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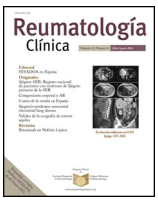

Special Article

Paget's Disease of Bone: Approach to Its Historical Origins☆

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ABSTRACT

Paget's disease of bone is the second most common bone disease after osteoporosis. It is characterized by focal regions of highly exaggerated bone remodeling, with abnormalities in all phases of the remodeling process. This study aims to investigate the hypothesis of a possible British origin of Paget's disease of bone by studying the worldwide geographic distribution of cases identified in ancient skeletons excavated from archeological sites. The methodology consists in reviewing cases of Paget's disease of bone described in the literature.

Enfermedad ósea de Paget: aproximación a sus orígenes históricos

Palabras clave:
Osteítis deformante
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RESUMEN

La enfermedad ósea de Paget es la segunda enfermedad ósea más común después de la osteoporosis. Se caracteriza por la aparición de regiones focales que presentan una remodelación ósea muy exagerada, con anormalidades en todas las fases del proceso. Este estudio tiene como objetivo investigar la hipótesis del posible origen británico de esta enfermedad estudiando su distribución geográfica mundial en esqueletos antiguos excavados en yacimientos arqueológicos. La metodología utilizada consiste en una revisión de la literatura que presenta diagnóstico de la enfermedad ósea de Paget.

Characterization of Paget's Disease of Bone

Paget's disease of bone is a chronic disorder of unknown origin. It was described for the first time by Sir James Paget in 1877. It was initially referred to as *osteitis deformans*, as it was considered to be chronic inflammation of the bone. At the present time, it is regarded a chronic bone remodeling process in the absence of an inflammatory component. Thus, some authors suggest that a more suitable term would be *osteodystrophia deformans*.[1]

Paget's disease of bone involves a disorganization in focal bone remodeling. There is an increase in osteoclast activity, which results in greater bone resorption, the clinical expression of which is the development of lytic bone lesions observed in conventional radiography.[2–4] In response, there is accelerated and chaotic bone formation, which results in sclerotic bone that is functionally weaker than normal bone, without the characteristically laminar pattern. The clinical signs are usually expressed years later with the onset of bone deformity, accompanied by pain, osteoarthritis and pathological fractures.[2,5–7] The most frequently affected bones are the pelvis, femur, spine, skull and tibia. Other less common clinical manifestations are entrapment neuropathy, sensorineural hearing loss, high-output heart failure and malignant transformation with the development of osteosarcoma.[2,3,6,8–14]

The disease is usually detected in individuals over the age of 55 years. It becomes more frequent as individuals get older, and there is a slight predominance of men. The most common clinical signs

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are bone pain, osteoarthritis and bone fracture. It is frequently diagnosed incidentally on the basis of a compatible radiological image taken during an examination for some other medical concern, given that it can develop without being detected for years. For this reason, the disorder is considered to be underdiagnosed in the general population.[8]

The geographic distribution is irregular. In epidemiological studies performed over the past 30 years, the prevalence of Paget's disease has been seen to be high in northwestern European populations. It is markedly more frequent in Great Britain (3%–5% of the population over 55 years of age) and in areas to which this population has emigrated, such as Australia, New Zealand and the United States. Other regions in which the rate is high are France and Spain (0.7%–1.3%). Moreover, within these countries, there are foci in which the disease burden is even greater. The most widely known of these is Lancashire, in England, where the prevalence is 6.3% of the population over 55 years of age with respect to 4.3% in the remainder of the areas studied, focusing on the population of the same age.[15,16] In Spain, the Sierra de la Cabrera in the Community of Madrid and the region of Vitigudino in Salamanca, in the western region of the country, are also areas of high prevalence.[17] There are more cases in the interior than along the coastline. The disease is less frequent in Scandinavian countries and Asia, where the rate is less than 1%.[17–19]

The reason for this irregular expression of the disease is not well known. A number of theories, including an autoimmune process, an endocrine disorder, an infectious disease and a neoplastic condition, have been proposed. The origin remains unclear, although it is evident that there is a marked familial aggregation that suggests an underlying genetic factor. Study findings support the existence of autosomal dominant inheritance, with variable penetrance and the implication of specific mutations, particularly that involving the *sequestosome-1* gene (*SQSTM1*). This mutation has been related to the most aggressive expression of Paget's disease of bone.[20] This hereditary component would be subjected to environmental influences that would trigger the disease. Several exogenous factors have been proposed, including paramyxovirus infection, consumption of untreated water and unpasteurized milk, and vitamin D deficiency during childhood. We consider the findings of a study conducted in the Sierra de la Cabrera in Madrid, one of the Spanish foci in which the disease is highly prevalent, to be especially interesting. The conclusion was that the possible causative agent would not be a canine virus, but the consumption of bovid meat without monitoring by health authorities. The result was the ingestion of the infectious agent from the tissues of infected animals (as occurs in Creutzfeldt-Jakob disease). The development of a slow-acting agent is consistent with the advanced age of the patients and their infection during childhood and adolescence, when health monitoring of livestock in Spain was limited or nonexistent.[21] On the other hand, the Lancashire focus was related to a high arsenic concentration in the pesticides used in the cotton industry, which was eliminated by means of the rivers. However, none of the studies performed has demonstrated solid evidence of the role of any of them in the development of the disease.[22]

In recent years, there has been evidence of a decrease in the incidence of the disease and of the severity of the clinical manifestations. This may be due to changes in the ethnic composition of the populations because of migration and to improved hygienic conditions introduced as public health measures (vaccination programs and reduced exposure to zoonosis).[5]

The diagnosis in symptomatic patients is based mainly on clinical findings, supported by laboratory tests and radiological images. There is an increase in bone formation and resorption markers. The marker of choice for diagnosis is serum total alkaline phosphatase, the level of which is usually increased. In the radiological study, there is generally local enlargement of the bone with cortical thickening, changes in the trabecular pattern and the coexistence of lytic and blastic lesions. Management of the active disease is based on bisphosphonates, the most widely utilized being zoledronic acid. It is an effective treatment that relieves pain and improves quality of life. Normalization of alkaline phosphatase levels is a useful marker for monitoring the response to treatment. Orthopedic surgery is also utilized to repair fractures.[2,8]

Historical Notes on the Origin of Paget's Disease of Bone

Data concerning the origin of Paget's disease of bone, like anything that has to do with this disorder, are unclear and ill-defined.[6,7,23] It gets to the point in which key sourcebooks on paleopathology do not coincide in its classification, presenting it as a metabolic disease,[24–28] whereas other authors are not so clear, including it in a miscellaneous section.[29–31]

We find that the prevalence rates of the disease are currently high in the British Isles, which is exactly where the most abundant paleopathological evidence is discovered. Moreover, different studies seem to indicate the existence of a higher predisposition of Europeans to develop the disease, leading to the establishment of the hypothesis that the origin of Paget's disease of bone can be found among the populations of northwestern Europe.[32] In any case, the prevalence and severity now appear to be decreasing.[33–35]

This theory was endorsed in a recent work by Mays[36] who presents evidence from the paleopathological study of Paget's disease of bone, confirming that, with a marked difference, the greatest number of documented cases (up to 94%) corresponded to the British Isles. In fact, the disease has a strong genetic component.[37] For example, there is evidence that an optineurin (*OPTN*) gene variant affects the susceptibility of developing Paget's disease of bone and interacts with the TNFRSF11A polymorphism to produce a greater severity of the disease in sporadic cases.[38] The presence of certain mutations may lead to other complications like dementia.[9] Paget's disease of bone has also been seen to share a common molecular mechanism with multiple myeloma, represented by the receptor activator of the nuclear factor-kappa B ligand (RANKL)/osteoprotegerin, and the 2 diseases can occur simultaneously.[10]

According to Mays,[36] some of these factors could have led to the recent extension of the disease to other parts of the world with the arrival of residents of Britain due to colonial conquests.[39] This would explain its existence with prevalences similar to those found in Europe in the United States[11] and New Zealand.[12]

However, we consider that there are two elements of the study that can bias the result and, thus, the conclusions. First, it includes only those cases in which the findings are double-checked by means of a radiological study, in addition to a histological study, which is considered to be essential for the diagnosis of the disease[35]; the current clinical diagnosis is normally radiographic, based on a wide range of changes, and bone biopsy is little utilized.[3,4,13,14] Second, there is a certain publication bias with regard to the paleopathological evidence in Mediterranean countries which, to a large extent, is caused by the existence of something of a lag in the methodological approach to the paleopathological analysis in these areas, as there is no consolidated tradition for performing those studies and publishing the findings. There is also a systematic lack of knowledge about those studies that are not written in English.

As a consequence, although double-checking the evidence is important, we consider that not every case in which that condition is not met should be rejected, especially if a radiological study has been performed.[28,30,31,40] If we extend the search with this criterion, we may find that the total of cases increases, both in number and in geographic regions, including those outside the European continent. Hence, the thesis of the British origin of the disease would come to be seriously debatable.[26]

Butlin diagnosed the disease in a Neanderthal skull in 1885 and, likewise, at the beginning of the 20th century, attempts were made to document its presence in bones from the Upper Paleolithic period or in findings from Egypt.[41] At the present time, there are serious doubts about the accuracy of that diagnosis. It must be taken into account that the disease was not reported by Paget until 1876, and the differential diagnosis for the condition had not yet been well established. The origin of the disorder was the subject of an important debate throughout all of Europe.[42] On the other hand, if the presence of the disease were to be confirmed in humans prior to the domestication of dogs, we could find an argument that would invalidate the hypothesis of the viral origin of the disease,[43] although it has been detected in present-day dogs[44] and other animals, and even in the remains of a dinosaur from the Jurassic period.[45]

Its prevalence in the past could be disguised with respect to the current rate due to the existence of a shorter life expectancy at birth.[28,46] Moreover, the poorly preserved condition of the skeleton hampers diagnosis, which is sometimes performed to distinguish it from the disorder considered to be the primary disease. The differential diagnosis of Paget's disease of bone is studied in a variety of remains from distinct periods and regions using paleopathological techniques. For example, a human skull from the Middle Pleistocene in Kenya, which exhibits porotic lesions and a marked enlargement of a few bones of the calvaria attributed to some type of chronic anemia during youth as a consequence of environmental pressure, whose differential diagnosis includes Paget's disease of bone.[47] Paget's disease of bone is also included in the differential diagnosis in cases of treponematosis, as in certain American instances,[31] or in a Roman skeleton of the 2nd to 3rd century AD from Gavà in northeastern Spain.[48] On the other hand, there is certain paleopathological evidence that could be a secondary result of Paget's disease of bone. This is the case of hypercementosis, a hyperplasia of dental cementum—prominent thickening of the tissue—with involvement of a tooth or a whole set of teeth. This can be associated with different systemic conditions, like calcium deficiency, hypothyroidism, fibrous osteodystrophy and Paget's disease of bone.[49] Hypercementosis can be documented in the Late Medieval Stara Torina graveyard in Serbia,[50] in the Late-Anquity site in Sains-en-Gohelle, in France, or in that occupied for a prolonged period of time—from the AD 7th to the 17th century—of Jau-Dignac-et-Loirac, also in France.[51] Finally, another possible indication of the existence of Paget's could also be the diagnosis of leontiasis ossea, an uncommon disorder that, for some authors, has its own entity,[29,31] although, for others, could simply be a complication of Paget's disease of bone.[52] This disease is observed in some sculptures from Classical Antiquity[53] and, in Spain, one of its most famous cases is documented in the paleo-Christian cemetery of the northern town of La Olmeda.[52]

The earliest case of Paget's disease of bone usually accepted, with reserves, is that reported in 1927 by Pales describing a Neolithic femur from the French department of Lozère.[30,31] Concerning other numerous cases diagnosed in pre-Columbian America, doubts are still being expressed even recently. These doubts have led Mays to consider that the earliest cases correspond to the Roman Empire (I-IV centuries AD), documenting 7 cases in Great Britain, 1 in France and another in Portugal.[36] He thus follows the general working model that intends to demonstrate the existence of a geographic pattern centered on northwestern Europe, with the immense majority of specimens from England, and no paleopathological evidence from outside this geographic scope.

However, if we add other cases reported with less restrictive criteria—limiting ourselves to periods before the spread of Europeans throughout the world, we can discern 2 tendencies. First, there is an increase in the European distribution throughout the Mediterranean area and southwestern Europe, with evidence in Greece,[54–56] Italy,[57,58] France[59,60] and Portugal[61] (Table 1), as well as a growing importance acquired by the sample of this disease in Spain, which is especially significant during the Roman period or immediately before[52,62–65] (Table 2; Fig. 1). Second, there is a marked increase in the geographic distribution of this disorder, which comes to be present in both South and North America (Table 3).

Table 1
Paleopathological Evidence of Paget's Disease of Bone in Europe (Except Great Britain).

France[26]	Neolithic (3500–2000 BC)
France[26]	Neolithic (3500–2000 BC)
Italy[26]	Neolithic (3500–2000 BC)
Greece[54–56]	Late Bronze
Belgium[26]	650 BC–43 AD
Portugal[61]	Roman
Italy[57,58]	Roman
France[60]	Roman
France[41,92]	Roman
France[26,93]	AD 750–1550
France[26]	AD 750–1550
Denmark[26,94]	750–1550 BC
Russia[26,95]	AD 750–1550
France[60]	AD 1000
Serbia[24]	Medieval
Serbia[24]	Medieval

AD: anno Domini; BC: before Christ.

From these observations, we can deduce that, the origin of the disease is either multifocal or is prehistorical, prior to the arrival of man to America. In this respect, the data on America offer 2 sites with a highly reliable diagnosis when compared either by visual observation or by radiodiagnostics and a histological study. We refer specifically to a site in the Southern Cone of South America, Los Marinos, in the Upper Delta of the Paraná in Argentina, with a chronology of 590 ± 60 BP (before present, established by convention for radiocarbon dating in 1950),[66] and another in North America, in Ontario in Canada, dated between AD 800–1200[26,67] (Table 3).

In agreement with these observations, the hypothesis placing the origin of the disease in northwestern Europe would be invalidated, as certain authors suggested regarding the initial proposals by Ross.[26] Likewise, it does not seem to be the European source, either. The earliest cases point constantly to the Mediterranean region (Table 1): French Neolithic, Aegean Late Bronze and, very significantly, the Roman period, in which the cases multiplied, both numerically and geographically, with paleopathological evidence,

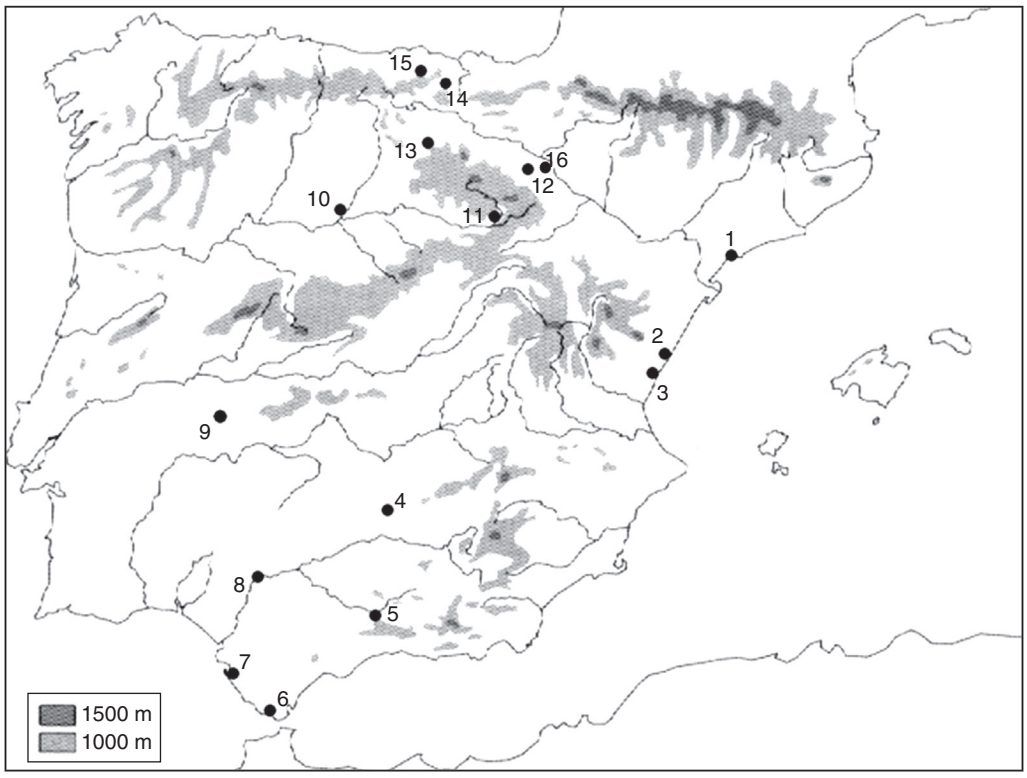
Table 2
Paleopathological Evidence of Paget's Disease of Bone in Spain.

Site	Province	Historical period
Valencia	Valencia[62]	Roman
Cadiz[a]	Cadiz[63,64]	Late Punic-Roman
Baelo Claudia	Cadiz[65]	Roman
Mas Rimbau	Tarragona[27]	Roman
Francolí	Tarragona[27]	Roman
Sevilla	Sevilla[96]	13th–14th centuries (Jewish)
San Juan de la Hoz	Burgos[97]	Medieval
San Martín del Castillo	Soria[98]	14th–15th centuries
Santo Tomás de Mendraka[b]	Vizcaya[99]	Medieval
Santa María la Vieja	La Rioja[110]	14th–15th centuries
–	La Rioja[100]	Medieval
Calle Agua de Cartuja	Granada[101]	Islamic Medieval
Paterna	Valencia[102]	16th–17th centuries
Wamba	Valladolid[103]	17th century
San Andrés de Astigarribia	Guipuzcoa[104]	13th–17th centuries
Linares	Jaén[105]	19th century

Late Punic (boundary between the arrival of Rome and the preceding Phoenician-Carthaginian civilization).

[a] Two affected skeletons.

[b] Seven affected skeletons.



1.- Tarragona
2.- Paterna
3.- Valencia
4.- Jaén
5.- Granada
6.- Baelo claudia
7.- Cádiz
8.- Sevilla
9.- Torre de Palma (Portugal)
10.- Valladolid
11.- San Martín del Castillo
12.- La Rioja (indeterminate site)
13.- San Juan de la Hoz
14.- San Andrés de Astigarribia
15.- Santo Tomás de Mendraka
16.- Santa María la Vieja

Fig. 1. Cases in which there is paleopathological evidence of Paget's disease of bone in the Iberian Peninsula.

and iconographic, as well. Some of the sculptures found in the Gallo-Roman sanctuary in Fontes Sequanae in Dijon, France, may have been seen to represent this disease.[59] During that period, populations were moving constantly. The case of England especially documents this reality. Indeed, novel techniques for isotopic analysis applied to the study of burials in Roman and Anglo-Saxon England have enabled us to see that there were movements of the local population and of residents from the Mediterranean.[68–70] However, for the initial Anglo-Saxon period, that is, at the time of the supposed invasions from the European continent, the data show that an immense majority of the population was of local origin. There were very few foreigners, and most were from the Scandinavian region. A large-scale substitution of the Britain-Roman inhabitants does not seem probable.[71–75] Data from the archeological registry suggest looking in this same direction.[76]

Consequently, all of this seems to demonstrate the fact that the origin of Paget's disease of bone is not to be found in the British Isles, but that it must have been introduced during the Roman occupation. This is suggested by the fact that there were numerous cases at the time,[36] but also because the foreign non-Mediterranean population, aside from having arrived after the fall of the Roman empire, came from areas like Scandinavia, Germany and Ireland, in which the current prevalence of the disease is especially low.[77,78] In fact, the diagnosis of this disorder based on the description of a series of diseases in "Egil's bones"[79]—an Icelandic saga of the 13th century, but that could provide data from 2 centuries earlier—would more likely be evidence of fluorosis, as a consequence of the consumption of plants and animals that had been in contact with volcanic ash, more than Paget's disease of bone.[80]

In this respect, it was impossible not to observe that, if we analyze the prevalence data in detail, we can see that certain regions of France have rather high rates and that some of the foci with the greatest prevalence, together with England, are now found in Spain (Autonomous Communities Castile and León, Castile-La Mancha) and Italy (Siena and the region of Campania),[5,17,18] that is, in southern Europe.

Table 3
Paleopathological Evidence of Paget's Disease of Bone in Pre-Columbian America.

Site	Country	Historical period
River Valley[a]	United States[30,31]	AD 1300
Crawford County[b]	United States[30,31]	AD 1300
Ontario	Canada[67]	AD 800–1200
Aguazuque	Colombia[106]	3850 BP
–	Belice[31,107,108]	AD 800–1000 (Maya)
Tlatelolco	Mexico[46,108]	Post-Classic
Western Mexico	Mexico[108,109]	Post-Classic
Western Mexico	Mexico[108,109]	Post-Classic
Los Marinos[c]	Argentina[66]	590 ± 60 BP
Brazo Largo	Argentina[66]	Pre-Hispanic
Cerro Lutz	Argentina[66]	Pre-Hispanic
El Cerrito	Argentina[66]	Pre-Hispanic

AD, anno Domini (before Christ); BP, before present (established by convention in 1950 for radiocarbon dating).
Post-Classic (late period, AD 900–1500, of the Maya civilization).
Pre-Hispanic (refers to a period prior to the arrival of Spaniards to a given American territory).

[a] Five cases.
[b] Two cases.
[c] Two cases.

Has the prevalence of Paget's disease of bone changed since the past? While some initial studies were performed using skeletons from a long-standing burial ground, like that of Barton in Humber, in Great Britain, and the prevalence of the disease appeared to show a certain trend to increase after 1500 years.[77] Later reviews of this study have shown that it has not changed during the period of time covered by those burials, and that there has been no increase.[25,81] This fact has come to be confirmed by other studies in Central Europe,[82] although the existing data is not sufficient to substantiate the current prevalence, which is at least 1%,[14] it was similar in ancient times.[31]

In fact, one of the problems to be considered is how to link the present low rate of the disease among Asian people with the genetic transmission through those populations to the American continent at a time before the arrival of Europeans in recorded history. Archeological findings and genetic studies confirm that the first humans reached the American continent between 13,000 and 15,000 years ago from Siberia and other regions of Central Asia. They had left, perhaps, 23,000 years earlier, and had remained isolated for 8000 years in Beringia, to later enter the American continent in several waves.[83–86] Although the problem can extend to European populations, given that during the Bronze Age (c. 3000–1000 BC), we find a long dynamic period during which large-scale migrations of Eurasia populations followed one another—from the region of the Ukraine and Russian steppes—propagating Indo-European languages and supplanting populations, just as archeology and a recent genetic study seem to demonstrate.[87–91] It was a moment when, for example, European populations already had a fair skin, but lactose tolerance had not yet developed.

In short, data indicate that Paget's disease of bone has been with us since ancient times, and was even present in a dinosaur from the Late Jurassic period (150 million years), diagnosed in a specimen from Tanzania.[45] The diverse findings from numerous archeological sites correspond to widely ranging historical times and seem to support the multifocal origin of this disorder. In terms of the European focal point, the radiations seem to be produced in the circum-Mediterranean region and not in northwestern Europe.

Ethical Disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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