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Editorial

Has Paget's bone disease become rare?

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1. Introduction

Paget's bone disease is a focal metabolic bone disease characterized by a major and random increase in osteoclastic resorption and bone remodeling. The distinctive bone structure alterations due to these changes produce abnormalities on standard radiographs including hypertrophy and deformities of the affected bones, irregular sclerosis with a fibrillar or cotton wool appearance, blurring of the difference between the cortex and medullary cavity, increased cortical porosity, and thickening of the bone trabeculae. The initial osteolysis may be visible on radiographs of the skull, as osteoporosis circumscripta, or of the long bones, as a V-shaped lucent leading edge. Picture frame vertebral sclerosis is typical, as well as neural arch involvement, which is demonstrated clearly by computed tomography (CT).

The symptoms of Paget's disease are often delayed. One or more bones may be affected, often in an asymmetrical distribution. The most common sites of involvement are the skull, pelvis, spine, femurs, and tibias. A noticeable proportion of patients may remain asymptomatic, despite having extensive bone alterations in some cases. As a result, Paget's disease may be an incidental finding when imaging studies are obtained or bone turnover markers assayed.

Paget's disease is genetically determined in about one-third of cases. The pattern of inheritance is autosomal and dominant. In the sporadic forms of Paget's disease, various environmental exposures, notably related to lifestyle, may be contributing factors.

In north-western Europe, where Paget's disease was extremely common in the past, dramatic declines have occurred in prevalence, incidence, severity.

2. Changes in Paget's disease epidemiology over time

2.1. Decrease in Paget's disease in Caucasians from northwestern Europe

The first reported change was a decrease in mortality related to Paget's disease, which was particularly noticeable in Britain between 1950 and 1970. Mortality was highest in the cohorts born around 1880 [1]. In 31 British towns in the 1970s, the prevalence of radiographic Paget's disease in admitted patients older than 55 years was 5% overall, 6.2% in males, and 3.9% in females [2]. In addition, the prevalence varied substantially across towns, from 8.3% in Lancaster (Lancashire) to 2.3% in Aberdeen. A similar study done in 10 British towns in the 1990s revealed a marked decrease in prevalence, to 2.5% among males and 1.6% among females (Table 1) [3]. The declines were largest in Lancashire, in the towns where the prevalences were highest in the earlier study. Thus, in Lancaster, the prevalence was 3.5% compared to 8.3% in the 1970s. In addition, studies in several European towns demonstrated a decrease in the radiographic prevalence of Paget's disease between the late 1970s and the first decade of the 2000s (Table 2) [4,5].

In France, the prevalence of Paget's disease among admitted patients older than 55 years of age was 2.7% in Bordeaux, 2.4% in Rennes, and 2% in Nancy [4]. The prevalence was estimated in Spain at 0.5% to 1%. A 2018 report estimated the prevalence of Paget's disease at 0.1% to 0.2% in the general population [6]. The results of a systematic literature review and metaanalysis demonstrated a significant decline in the incidence of Paget's disease in the 1980s and 1990s; prevalence also diminished significantly in most countries populated by Europeans (odds ratio, 0.64; 95% confidence interval, 0.45–0.91) [7]. However, this marked decline was found neither in Spain nor in Italy, where a recent estimate showed a prevalence of at least 1% in the general population older than 55 years [8,9].

2.2. Decline in the clinical severity of Paget's disease

A systematic literature review of studies published between 1958 and 2014 and including over 4000 patients showed overall frequencies of 38% for bone pain, 10% for fractures, 20% for bone deformities, and 6% for hearing loss [10]. The clinical presentation of Paget's disease has changed over time. The proportion of patients with bone pain increased in recent years from 48% to 65%. In contrast, decreases were seen for fractures, from 11% to 4%, and for bone deformities, from 22% to 10%; and the frequency of hearing loss remained unchanged [10]. A similar decrease in clinical severity was also demonstrated recently in a cohort of patients in Australia, among whom only 36% had symptoms [11]. A comparison of Paget's disease phenotypes in the 1980s versus more recent years showed decreases in the mean number of involved bones from 4.8 to 2.4 and in the mean alkaline phosphatase (ALP) level from 751 to 151 IU/L. During the same period, the age at diagnosis increased from 45 to 65 years. In familial Paget's disease due to *SQSTM1* gene mutations, which is characterized by a younger age

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Table 1
Decline in the prevalence of Paget's disease of bone in Britain between the 1970s and the 1990s [2,3].

Town[a]	1970s			1990s		
	Prevalence in males, %	Prevalence in females, %	Overall prevalence, %	Prevalence in males, %	Prevalence in females, %	Overall prevalence, %
Bath	5.3	4.7	5.0	3.8	1.3	2.2
Cardiff	6.6	3.3	4.9	1.5	1.5	1.5
Carlisle	3.9	1.5	2.7	1.6	0.9	1.2
Lancaster	6.5	10.0	8.3	3.7	3.8	3.7
Newcastle	3.9	2.6	3.2	3.9	2.3	3.1
Portsmouth	5.4	3.9	4.6	2.6	1.7	2.1
Preston	8.6	6.3	7.5	3.3	1.7	2.4
Southampton	6.6	3.6	5.1	3.7	1.8	2.7
Warrington	4.5	3.9	4.2	4.6	1.9	3.1
Wigan	8.1	5.4	6.8	4.2	2.8	3.5

[a] Only the towns also studied in the 1990s are shown.

Table 2
Decline in the prevalence of Paget's disease of bone in Europe between the 1970s and 2000s [4,5].

Town (country)[a]	1970s			2000s		
	Prevalence in males, %	Prevalence in females, %	Overall prevalence, %	Prevalence in males, %	Prevalence in females, %	Overall prevalence, %
Athens (Greece)	0.6	0.3	0.5	0.3	0.3	0.3
Copenhagen (Denmark)	1.4	0.8	1.1	0.4	0.2	0.3
Innsbruck (Austria)	0.7	0.6	0.7	0.1	0.3	0.2
La Coruña (Spain)	1.0	0.9	0.9	0.6	0.3	0.4
Malmö (Sweden)	0.2	0.6	0.4	0.2	0.4	0.3
Valencia (Spain)	0.7	1.9	1.3	0.7	0.2	0.5

[a] Only towns also studied in the 2000s are shown.

at diagnosis and higher number of involved bones, a decrease in clinical severity has also been documented [12]. In patients with *SQSTM1* gene mutations, the secular changes manifested as a 10-year increase in age at diagnosis compared to the affected parents and by a decrease in bone involvement from 37% to 4%, with the total ALP level remaining within the normal range. No guidelines exist in France about the indications of genetic testing for *SQSTM1* mutations. In Canada, there are also no relevant clinical practice guidelines, and the test is not reimbursed by the health insurance system. Testing for *SQSTM1* mutations in the general population is unlikely to be useful, as both sensitivity and specificity are low and, in any case, lower than those of imaging.

3. Geographic variations in the epidemiology of Paget's disease

3.1. Paget's disease is exceedingly rare in Asia

Paget's disease has always been extremely uncommon in Asia. A survey of orthopedic surgeons in Japan found that only $2.8/10^6$ population were affected [13]. The phenotype differs somewhat in Japanese compared to Caucasian patients. Thus, in Japan there is a slight female predominance, with a male/female ratio of 0.86; only 6% of cases are familial; monostotic disease is slightly more common than polyostotic disease; and only 25% of patients have no symptoms. In countries where Paget's disease is uncommon, a bone biopsy is required to establish the diagnosis in about half the patients, and the limited availability of medications licensed for use in Paget's disease can raise therapeutic challenges [13]. Paget's disease is also extremely rare in China, with only 9 reported cases in Chinese individuals so far [14].

The clinical phenotype of Paget's disease in Asians is similar to that in Caucasians regarding age at diagnosis and sex ratio. However, the disease is monostotic in 44% of cases, familial forms are rare, and only 22% of patients experience symptoms.

The very low frequency of Paget's disease in South-east Asia and the massive immigration from that area of the world to the UK has been suggested as a possible contributor to the decline in the prevalence of Paget's disease in the UK [3]. However, 48 cases of Paget's disease in Indians seen over a period of only 9 years was reported recently [15]. In keeping with previous reports, familial forms were very rare and only 21% of cases were symptomatic. Nonetheless, the disease was polyostotic in 87% of patients.

The limited availability of diagnostic investigations in many Asian countries may result in underestimation of the frequency of Paget's disease. Support to this hypothesis comes from a study done in New Zealand, where the incidence of Paget's disease among immigrants from South Asia was similar to that in individuals of European descent [16].

3.2. Paget's disease seems similarly rare in Africa

In Africa, Paget's disease is rare, although the data are limited to anecdotal case reports. However, underestimation is likely, as the prevalence of Paget's disease in the US is 0.7% in both Caucasians and African-Americans [17].

4. May the source of these variations lie in the pathophysiology of Paget's disease?

4.1. Role for environmental factors

A role for environmental factors is often suggested as an explanation to the variations in Paget's disease epidemiology [18]. For instance, river water pollution by arsenic in a pesticide used to treat cotton bales may explain the high prevalence of Paget's disease in the 1970s in Lancashire. Contact with animals has been reported to be a risk factor for Paget's disease and has declined over the last few decades due to increasing urbanization. In addition, improved infection prophylaxis in domestic animals may have played a role. The potential pathogenic effect of the measles virus nucleocapsid remains controversial despite active research [19]. The introduction of the measles vaccine in the US in the early 1960s and subsequently in other countries may have contributed to the

decline in Paget's disease [18]. Other environmental factors such as cigarette smoke [20] and smoke from wood stoves in childhood [21] have also been associated with Paget's disease. Lifestyle changes over time have decreased these exposures.

4.2. Role for genetic factors

The fast pace of the declines in the prevalence, incidence, and clinical severity of Paget's disease is not consistent with a role for changes in genetic influences, such as the appearance of protective genetic factors. Genetic causes such as *SQSTM1* mutations continue to exist and are still transmitted on an autosomal dominant basis. Nevertheless, changes in interactions between the genome and environmental factors may have affected the clinical expression of Paget's disease. In addition, the relative stability of the prevalence and clinical severity of Paget's disease in Italy [22] and Spain [9,23] suggests that the genetic founder effect found in these hot regions may contribute to maintain a fairly constant number of incident cases, thereby limiting the decline seen in other countries.

5. Clinical implications of the decrease in Paget's disease

5.1. Implications for the diagnosis

Widespread access to the most sensitive investigations for Paget's disease can influence the number of incident cases. Patients with limited pagetic lesions or low metabolic activity may have total ALP levels within the normal range. An epidemiological survey conducted by the Mayo clinic from 1950 to 1994 showed an increase in the incidence of Paget's disease followed by a decline [24]. This finding was attributed to the introduction of routine total ALP assays in the early 1970s, resulting in the detection of patients with asymptomatic Paget's disease, followed by attrition of the reservoir of incident cases.

A recent systematic literature review and metaanalysis found that sensitivity for detecting Paget's disease ranged from 69% to 100% for total ALP, 82% to 100% for bone ALP, 94% to 100% for urinary N-terminal telopeptide of type 1 collagen (NTX), and 77% to 100% for N-terminal propeptide of type 1 procollagen (P1NP). This last assay is not widely available but may be the best test for monitoring patients with Paget's disease [25]. Among imaging studies, the highest sensitivity for detecting Paget's disease, over 98%, is noted with whole-body 99 m technetium bone scintigraphy. In addition, bone scintigraphy provides a map of the distribution of the pagetic lesions, thus evaluating the extent of the disease and detecting any asymptomatic sites. Standard bone radiography is the most specific investigation for establishing the diagnosis of Paget's disease [26]. Repeated bone scintigraphy is not recommended in the absence of suspected complications.

5.2. Therapeutic implications

Whether bisphosphonates should still be used to treat Paget's disease remains controversial. The PRISM EZ study is a 3-year extension of a randomized controlled trial comparing symptomatic treatment to intensive bisphosphonate therapy targeting total ALP normalization [27]. Bisphosphonates had no clinical benefits. However, this finding should be interpreted in the light of several methodological weaknesses. A recent Cochrane systematic review of bisphosphonate therapy for Paget's disease in adults highlighted bone pain relief as the main therapeutic benefit of bisphosphonates, which had few serious adverse effects [28].

Clinical acumen is key valuable when making treatment decisions in situations for which the only available guidance comes from expert opinion [29]. An example is the administration of bisphosphonate therapy before orthopedic surgery to decrease intraoperative blood loss and the risk of postoperative complications.

The increasingly advanced age at the diagnosis of Paget's disease and decrease in clinical severity are changing the therapeutic requirements. Another source of change is the availability of increasingly potent bisphosphonates whose effects last several years. Thus a single dose of zoledronic acid may now provide lifelong control of Paget's disease in most patients [30].

5.3. Consequences for the future management of Paget's disease

In addition to the increasing sensitivity of diagnostic investigations, which can now detect cases of Paget's disease that produce no symptoms or have low metabolic activity, and to the need for adjusting the treatment strategies to the new clinical phenotypes, the decreased frequency of Paget's disease may raise diagnostic challenges for rheumatologists and radiologists, who are unlikely to see many cases during their training. Paget's disease may thus disappear from the diagnostic repertoire, as is the case for our Asian colleagues. A greater number of investigations would then be necessary to establish the diagnosis. In a few years, referral centers for diagnosing and managing Paget's disease may well emerge. The resulting multidisciplinary approach would concentrate the relevant medical and scientific expertise, thereby benefiting patients with Paget's disease.

6. Conclusion

Paget's disease is already rare in Africa and Asia. Since the 1970s, the prevalence, incidence, and clinical severity of Paget's disease have declined in countries previously known to have very high prevalences, such as the UK, New Zealand, Australia, and France. Although poorly understood, the causes of these epidemiological changes may be related to modifications in environmental factors and lifestyle.

Disclosure of interest

The authors declare that they have no competing interest.

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