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Paget Disease of Bone in Cyprus: Prevalence, Clinical Characteristics and Physicians' Awareness

George A. Samoutis, MD, PhD
St George's University of London Medical School at University of Nicosia, Nicosia, Cyprus

Alexis A. Samoutis, MD, MSc, PhD
School of Health Sciences, Frederick University, Nicosia, Cyprus

Correspondence: Alexis Samoutis, Lecturer, School of Health Sciences, Frederick University, Nicosia, Cyprus E-mail: alexis_samoutis@gmail.com

Abstract

Background Paget's disease of bone (PDB) is a relatively uncommon medical condition.
Objective This study was conducted to estimate the prevalence and describe the clinical characteristics of PDB in Cyprus.
Methodology A questionnaire was mailed, in two phases, to all orthopedics and rheumatologists at hospitals and private practices in Cyprus. Phase 1 determined the number of PDB patients followed at each hospital or practice, while Phase 2 gathered information on the clinical presentation of current patients.
Results A total of 11 patients were located among the 45 physicians surveyed. The response rate of Phase 1 was 68.5%. All physicians who reported a PDB patient in Phase 1 also participated in Phase 2. Prevalence of PDB was estimated at 2.04 per 100.000 people. Male patients were seen more frequently compared to females (72.7% vs. 27.3%). The majority of patients (82.8%) reported the presence of at least one symptom. The most frequently reported complication was fracture, while no sarcomas were reported. The most frequent location of bone fracture was the spinal column, followed by the femur (45.5% vs. 36.7%). Rarity of the disease and lack of physician's information about the disease were the two most frequently reported difficulties by physicians for the diagnosis of PDB (20.8% vs. 22.9%).
Conclusions This is the first study estimating prevalence and describing clinical characteristics of PDB in Cyprus. PDB is a very rare disease in this country affecting primarily the male population. Bone involvement is present in most cases and fractures are the most prevalent complications.

Keywords: Paget Disease, Prevalence, Cyprus

Introduction

Recent observations in Caucasian populations set the prevalence of Paget's Disease of Bone (PDB) to 3% while the percentage of sufferers, as proportion of the general population, increases substantially with aging (Josse et al., 2005). PDB is described as a metabolic disease characterised by increased bone resorption leading to excessive, unregulated bone formation, possibly due to abnormalities of osteoclast function that can be attributed to genetic predisposition and/or viral infection. The most prominent candidate for hereditary PDB is the sequestosome 1/p62 gene (SQSTM1/p62) (Hocking et al., 2002; Laurin et al., 2002). Mutations of the *SQSTM1/ p62* gene have been identified in approximately one third of the affected family members and in up to 15% of patients with no family history of the disease (Laurin et al., 2002). *SQSTM1/p62 gene* codes the SQSTM1/p61 protein (ubiquitin-binding–protein p62), a selective activator of the transcription factor NF-kappaB, which acts on the osteoclast differentiation and activation, responding to cytokine stimulation (Durán et al., 2004). Paramyxoviruses such as measles and canine distemper viruses have also been implicated in the pathogenesis of PDB (Kurihara et al., 2000; Reddy et al., 2001; Kurihara et al., 2007). However, results regarding the viral pathophysiology of PDB

are still inconclusive (Helfrich et al., 2000).

The clinical manifestations of the disease are strongly dependent on the bones affected. The most frequently affected sites include the pelvis, the lumbosacral spine, the skull and the femur or tibia. Pain, deformities and pathologic fractures are reported as the most frequent complications (Bone, 2006), while osteosarcomas and malignant tumours develop rather rarely (Deyrup, 2007).

Data on the prevalence of the disease indicate that there is wide geographic variability and that it increases with age (Hashimoto et al., 2006). It affects both males and females (Josse et al., 2005), although gender predominance cannot be clearly deducted. Some of the geographic areas with the highest reported prevalence include United Kingdom, Italy, France and North America, while the disease is rarer in Northern Europe (Siesling et al., 2007) and Africa (Guyer and Camberlain, 1988) and, extremely rare in Asia (Hashimoto et al., 2006). Regional reports show a tendency for decreased incidence of the disease (Barker et al., 1977; Cooper et al., 1999), accompanied by ameliorated severity of novel cases (Doyle et al., 2002), particularly in areas with increased prevalence, which may also be attributed to attenuation of environmental factors such as viral infections.

Clinical experience and epidemiologic studies in Mediterranean countries indicate large national variation, possibly due to familial aggregation of the disease (Coleiro et al., 1999). The highest reported prevalence has been noted in Spain (Salamanca), where it reached 5.7%. In Italy, the overall prevalence of PDB has recently been estimated between 0,7% and 2,4% (Gennari et al., 2006).

Although PDB is the second most common bone disorder, following osteoporosis, its rarity and localised nature, coupled with the low percentage of symptomatic patients, may result to its underdiagnosis (Chaffins, 2007). Therefore, raising physician's awareness is essential for the early diagnosis and timely initiation of appropriate therapy.

The aim of our study was to estimate the overall prevalence of PDB in Cyprus. In addition, this study aimed at describing the clinical characteristics of PDB and also at providing an insight of the Cypriot physicians' awareness regarding PDB. To our knowledge, there is no previous attempt to estimate the prevalence of this disease in Cyprus.

Materials and Methods

A nationwide mail survey was conducted in two phases. The sample included all public and private orthopedic surgeons (N=31), rheumatologists (N=9), residents in orthopedics (N=3) and osteoporosis specialists (N=2).

Phase 1 of the survey was conducted to determine how many patients with PDB were followed at each department and/or hospital. The questionnaire aimed at collecting information regarding the prevalence of PDB in Cyprus and providing information on physicians' awareness. Hence, it was comprised of questions such as "*Have you ever treated a patient suffering from Paget's disease of bone in Cyprus?*", "*Symptoms from patients history of laboratory exams that make you suspect of Paget's disease*", and "*Have you ever diagnosed a patient with Paget's disease of bone in Cyprus*".

If the answer to Phase 1 question "*Have you ever treated a patient suffering from Paget's Disease of Bone*" was positive, then Phase 2 was initiated to gather information on the clinical presentation of current patients. The questionnaire aimed at collecting information regarding the clinical characteristics of current patients with PDB. It was comprised of questions aiming at describing the clinical features of current patients and employed questions regarding age, gender, the status of the patient (symptomatic vs. asymptomatic), the types of clinical symptoms, the skeletal localisation of the disease, the serum alkaline phosphatase levels, the treatment, the prognosis and any complications of the disease. Patients who were either deceased or beyond contact were excluded from this study. Lastly, we investigated physician's awareness of PDB. We employed questions regarding the level of information ("*How well informed are you for the Paget disease of bone")*, the

perceived difficulty of the diagnosis (*Difficulties in Cyprus for the diagnosis of Paget disease of bone)*, the frequency of treatment patient (“*Have you ever handled a patient with Paget disease of bone”)* and questions regarding the therapy of diagnosed patients (“*How pleased are you with patients' compliance to the usage of bisphosphonates”; “According to your opinion which is the most common cause of no compliance to bisphosphonate”;* and “*Which is the most common adverse event due to bisphosphonate, which leads to drug discontinuation").*

The data from all participated physicians were pooled and summarised for demographic characteristics. Exploratory analysis, regarding the management and clinical aspect of the disease, was performed using descriptive statistics. Summary statistics of categorical values were based on frequency distribution tables.

Results

Physicians

In Cyprus, PDB is traditionally diagnosed either by orthopedic surgeons or rheumatologists. A total of 45 physicians, 75.6% orthopedic surgeons, 20.0% rheumatologists and 4.4% osteoporosis specialists participated in this study, employed both in the public (20.0%) and the private (80.0%) sector. The majority of physicians reported to have some experience in the treatment of patients with PDB (64.4%, 29/45), while a substantially lower percentage reported to have diagnosed at least one patient with PDB (33.3%, 15/45).

Patients

A total of 11 patients with PDB were identified from a local population of 776.400 (2006). The estimated prevalence of PDB, taking into account the response rate of Phase 1 (68.5%) is calculated to be 2.04 cases per 100.000 capita, based on the following formula: 11 cases x (100% / 68.5%) x (100.000 / 776.400). In Table 1, we present patients’ demographic characteristics, whereas in Table 2 we delineate the diagnostic methods most frequently employed in PDB and, the preferred treatment strategies and the prognosis of PDB patients in Cyprus. Table 3 presents the most frequent difficulties encountered by physicians in the diagnosis of PDB.

The mean age of the patients was 64.3 ± 8.4. Data from the 11 current patients (8 males, 3 females) revealed that 88.9% showed single bone involvement, while the most frequent site affected was the spinal column (45.5%), followed by the femur (36.4%), the calf (18.2%) and the scalp (9.09%). Backache was the most frequent clinical symptom (36.3%), followed by bone deformities (27.7%). No sarcomas were reported.

Therapy

The medical management of PDB included bisphosphonates and non-steroidal anti-inflammatory agents (NSAIDs) for supportive therapy. In most of the cases, patients were prescribed risendronate and zolendronic acid. Alendronate was also prescribed for a smaller percentage of patients (10%). Most of the patients, under therapy, remained asymptomatic (72.7% vs, 27.3%).

Physicians’ awareness

In total, 86.6% of the physicians reported that they were informed about PDB, but only 6.67% were “very well” informed. The most frequently used laboratory indices and clinical symptoms to diagnose PDB were serum alkaline phosphatase (SAP ALP) levels (93.3%, 42/45), followed by X-ray scan (66.7% 30/45), bone pain (66.7%, 30/45) and bone enlargement (28.9%, 13/45). About half of the physicians reported that they do not recognise any difficulties in Cyprus for the diagnosis of PDB (Table 3), while “lack of physicians’ information” and “rarity” were the most frequently observed problems for disease diagnosis (24.44% vs. 24.44%). The most common cause of no compliance, according to physicians’ opinion, was adverse drug reactions (33.3%, 15/45), lack of communication between doctor and patient (33.3%, 15/45) and dose scheme (28.9%, 13/45). Low educational level and lack of drug efficacy were also reported (10.4%, 6.25%).

Table 1. Demographic and clinical characteristics of 11 PDB patients in Cyprus

Age – mean (± SD)	**64.3 (± 8.4)**	
Sex, male / female	**8 / 3**	
	Frequency	***%***
Presence of symptoms		
Asymptomatic	**2**	**18.2**
Symptomatic	**9**	**81.8**
Bone Involvement		
Monostotic	**8**	**72.7**
Polyostotic	**1**	**9.09**
Total	**9**	**81.8**
Skeletal distribution		
Tibia	**2**	**18.2**
Spinal Column	**5**	**45.5**
Femur	**4**	**36.4**
Skull	**1**	**9.09**
Symptoms – Signs		
Back pain	**4**	**36.4**
Bone deformities	**3**	**27.3**

Table 2. Diagnosis, treatment and prognosis of PDB in Cyprus

Diagnosis	***Frequency***	***%***
Biopsy	**3**	**27.27**
No biopsy	**6**	**54.54**
Unknown*	**2**	**18.18**
Complications		
Fracture	**10**	**90.1**
Sarcoma	**-**	**-**
Other	**1**	**9.1**
Total	**11**	**100**
Treatment		
NSAID**	**2**	**20.0**
Biphosphonates	**9**	**90.0**
Zolendronic acid	**4**	**40.0**
Risendronate	**4**	**40.0**
Alendronate	**1**	**10.0**
No drug	**1**	**10.0**

* Information not available from the designated number of patients
** NSAID: Non steroidal anti-inflammatory drugs.

Table 3. Difficulties reported by Physicians in the diagnosis of PDB in Cyprus.

	Frequency	***%***
None	**22**	**48.89**
Lack of doctors information	**11**	**24.44**
Rarity of the disease	**11**	**24.44**
Asymptomatic patients	**6**	**13.33**
No association between treatment and disease	**4**	**8.88**
Patients not cooperating	**2**	**4.44**
Difficulty in the laboratory assessment	**1**	**2.22**
Elder patients who do not visit specialists	**1**	**2.22**
Patients who do not pay attention to symptoms	**1**	**2.22**

Discussion

This study, aimed at estimating, for the first time in Cyprus, the prevalence of PDB, describing the clinical characteristics of current patients and investigating the issue of physician's awareness towards the disease. Prevalence of PDB was found to be very low, estimated at 2.04 cases per 100.000 capita. This finding appears to be in the low range compared to prevalence reported in other European and Mediterranean countries that set the prevalence of the disease between 0.7% and 5% (Josse et al., 2005; Coleiro et al., 1999; Gennari et al., 2006; Miron-Canelo et al., 1997; Rendina et al., 2006; Saraux et al., 2007).

Geographic areas with the highest reported prevalence include UK, Western Europe (Netherlands, France, Italy, Spain), North America, Australia and New Zealand, whereas lower prevalence has been reported in North Europe (Ziegler et al., 1985; Detheridge et al., 1982) South Africa (Guyer and Camberlain, 1988) and Asia (Hashimoto et al., 2006). In UK, a recent estimation sets the prevalence of the disease at 2% in elderly patients aged 55 years or older (Cooper et al., 2006), while one of the higher incidences in Europe, as suggested by recent observations, is seen in Netherlands (Eekhoff et al., 2007). In Italy, prevalence is estimated to range between 0.7 and 2.4%. Specific areas seem to present high prevalence (Campania in Italy, Salamanca in Spain) possibly due to familial aggregation of the disease (Josse et al., 2005; Rendina et al., 2006). In US, the prevalence is estimated at 2.32% ± 0.54% for the 65-74 age group. Similar reports have been published from Australia and New Zealand (Doyle et al., 2002; Barker, 1984; Reasbeck et al., 1983). Recent investigations, however, suggest a marked decrease in prevalence and severity of the disease in the last two decades and in areas with previously reported high prevalence (Cooper et al., 2006; Cundy, 2006). Similar to our own findings, a slight predominance of males over females has been reported from several studies in US (Altman et al., 2000), France (Saraux et al., 2007; Renier et al., 1995) and Japan (Hashimoto et al., 2006). However, other studies have failed to see any gender differences in the prevalence of PDB (Ziegler et al., 1985). Lastly, the prevalence of the disease seems to increase with age (Hashimoto et al., 2006; Miron-Canelo et al., 1997; Altman et al., 2000).

When trying to interpret incidence and/or prevalence results, special consideration should also be given to the rare nature of the disease. This information, together with the asymptomatic course of PDB, may contribute to the low prevalence estimates that are occasionally reported in several regions. On the other hand, physicians may employ a rather high threshold for the diagnosis of PDB, since rarity, coupled with limited experience and knowledge about the disease, may further increase, such a threshold of detection.

Familial aggregation of the disease ranges from 15% to 26% (Gennari et al., 2006). In another study, conducted to investigate the familial nature of PDB in an area of southern Italy with increased rates compared to the rest of the country, it was reported that 18% from the area of interest (23 from 125) and 23% from other Italian regions had at least one first degree relative affected by PDB. In a study conducted in Spain to estimate frequency and features of familial aggregation, it was reported that 40% of the index cases had at least one first-degree relative affected by PDB (Morales-Piga et al., 1995). Additionally, a study conducted in the US, which compared the results from patients with physician – diagnosed PDB and those from age-matched controls, showed that 12% of PDB patients had a first-degree relative who was affected by the disease, compared to 2% of the control group (Siris, 1994). Familial clustering seems to be lower in Asia (6.3%), compared to the aforementioned high-prevalence regions (Hashimoto et al., 2006). Based on the prevalence of monostotic / polyostotic bone deformities and back pain, we found that 81.8% of patients in Cyprus were symptomatic. Similar results have been reported in other studies (Hashimoto et al.,

2006). While the monostotic vs. polyostotic ratio seems to vary greatly between low and high prevalence regions (Hashimoto et al., 2006; Mirra et al., 1995), we found that 72.7% of the PDB cases in Cyprus were monostotic. The sites with the higher prevalence of bone involvement were the spine and the femur (45.5% vs. 36%).

Pagetic bone pain occurs in a small percentage of patients. It can be constant, present at rest, localised, increasing with weight bearing. Very often, it arises from micro-fractures or localised lytic lesions (Walsh, 2004). In our study, 36.4% of patients reported back pain. This is considered as the most frequent clinical symptom associated with pagetic disease of the spine. In our study, the spinal column was also the site most frequently affected by the disease. Back pain in PDB is caused by increased blood flow and the modeling / remodeling process associated with the vertebral involvement, including periosteal stretching and micro-fractures (Dell'Alti et al., 2007). Pagetic bone pain differs from arthritic or mechanical pain and is characterised by aching and stiffness unrelated to activity and, hence, not relieved by rest or NSAIDs. Other studies report that between 11% and 54% of PDB patients suffer from back pain (Altman, 1980; Hadjipavlou et al., 2001).

The most frequent complication observed in this study was fractures (90.1%), while no sarcomas were detected. The incidence of osteosarcoma complications in PDB is estimated to be less than 1% (Hansen et al., 2006). Therefore, lack of observed sarcomas in PDB patients in Cyprus is not unexpected, given the very low prevalence of the disease in the country in general. Osteosarcoma occurs mostly in patients with long standing, polyostotic disease, while the percentage of polyostotic PDB deformities was only 9.09% in this study. It accounted for 1 case out of 11 patients.

Diagnostic bone biopsy was performed to 27.27% of patients as opposed to 55% (Hashimoto et al., 2006). Bone biopsy is usually avoided especially in high prevalence countries (Whitehouse, 2002). SAP ALP levels and X-rays were used in more than half of the cases, contributing to PDB diagnosis with 93.7% and 62.5% respectively. Other indices, such as clinical features, bone enlargement and fractures, were reported in lower frequencies. The medical management of PDB involves second and third generation bisphosphonates (Gillian et al., 2007; Body and Sternon, 2005) to normalise biochemical markers of bone turnover and induce radiological improvement (Reid et al., 1996) as well as to reduce pain (Miller et al., 1999). In this study, 90% of the patients received second and third generation bisphosphonates. Zolendronic acid was administered in 40% of the cases (Tziomalos et al., 2007), similar to 40% risendronate and 10% alendronate. NSAIDs were administered as surrogate therapy to 20% of the cases.

Lastly, while 51.1% of physicians were either *"well"* or *"very well"* informed, only 6.67% were *"very well"* informed about PDB. In addition, the second most frequent *"difficulty*" for the diagnosis of PDB, was "*lack of doctor's information*", suggesting that actions need to be taken to increase physician's awareness for the disease, followed by informative actions about the disease that will raise the level of information of the physicians most likely to encounter a patient with PDB. This is also warranted by the finding that one of the most important reasons for discontinuation of the therapy is *"lack of communication between doctor and patient"*.

In conclusion, this study aimed at estimating the prevalence and clinical characteristics of PDB disease in Cyprus. The prevalence of the disease appears to be very low, compared to other Mediterranean and South European countries. The clinical characteristics of the disease seem to be similar to those described by very low prevalence countries. We believe that our study also contributes to raising awareness of the disease among physicians, which in turn may lead to an earlier and more frequent diagnosis. This could yield a better treatment outcome and prevention of significant complications in PDB. Further investigations are needed regarding treatment outcomes of newly treated patients with novel therapeutic regimes, followed by actions to

increase physician's awareness and patients' information.

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Conflict of interests

All authors have no conflicts of interest. This study was supported by an unrestricted educational grant from Novartis Pharma Services in Cyprus.

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