Prevalence of chondrocalcinosis in Italian subjects from northeastern Italy. The Pro.V.A. (PROgetto Veneto Anziani) Study

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ABSTRACT

Objectives. *To undertake an epidemiological survey of the prevalence of radiological chondrocalcinosis (CC) of the lower limbs in the elderly Italian population of the Pro.V.A. study.*

Methods. *Knee and pelvic basin radiographs were performed on 3099 subjects aged 65 and older, residing in the Veneto Region of Italy (Rovigo and Camposampiero areas). Two readers independently analysed the knee, coxofemoral and pubic symphysis x-rays of a consecutive sample of 1629 subjects according to Altman. Some laboratory indexes, such as serum parathyroid hormone (PTH), vitamin D (vit D), bone alkaline phosphatase (bALP), deyidroepiandrosterone (DHEA), urinary CrossLaps (XL), and inflammatory biomarkers were evaluated. Quantitative variables were summarised as mean ± standard deviation and qualitative ones as distributions. Unpaired t-test was used to compare mean values among groups for normally distributed variables, and non-parametric Mann-Whitney test for non normal variables.*

Results. *CC was found in 169 (mean age 78.2±8.0 yrs) out of the 1629 subjects studied (10.4%). After adjusting for the sex and age structure of the target population, the prevalence was 10.0%. CC was more often observed in women than in men (M: 7.0%; F: 12.8%, p=0.0002), and increased in occurrence with age, rising from 7.8% in subjects aged 65–74 yrs, to 9.4% in those aged 75–84 yrs, and to 21.1% in subjects older than 85 yrs. The knee was the most prevalent location since it was affected in 94.1% of all the subjects with CC, in particular the right limb. Knee CC was bilateral in 71.7% of the affected patients. The occurrence of rheumatic disorders did not differ significantly between the subjects with CC and those without (rheumatoid arthritis 0.59% vs. 0.48%, p=ns).*

Conclusions. *Although the detection of CC was limited to few joints with the knee being the most affected location, our study confirms the frequent presence of CC at different sites, in keeping with the possible role of systemic factors. Articular CC is an age-related disorder, which could partly explain the prevalence discrepancies reported by various studies. The prevalence of CC found in our survey based on standardised x-ray reading was high, suggesting that CC could be an underdiagnosed disease in the absence of radiographic investigation.*

Introduction

Chondrocalcinosis (CC) is characterised by radiological calcification of articular fibro or hyaline cartilage, mainly due to intra-articular deposition of calcium pyrophosphate dihydrate (CPPD) crystals. In most cases it is asymptomatic and may be observed as an incidental radiographic finding. In other occasions it may be associated with acute or chronic arthropathy, in which case the typical CPPD crystals are found in the synovial fluid (1). While CC is a common pathological finding easily visualised on x-rays, large population studies are relatively few and no definite data are available concerning its frequency in most countries. According to the Framingham survey, which assessed subjects over 63 years, the prevalence of knee CC in the US is 8.1% (2). The HABC (Health, Aging, and Body Composition Study, subjects ages 69–80 yrs) and BOKS (Boston Osteoarthritis Knee Study, subjects' age 47–93 yrs), both carried out in Boston, report a prevalence of 18.5% and 9.0%, respectively (3). In European studies prevalence ranges from 7.0% in the UK (4) to 10.0% in Spain (5). The only available data in Italy are those by Salaffi *et al.*, who obtained information by questioning subjects with musculoskeletal symptoms in a population from Central Italy (6).

In order to investigate the prevalence of radiographic CC in knees, hips and pubic symphysis, a large population-based survey was carried out in elderly Italian subjects living in northeast Italy.

Patients and methods

The Pro.V.A. (Progetto Veneto Anziani) Study is a large observational community-based cohort survey on 3099 subjects aged 65 and older (1245 males and 1854 females), residing in the Veneto Region (Rovigo and Camposampiero

areas, in northeast Italy). The cross-sectional phase began in 1995 and ended in 1998, while the longitudinal one still is ongoing.

The study was designed to assess the functional status and the prevalence of disability of a representative sample of the Italian population of the Venetian Region (7). All the participants were interviewed at home and subsequently referred to their local hospital for a detailed medical evaluation. All underwent biochemical assessments and x-rays of knees and pelvis were taken. Special transportation was provided for the disabled. Home visits by nurses and physicians were arranged for the homebound and severely disabled, in which case x-rays were taken in mobile-units. The study was approved by the local research ethic committee and informed consent was obtained from all the participants.

Patients

The prevalence of CC was investigated in the present work in a subpopulation of the Pro.V.A. Study cohort, consisting of 1629 consecutive subjects of both sexes (42% males, 58% females) aged 65 or older (mean 75.3±7.3 yrs, males 75.8±7.6 yrs, females 74.9±7.0 yrs). No exclusion criteria was used.

Laboratory investigations

A fasting blood sample was obtained by acupuncture from 99% of the subjects and routine biochemical assessments were performed at the local hospital. The more complex investigations such as determination of serum parathyroid hormone (PTH), vitamin D (vit D), bone alkaline phosphatase (bALP), dehydroepiandrosterone (DHEA), and urinary CrossLaps (XL) levels were performed at the Central University Laboratory.

X-ray reading

All the x-rays were made with standardised procedures, focus to film distance 100 cm, 55 kV, 8 mA/s. Anteroposterior projection of the hip and extended knee were performed in orthostatic position. When disabled patients were being assessed, the different position (seated or lying) was recorded. The x-ray reading was performed centrally by specifically trained expert readers according to Altman (8). CC was recorded as present or absent in the medial and lateral joint spaces at the knee level, and in the pubic symphysis, the sacroiliac and the coxofemoral spaces at the hip level. Only x-ray detectable, linear calcifications typical of CPPD deposition were taken into consideration.

Statistical analysis

Quantitative variables were summarised as mean ± standard deviation and qualitative ones as frequency distributions. The sex- and age-standardised prevalence was estimated using the direct standardisation method performed on the target population structure. Unpaired *t*-test was used to compare mean values among groups for normally distributed variables, and non-parametric Mann-Whitney test for non-normal variables. Chi square test was applied to compare categorical distributions. A *p*-value lower than 0.05 was considered significant. All statistical analyses were performed using SAS Statistical Software Package version 9.1 (SAS Institute, Cary, NC, USA).

Table I. General characteristics and laboratory features in 1629 subjects, 169 with chondrocalcinosis (CC) and 1460 without CC (no-CC).

Variable	CC n=169	no-CC n=1460	*p*-value	Age-adjusted *p*-value
Age (yrs)	78.2 ± 8.0	74.9 ± 7.1	0.0001	
Females (%)	71.6	56.5	0.0002	0.002
Weight (kg)	67.4 ± 12.6	69.7 ± 12.8	0.0003	ns
Height (cm)	156.2 ± 8.9	158.4 ± 9.2	0.0004	ns
BMI (kg/m^2)	27.6 ± 4.7	27.8 ± 4.6	ns	ns
Knee OA (%)	28.4	18.5	0.002	0.05
Hip OA (%)	10.1	9.5	ns	ns
Calcium (mg/dl)	9.3 ± 0.5	9.5 ± 0.5	0.0005	0.0003
Iron (mcg/dl)	88.1 ± 27.8	85.7 ± 28.7	ns	ns
Albumin (mg/dl)	4.3 ± 0.4	4.2 ± 0.4	0.0009	0.009
ALP (U/l)	86.0 ± 40.9	87.0 ± 32.7	ns	ns
Urea (mg/dl)	41.0 ± 13.9	43.7 ± 13.3	0.01	ns
Uric Acid (mg/dl)	5.4 ± 2.2	5.3 ± 1.4	ns	ns
ESR (mm/h)	19.8 ± 18.9	22.5 ± 18.8	ns	ns
Fibrinogen (mg/dl)	355.7 ± 100.8	352.2 ± 90.7	ns	ns
PTH (ng/l)	39.2 ± 22.9	43.6 ± 22.4	0.02	ns
Vit D (nmol/l)	87.4 ± 58.2	74.7 ± 58.0	0.01	ns
bALP (U/l)	19.4 ± 14.6	20.8 ± 15.8	ns	ns
DHEA (micromol/l)	2.1 ± 1.7	1.7 ± 1.4	ns	ns
CrossLaps/Cr (mg/mol)	324.9 ± 209.5	356.0 ± 266.3	ns	ns

Results

The response rate to x-rays was 81.3% for the female population and 85.7% for the males. The main population characteristics and results are outlined in Table I. CC was found in 169 (mean age 78.2±8.0yrs) out of the 1629 subjects studied (10.4%, M: 7.0% and F: 12.8%, *p*=0.0002). After adjusting for the sex and age structure of the target population, the prevalence was 10.0%, 5.4% and 13.8%, for the population as a whole, males, and females, respectively. When patients were subdivided into three different age groups, CC percentage varied remarkably and increased with age: 7.8% in 65–74 yrs (M: 4.2%, F: 10.3%), 9.4% in 75-84 yrs (M: 5.2% and F: 12%) and 21.1% in >85 yrs (M: 16.9% and F: 26.1%) (Fig. 1). The occurrence of rheumatic disorders such as rheumatoid arthritis did not differ significantly between subjects with CC and those without (0.59% *vs*. 0.48%, *p*=ns), while clinical knee osteoarthritis (OA) was more prevalent in the CC group (adjusted p=0.05) (Table I).

With regard to the main anthropometrical features, CC patients showed lower values than no-CC for weight (67.4±12.6 *vs*. 69.7±12.8 kg, *p*=0.0003) and height (156.2±8.9 *vs*. 158.4±9.2 cm, *p*=0.0004), while no difference was observed for body mass index (BMI). With regard to laboratory findings, no

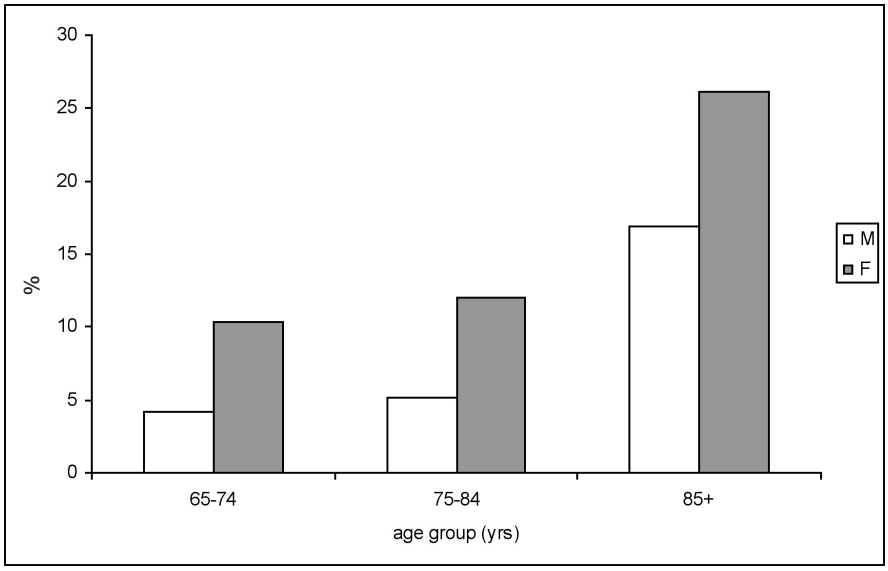

Fig. 1. Prevalence of CC in the Pro.V.A. Study by sex and age groups.

difference between the two groups was found at the univariate analysis for iron, total and bALP, uric acid, fibrinogen, DHEA and XL/Cr, while differences were observed for the levels of: calcium, higher in no-CC (9.5±0.5 ng/dl) than in CC (9.3±0.5 mg/dl, p=0.0005); albumin, higher in CC (4.3±0.4 mg/dl) than in no-CC (4.2±0.4, p=0.0009); urea, higher in no-CC (43.7±13.3 mg/dl) than in CC (41.0±13.9 mg/dl, p=0.01); PTH, higher in no-CC (43.6±22.4 ng/l) than in CC (39.2±22.9 ng/l, p=0.02) and vit D, higher in CC (87.4±58.2 nmol/l) than in no-CC (74.7±58.0, p=0.01). It is noteworthy that, when all the data were adjusted for age, the only differences persisting between the two groups were those concerning calcium and albumin. With respect to CC location, knees were affected in 159 of the subjects (94.1%), 71.7% of these bilaterally. In unilateral involvement, the left knee was less affected (10.7%) than the right one (17.6%). Moreover, the lateral side was preferentially involved both in the left (18.8%) and in the right knees (16.2%) as compared to medial side (left 6.2% and right 4.9%, respectively). With regard to the frequency of CC location in the pelvic basin, the pubic symphysis was affected in 56/169 subjects (33.1%), with 8 showing isolated involvement, and the coxofemoral joint in 6/169 subjects (3.5%), one with isolated involvement. Sacroiliac CC was found in 3/169 patients (1.8%), with isolated involvement in one.

Table II. CC in epidemiological studies: comparison with the Pro.V.A Study.

Authors	Study (country)	Subjects (n)	Age (yrs)	location	%
Felson *et al*. 1989	Framingham (US)	1402	63–93	K	8.1
Sanmarti *et al*. 1993	Spain	261	≥ 60	K (W)	10.0
Neame *et al*. 2003	United Kingdom	1727	>40	K	7.0
Neogi *et al*. 2006	HABC	265	69–80	K	18.5
	BOKS* (Boston, US)	230	47–93	K	9.0
Neame *et al*. 2003	United Kingdom	1727	>40	K	7.0
Zhang *et al*. 2006	BOA§ (Beijing, China)	(2506) 1787	≥ 60	K (W)	2.3
Ramonda *et al*. 2009	Pro.V.A Study (Italy Venetian Region)	1629	≥ 65	K, (H, PS, SI)	10.0

K: knee; W: wrist; H: hip; PS: pubic symphysis; SI: sacroiliac.
Only the prevalence of knee CC is reported in the Table.
*BOKS: Boston Osteoarthritis Knee Study; HABC: Health, Aging, and Body Composition Study; §BOA: Beijing Osteoarthritis Study

Discussion

Despite its high prevalence, only a few epidemiological studies worldwide have investigated the presence of radiographic CC in the general population (Table II). The CC prevalence observed in our survey (10.4%) was within the 7.0 to 18.5% range reported by other European and American epidemiological studies (2-5). As a lower prevalence of knee CC, 1.8% in men and 2.7% in women, was reported by a recent Chinese study (9), it has been hypothesised that there could be racial implications and environmental risk factors, suggesting the need for further studies in subjects of diverse ethnicities and living in different geographic areas (10-11). In agreement with previous studies, CC was more frequent in our female participants and increased with age in both sexes, ranging from 7.8% in 65–74 yrs to 9.4% in 75–84 yrs and 21.1% in >85 yrs (M 16% and F 26%). As expected, the knee was the most affected joint, since CC was found in 94.1%, alone or associated with CC at other sites. In 71.7% of the cases knee, CC was bilateral and, when unilateral, the left knee was less involved than the right one. Interestingly, the lateral compartment was more commonly affected in both knees. It is difficult to compare these data with others since, to our knowledge, very few epidemiological studies have addressed the type of CC distribution in knee joints (2). The Framingham study, which assessed the frequency of unilateral and bilateral CC, reported a more frequently affected lateral compartment, in accordance with our own findings (2).

With regard to other possible locations, since the Pro.V.A. study patients underwent knee and pelvis radiographs, we were able to investigate the presence of CC also in the pubic symphysis, sacroiliac and hip joints. The most affected among these was the pubic symphysis, in which CC was found in

33.1% of cases, with 8 showing isolated involvement, followed by the hip joint (3.5%) isolated in one case, and sacroiliac (1.8%), isolated in one case. The presence of CC in the pelvic joints has been reported in very few studies (12). However, it is possible that the prevalence found in our study is underestimated. This may be due at least in part to technical reasons, because coxofemoral CC is difficult to detect in the presence of severe joint space narrowing, as observed in the case of concomitant osteoarthritis. Another infrequent CC location is the cervical spine that requires CT scan analysis for diagnosis and is associated with acute attacks of neck pain and functional impairment. This location was not investigated in the present study but its presence in an Italian elderly population was reported by Salaffi *et al*. (13).

Although assessment for CC was carried out in only a few joints, our study confirms the frequent occurrence of CC at different sites, in keeping with the possible role of systemic factors. Some of these, such as calcium, iron, and bALP (14), are well known and have been investigated in our study. At the univariate analysis, a difference between the CC and the no-CC groups was found for vitamin D and albumin levels, both higher in the CC group, and for PTH and calcium levels, both lower in CC subjects. After adjustment for age, no differences were however observed between the CC and no-CC groups with regards to these factors, with the exception of calcium and albumin levels, although they both remained within the normal range. The higher vitamin D level as well as the lower calcium value in the CC population are intriguing findings, and they may be related. To our knowledge, the data available in the literature do not support the hypothesis that their role is crucial in the pathogenesis of CC. Moreover, in our study, calcium levels refer to total calcium and not to the ionised fraction which is more directly concerned with calcium homeostasis. These findings seem to imply that the vitamin D-serum calcium axis may be a possible risk factor in the pathogenesis of CC in the elderly. Finally, as has recently been suggested (15-17), aspects other than those investigated in the present study, among which magnesium levels, may be relevant.

In conclusion, the prevalence of intra-articular CC reported by us is at the upper level compared with that found in other Western countries (11), with the age-related incidence having a role in the reported discrepancies. The high prevalence found in our study, based on standardised x-ray readings, suggests that CC could be an underdiagnosed disease in the absence of radiographic investigation.

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