Generalized Osteoarthritis in Women: Pattern of Joint Involvement and Approaches to Definition for Epidemiological Studies

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ABSTRACT. ***Objective.*** To ascertain whether clustering between joint sites in osteoarthritis (OA) is more common than would be expected simply from the rising prevalence of the disorder with age, and to explore a definition of generalized OA (GOA) by determining the pattern of joint group involvement, in a population sample of peri and postmenopausal women.

Methods. Radiographs of the hands, knees, and hips were obtained in a population sample of 702 women aged 45 to 64 years. Distal interphalangeal, proximal interphalangeal, carpometacarpal, knee, and hip OA were assessed using the Kellgren-Lawrence grading system. Logistic regression was used to test for overall clustering of OA between joint sites, and log linear models were used to study the patterns of association between different sites.

Results. Multiple involvement of the 5 joint groups studied occurred significantly more frequently than could be expected by chance alone ($\chi^2 = 52.3$, df = 5, $p < 0.001$), and this clustering remained significant after age adjustment ($\chi^2 = 26.1$, df = 5, $p < 0.001$). Thresholds could be defined for the number of involved joint groups that distinguished a polyarticular subset of OA. These thresholds varied with age and the radiographic cutoff at which OA was assigned. Thus, for grade 2+ disease, GOA could be defined by involvement of 2 or more joint groups at age 45–47 years, but required involvement of all 5 joint groups at age 60–64 years. Symmetry within joint groups was the most pronounced feature in the pattern of joint involvement in the sample as a whole, with associations between different joint groups being substantially weaker than those for symmetrical bilateral involvement of a particular joint.

Conclusion. There is a clear tendency towards polyarticular OA among women aged 45–64 years. However, there is no single threshold number of joint sites that can be used to define GOA. The pattern of joint involvement in OA is primarily symmetrical, and this pattern strongly suggests a systemic etiology in this subset of postmenopausal women. (*J Rheumatol 1996;***23:1938–42**)

Key Indexing Terms:
EPIDEMIOLOGY OSTEOARTHRITIS MENOPAUSE JOINT INVOLVEMENT

Osteoarthritis (OA) is the commonest joint disorder to affect Western populations, and is a major cause of disability and ill health[1]. The term OA refers to the endstage of a multifactorial process of joint failure characterized by cartilage loss and subchondral bone reaction[2]. The causes of OA fall into 2 broad groups — those influencing generalized susceptibility to the process, and those causing biomechanical instability or stress at specific joint sites. The concept of generalized susceptibility is supported by studies indicating a subset of patients with polyarticular disease known as "generalized osteoarthritis" (GOA)[3]. However, the pattern of joint involvement found among affected individuals has not been clearly established in population based epidemiological studies, and the existence of GOA remains questionable. Although many studies have commented on multiple joint involvement among patients with OA referred to hospital[4–11], the prevalence of disease at any given joint site increases steeply with age[12], and it is not clear that clustering between sites is greater than would be expected from the effects of age. We addressed these issues in a population based survey of women aged 45–64 years.

MATERIALS AND METHODS

The study sample comprised 1003 women aged 45–64, selected from the age-sex register of a large general practice in Chingford, East London.

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Supported by a grant from LORS NETRHA and by the Medical Research Council of Great Britain.

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Submitted November 20, 1995 revision accepted May 15, 1996.

Women from this practice are similar to the UK general population in terms of weight, height, body mass index, and smoking characteristics[13]. Each woman was asked to have a radiographic examination of both hands, knees, and hips. All radiographs were obtained under standardized conditions at the same examination. Posteroanterior views of the hands and anteroposterior views of the knees and hips were taken. Knee radiographs were obtained with the subjects standing in full extension, and hip films with 15° of internal rotation. All radiographs were assessed by a single trained observer blind to the identity of the subjects; scoring at different joint sites was performed with the observer unaware of the scores recorded on other films. OA in the peripheral joints was graded according to the scheme devised by Kellgren and Lawrence, using the figures and legends of the original atlas[14]. Where necessary, these were supplemented by written rules to make the original descriptions more explicit. At the hand and knee, the definitions of Kellgren-Lawrence grades were as follows: Grade 0: no features of OA; Grade 1: minute osteophyte, doubtful significance; Grade 2: definite osteophyte, unimpaired joint space; Grade 3: moderate diminution of joint space; Grade 4: joint space greatly impaired with sclerosis of subchondral bone. The reproducibility of the Kellgren-Lawrence grading system at the hip is worse than that at the hand and knee, and we therefore adopted the modification proposed by Croft, *et al*[15]. Thus, the presence of definite osteophytes at any site resulted in a score of 2, while the definite presence of both osteophyte and joint space narrowing gave a score of 3.

Twenty-five joints in 5 groups were assessed in each woman: 8 distal interphalangeal (DIP), 10 proximal interphalangeal (PIP) (which included the thumb IP joint), 2 thumb bases, [carpometacarpal (CMC)], 2 knees, and 2 hips. The within-observer reproducibility of radiographic assessment at these joint groups has been assessed and shown to be sufficient for epidemiological use (within-observer kappa statistics > 0.75)[16,17].

To test for overall clustering of joint involvement, we first derived estimates for the prevalence of OA in at least one joint of each group. We then applied a binomial model to calculate the numbers of women in the study sample who would be expected to have involvement of 0,1,2,3,4, or 5 joint groups. This model assumed that the occurrence of disease in different groups in the same person was independent, e.g., that involvement of a DIP joint made no difference to the probability that the knee or hip was affected. Finally, we compared the observed frequencies of joint group involvement with those expected, and assessed the significance of any deviation from the expected distribution using a χ^2 test. This procedure was repeated with age adjustment in a logistic regression model[18]. The observed to expected (O:E) ratio for involvement of multiple joint groups was used to explore thresholds that might be used to define GOA.

We initially explored the pattern of clustering between different joint groups using classical cluster analysis[19]. The strength of associations between different joint groups was analyzed using logistic regression. For each pair of joint groups, the relationship was summarized by an odds ratio (OR) (the relative odds of having OA in one group if the other group also had OA) using a log-linear model[20]. In addition we tested for symmetrical involvement of the hip and knee using a similar technique.

RESULTS

Complete radiographic information was obtained on 702 women (70%) and the analysis was restricted to this subset. Figure 1 shows the prevalence of grades 2+ and 3+ radiographic OA at different joint sites with advancing age among these 702 women. The sites most frequently involved were the DIP and CMC joints of the hand. The prevalence of grade 2+ involvement of the DIP joint rose from 5% at age 45–48 years to 54% at age 63–65 years. There was also a marked increase in the prevalence of PIP and knee involvement over the 20 year age span of the study. A similar pattern was observed for the prevalence of grade 3+ OA, but the prevalence was substantially lower for all joint sites in each age category.

Table 1 shows the distribution of the number of joint groups involved per person and the expected frequencies, before and after age adjustment and assuming no clustering within individuals. Data are presented using both a grade 2+ and grade 3+ radiographic cutoff for definition. Using the grade 2+ cutoff, 66 of the 342 women with OA in any joint had disease in 3 or more joint groups, compared with 23 expected. This clustering of joint group involvement was highly statistically significant ($\chi^2 = 52.3$, df = 5, $p < 0.001$), and remained significant ($p < 0.001$) after adjusting for age. When the grade 3+ cutoff for OA was used, 8 of the 103 women with involvement of any joint had disease in 3 or more groups, compared with none expected. Again, this clustering was statistically significant both before ($p < 0.001$) and after ($p = 0.004$) age adjustment.

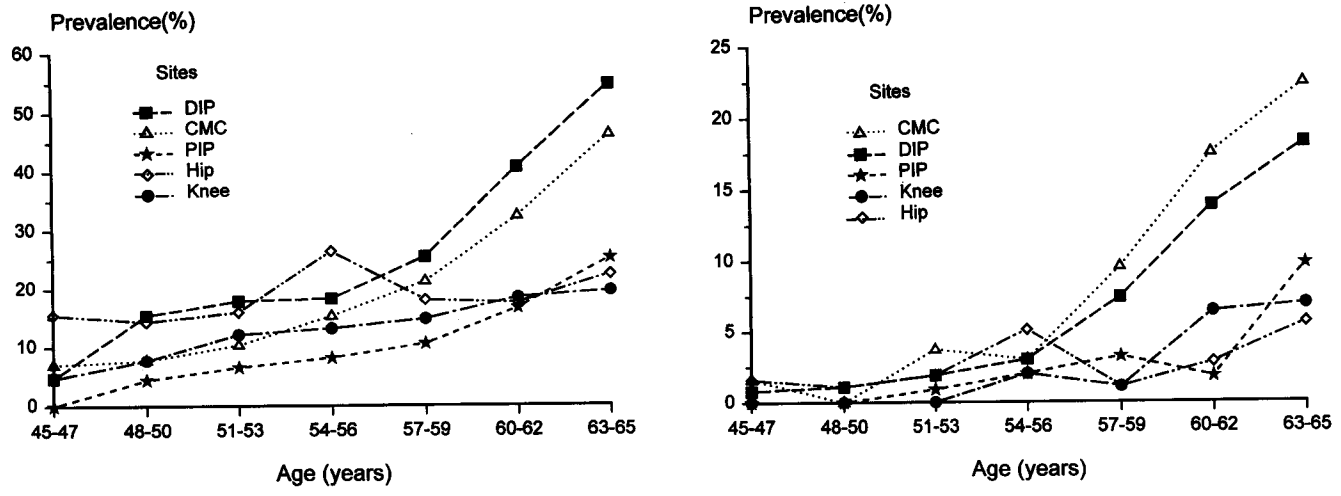

Figure 1. Prevalence of OA in at least one joint site among 6 joint groups in 702 women aged 45–64 years: (A) Kellgren-Lawrence grade 2+ and (B) Kellgren-Lawrence grade 3+. Figures in parentheses are numbers of women in each age category.

Table 1. Observed and expected number of joint groups involved by OA in 702 women aged 45–64 years; data are provided for 2 radiographic cutoffs (Kellgren-Lawrence grade 2+ and grade 3+).

Number of Joint Groups	Radiographic Definition of OA					
	Grade 2+			Grade 3+		
	Observed	Expected		Observed	Expected	
		Nonadjusted	Age adjusted		Nonadjusted	Age Adjusted
0	360	285	310	599	563	578
1	193	284	250	72	123	107
2	83	110	108	23	10	16
3	52	21	29	7	0	1
4	11	2	5	1	0	0
5	3	0	0	0	0	0
χ^2		52.3	26.1		27.2	14.0
df		5	5		4	4
p		< 0.001	< 0.001		< 0.001	0.004

Maximum number of joint sites = 5 (DIP, PIP, CMC, knee, and hip).

Table 2 shows the threshold numbers of joint groups that needed to be involved in women of different ages, in order that the O:E involvement ratio fell above various critical values (1.5, 2.0, 3.0). The table provides thresholds for grade 2+ disease, and also shows the number of women within each age category who would conform to a definition of GOA on this basis. There was no single threshold for definition of a polyarticular subset. With an O:E ratio ≥ 1.5, involvement of at least 2 joint groups was required at age 45–47 years, rising to all 5 groups by age 63–65 years. This approach would have defined 52 women as having GOA in the sample overall. Within age bands, the threshold numbers of joint groups remained similar at greater O:E ratio cutoffs. In a parallel analysis for grade 3+ disease, a similar pattern was observed, although the threshold numbers of joint groups were lower, and only 15 women were categorized as having GOA at an O:E threshold ≥ 1.5.

The pattern of clustering for different joint groups was initially studied using classical cluster analysis. Figure 2 gives a diagrammatic representation of the results. It plots the hierarchy of association between different joint groups involved by grade 2+ OA, with the strongest association (DIP and PIP joint involvement) closest to the origin, and the weakest (hip with hand/knee disease) at the other extreme. However, this technique does not permit quantitation of the strength of associations, or of their statistical significance. We therefore explored these associations further in a log-linear model where OR was calculated for involvement of a joint group if another group also had OA. Table 3 shows these OR for grade 2+ OA. The strongest association was found between DIP and PIP disease [OR 31.7, 95% confidence interval (CI) 13.8–72.5]. Associations between hand joint groups and knee disease were statistically significant, but of lower magnitude [DIP 1.8 (1.1–3.1), PIP 2.4 (1.3–4.4), CMC 2.4 (1.5–4.1)]. Hand–hip associations

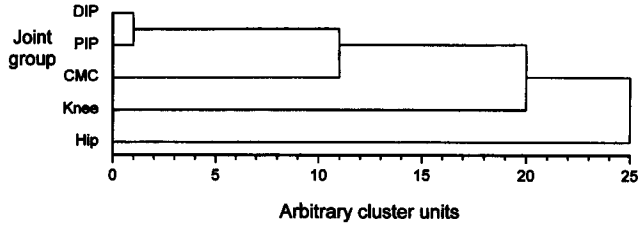

Figure 2. Results of cluster analysis examining pattern of association between joint groups involved by grade 2+ OA. The strongest associations are closest to the origin, and the weakest lie furthest to the right.

Table 2. Thresholds for the definition of GOA and number of women meeting such definitions, by age group for radiographic grade 2+ disease.

Age (yrs)	Threshold No. of Joints			No. of Women Affected			Total No. of Women
O:E	1.5	2.0	3.0	1.5	2.0	3.0	
45–47	2	–	–	6	–	–	129
48–50	3	3	3	3	3	3	91
51–53	3	3	3	6	6	6	107
54–56	4	4	4	3	3	3	99
57–59	3	3	4	12	12	2	95
60–62	3	4	4	21	7	7	109
63–65	5	5	5	1	1	1	72

O:E = Cutoff for ratio of observed to expected numbers of joint groups involved.

Table 3. Pattern of multiple joint involvement among 702 women aged 45–64 years using Kellgren-Lawrence grade 2+ radiographic cutoff.

	Joint Groups			
	PIP	CMC	Knee	Hip
DIP	31.7 (13.8–72.5)	2.3 (1.5–3.5)	1.8 (1.1–3.1)	1.1 (0.7–1.7)
PIP		4.8 (2.7–8.4)	2.4 (1.3–4.4)	0.7 (0.3–1.4)
CMC			2.4 (1.5–4.1)	1.4 (0.8–2.2)
Knee				2.1 (1.2–3.4)

Figures are OR with 95% confidence intervals, after adjusting for age in seven 3-year groups.

seemed the weakest of all. The results of the cluster analysis and log-linear modelling revealed similar results for the pattern of grade 3+ disease.

Symmetry of joint involvement was examined in a separate log-linear model. We have reported the strongly symmetrical pattern of hand joint involvement[21]. Knee and hip disease were also markedly symmetrical. Thus, involvement of one knee greatly increased the likelihood of involvement of the contralateral knee (OR 119.5; 95% CI 21.4–665.8). The corresponding OR for bilateral hip disease was 54.7 (95% CI 12.6–237.4).

DISCUSSION

We studied a population sample of peri and postmenopausal women to examine the pattern of joint involvement in OA. Our results strongly support the existence of a subset of women with a syndrome of polyarticular disease. Multiple joint involvement occurred more frequently than would be expected by chance alone, or simply from the increasing prevalence of involvement at any one site with advancing age. However, there was no single threshold number of joint groups affected at which the entity of generalized OA could be defined. If such a threshold was arbitrarily set where the observed to expected ratio of involved joint sites reached particular values (for example 1.5, 2.0, or 3.0), the threshold changed with increasing age, and with the radiographic criteria for involvement of an individual joint. Finally, we examined the clustering within and between different joint groups in OA to show this is predominantly a symmetrical disorder, with associations between joint groups (such as the DIP, knee, and hip) being an order of magnitude weaker than those for symmetrical involvement of joints within a group.

Caution is required in generalizing these findings to an older or male population. We only studied women aged 45–64 years, a group in whom clinical studies suggest the greatest frequency of this polyarticular variant of OA[3,7,9]. A further limitation was the lack of data on the patellofemoral compartment of the knee joint and the first metatarsophalangeal joint, sites commonly involved in OA[12,22]. Finally, our definition of OA was based upon the Kellgren and Lawrence grading system. Although we and others have suggested alternative approaches for the assessment of OA at various joint sites[23,24], we felt that an explicit version of the 5-point Kellgren-Lawrence scale was most appropriate for this analysis. This permitted a consistent threshold (grade 2+ or grade 3+) for disease definition at each site, and ensured that similar criteria were applied across the sites. It was reassuring that the results were broadly similar whether a grade 2+ or grade 3+ threshold was adopted, although the threshold numbers of joint groups for grade 2+ disease were higher than for grade 3+ disease. Repeatability error was minimized by training of the observer, and where present, would normally be expected to obscure associations between sites, rather than throw up spurious associations.

A specific clinical subset of OA in which multiple joint groups were involved was initially proposed by Kellgren and Moore[3]. They suggested that the frequency distribution of joint involvement was bimodal, such that a specific subtype of OA, designated primary GOA, could be identified. In later work, they suggested this variant could be defined by the involvement of 3+ or 5+ joint groups, but provided little rationale for these thresholds[25].

Although several subsequent studies of hospital patients have documented the female preponderance and symmetrical pattern of involvement in polyarticular OA, there has been only one population study to determine whether GOA comprises a specific disease subset. In that study, which was confined to the hand, O'Brien, *et al* studied 1334 men and women aged 21 years and over from New Haven[26,27]. They examined the frequency distribution of affected joints and, finding no evidence for bimodal distribution, concluded that no GOA subset exists. In contrast with the New Haven study, we found unequivocal evidence that polyarticular joint involvement in OA occurs more frequently than would be expected on the basis of age and chance.

We were unable, however, to identify a simple, clinically useful definition of GOA in women, and our results highlight several conceptual problems that are not widely recognized. First, there is no universal statistical cutoff in the total number of joint groups involved. We were able to define various thresholds according to number of joint groups involved, at which the O:E ratio of numbers was greater than 1.5, 2.0, or 3.0. For each of these cutoffs, the definition changed with advancing age and, to a lesser extent, with the sensitivity and specificity of the cutoff. Second, the addition of symmetry to number of joint groups as a criterion may alter the threshold. Finally, the generalizability of our observations is limited not only by the age and sex structure of our sample, but by the number of radiographs obtained. In surveys where radiographs are obtained on a smaller number of joints, the number of joint groups required will be correspondingly reduced.

We found the expected hierarchy of clustering between different joint groups. Thus, DIP disease was linked to PIP,

thumb base, and knee disease, while there appeared to be a less marked association between knee and hip disease[7]. However, the single greatest influence on pattern of joint involvement in this, and in our previous study[21], was symmetry. The tendency towards symmetrical involvement among all the joint groups examined was considerably greater than any of the associations between groups. This finding does not support an exclusively mechanical etiology for OA in these joint groups. It is more in keeping with a metabolic[28] or neuroendocrine[29] mechanism. It has been postulated that antidromic release of neuropeptides might account for the symmetry observed in rheumatoid arthritis. A similar mechanism might apply in this variant of OA.

ACKNOWLEDGMENT

We are grateful to the patients and staff at Chingford Hospital, Highams Park Health Partnership, and to Dalbir Nandra and Deborah Fajerman for data entry. The manuscript was prepared by Mrs. Gill Strange.

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