.08
Presence of cartilage damage, <i>n</i> (%)	93 (83)	165 (86.4)	28 (96.6)	0.23

Three groups for composite index 1 (pain and swelling). Values are means (s.d.) and median (IQR) except for dichotomous values. Inflammation: US signs of synovial hyperplasia and/or positive power Doppler signal.

**FIG. 1** Examples of abnormal US findings of the knee in the Bruneck population

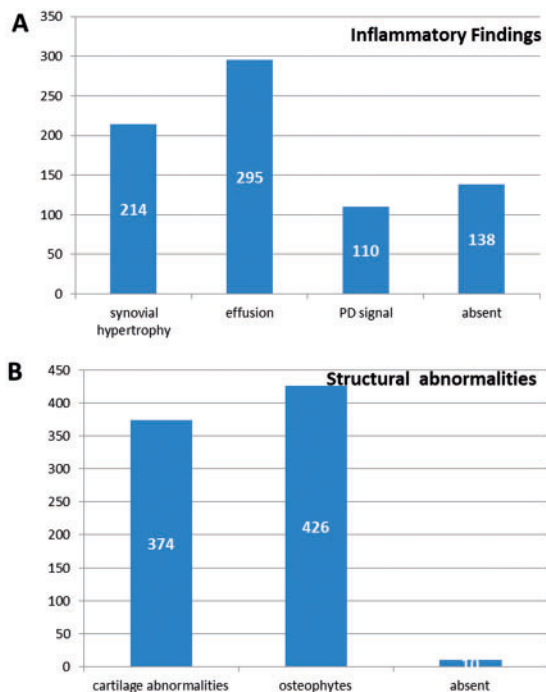
(A–D) show some example of US abnormal findings of the knee in the Bruneck population. (A) Longitudinal suprapatellar scan showing the presence of effusion (asterisks) and hypoechoic synovial hypertrophy (arrowhead). (B) Longitudinal suprapatellar scan showing the presence of a power Doppler signal within the synovial hypertrophy. (C) Longitudinal medial scan showing the presence of osteophytes (arrows). (D) Transverse suprapatellar scan showing femoral hyaline cartilage abnormalities: loss of the anechoic structure, irregularities of the margins and thinning of the layer.

inflammatory lesions result from the accumulation of structural damage during ageing. If so, these lesions represent a tissue response to anatomical changes such as degeneration of articular cartilage. Indeed, we demonstrated a statistically significant association between

inflammation and structural damage at US, which supports this concept.

The association of type 2 diabetes mellitus with inflammatory alterations at US was even more interesting and unexpected. It can be speculated that inflammatory

**Fig. 2** Distribution of all observed ultrasound findings in the total population



(A) and (B) show the distribution of all observed ultrasound findings in the total population. (A) Distribution of inflammatory findings: hypoechoic synovial hypertrophy (SH) in 214 subjects; effusion (E) in 295 subjects, and power Doppler in 110 subjects. In 138 cases no inflammatory abnormalities were present. (B) Distribution of structural findings: cartilage abnormalities (374 subjects) and osteophytes (426 subjects). In 10 cases no structural abnormalities were found.

lesions at US reflect the inflammatory state of diabetic individuals, which arises, at least in part, from the production of inflammatory mediators by adipose tissue, and which is considered to be of seminal importance in the triggering of insulin resistance. In this context, it is interesting that a recent analysis of the Bruneck cohort addressing the development of OA identified diabetes as an independent predictor for knee arthroplasty [10].

In addition to the higher incidence of inflammatory abnormalities in diabetic individuals, it is of interest that these subjects also had a higher BMI that, being associated with overweight, may also influence the occurrence of inflammation in a weight-bearing joint such as the knee.

It remains speculative whether inflammatory and structural abnormalities at US constitute signs of OA, because this study was not performed on an OA population cohort, but is based on an originally healthy population sample. Several points of evidence, however, support such a concept: inflammatory abnormalities coincided with structural abnormalities of the cartilage and bone in this study, suggesting that these findings are not spurious but are indeed

linked to deterioration of joint architecture. Furthermore, an association with symptomatic knee joint involvement was observed, suggesting that although many of these changes remain subclinical, their presence increases the likelihood of developing symptomatic joint disease. And finally, inflammatory lesions are the major precipitators of symptoms and progression to joint failure and arthroplasty in patients with OA [16, 17]. In fact, inflammation is currently being studied to better explain the pathogenesis of OA [19, 20].

The strategy to focus on the presence or absence of knee complaints in this cohort while not addressing their side specificity is a limitation of this study. Hence, we cannot answer whether uni- or bilateral involvement would make a difference with respect to symptoms. However, we have focused on a per patient rather than per joint analysis in this cohort study. Therefore, we analysed both knee joints (not just one knee joint) by US and present all results as the sum of the pathologies in both knee joints, which we think is more relevant from the patient perspective. This approach also allowed us to get a more comprehensive picture of the patients' structural burden of disease as well as their global impairment with respect to signs, symptoms and function related to knee joint disease.

In summary, these data show the abundance of inflammatory lesions in the knee joints of the elderly population. This finding may revise our understanding of joint disease during ageing, in particular of the development of OA, which is almost exclusively confined to aged individuals in the absence of other biomechanical factors. Inflammation, if present, may be the key trigger facilitating the progression from asymptomatic to symptomatic joint disease in such a population. The observation that NSAIDs work in OA supports this concept, as these drugs primarily inhibit inflammation and not the structural changes of OA.

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