Pain in Paget's disease: a retrospective study of treatment efficacy

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Submitted: 2011-02-19 Accepted: 2011-03-11 Published online: 2011-04-29

Key words: **Paget's disease; bisphosphonates; calcitonin; pain**

Neuroendocrinol Lett 2011; **32**(2):127–132 **PMID:** 21552192 NEL320211C01

Abstract

The authors addressed the role and the management of pain in Paget's disease by a retrospective study. The objectives were: to assess the presence of pain in Paget's disease; to look for a relationship between pain and the levels of total alkaline phosphatase (total ALP); to verify if the most commonly used drugs in Paget's disease, calcitonin and bisphosphonates, were able to reduce the pain and the levels of total ALP. The study analyzed 107 Italian patients with Paget's disease who were hospitalized at the same Institute between 1970 and 2010; all patients affected by severe arthritis were excluded.

From the analysis of the clinical records it emerged that as many as 85% of patients had pain and that total ALP was also increased in most of the patients with pain in comparison with patients without pain. The clinical and metabolic effects of different therapies were then assessed: many patients had not received any specific therapy (58%), others had been treated with calcitonin (25%) and others with bisphosphonates (17%). In fact, the patients treated with bisphosphonates had significantly lower levels both of pain and total ALP. The authors hypothesize that the pain in Paget's disease has a primary origin and is correlated to the degree of bone metabolic hyperactivity. Finally, treatment with bisphosphonates appeared to be the most appropriate treatment, having been able to control both the pain and the metabolic hyperactivity.

CASE REPORT

INTRODUCTION

The presence or absence of pain in Paget's disease is much debated. For some, the disease is asymptomatic, at least until complications cause pain (Langstone *et al.* 2004; Noor & Shoback 2000). According to this opinion, the bone affected by Paget's disease is painful only when the lesion grows and compresses nearby structures. For others, instead, it is the bone hyperactivity itself that causes the pain, inducing a brittleness that manifests with sub-clinical microlesions (Ankrom & Shapiro 1998; Kotowicz 2004).

The reduction of pain and the normalization of bone metabolism in Paget's disease are the main aims of therapy, which in the last 30 years has been represented above all by two drugs: calcitonin and bisphosphonates. These drugs, which differ a great deal in composition, both exert an inhibitory effect on osteoclasts.

Calcitonin was the undisputed protagonist of the 70s, when all the literature reported its superiority (Martin 1979; Singer 1977; Trzenschik *et al.* 1978; Verrina 1977) compared to the then only available bisphosphonate: etidronate.

From the end of the 70s to the beginning of the 90s, enthusiasm towards calcitonin progressively waned, since this therapy was found to be limited in controlling the symptoms both in the short and long term (Singer 1991; Tiegs 1997). Subsequently, calcitonin has suffered from comparison with more and more evolved molecules of bisphosphonates, such as clodronate (Atkins *et al.* 1987; Douglas *et al.* 1980 ; Reginster *et al.* 1988; Rousiere *et al.* 2003; Varenna *et al.* 2010). The 90s witnessed a progressive reduction in the role of calcitonin in Paget's disease treatment in favour of the new bis-bisphosphonates, whose better results are reported in the literature (Chakravarty *et al.* 1994; Filipponi *et al.* 1998; Hosking 2006; Hosking *et al.* 1998; Miller *et al.* 1999; Roux 1995; Siris *et al.* 1996).

The objectives of our retrospective study were:

- to assess the role of pain in Paget's disease, to look for a relationship between pain and the levels of total alkaline phosphatase (total ALP)
- to verify if the most commonly used drugs in Paget's disease, calcitonin and bisphosphonates, are able to reduce the pain and the levels of total ALP.

MATERIALS AND METHODS

In the study we included 107 patients affected by Paget's disease, who were hospitalized at our Orthopaedic Institute in the period between 1970 and 2010 for tests and treatments related to Paget's disease. All the patients were white Italians from various regions. Their mean age was 61.32 ± 12.84 years; range 24 to 88 years; 30 patients were women (28%) and 77 were men (72%).

We did not include patients treated before 1970 because clinical and laboratory tests were not sufficiently homogeneous before this period. We also excluded patients with Paget's disease who were affected by severe hip or knee arthritis (12 individuals), since the literature suggests that specific therapies for Paget's disease (calcitonin and bisphosphonates) might not be effective in this type of pain (Calderoni *et al.* 2002; Vasireddy *et al.* 2003; Wienfiled & Stamp 1984). Furthermore, we did not include patients with pain resulting from occasional traumatic events. Discontinuous use of NSAIDs (no more than twice per week) was tolerated. In this study we considered the following parameters: pain, total ALP and therapy.

Pain

Most patients reported a chronic type of pain (91 individuals out of 107 = 85%). Despite lacking a precise score, the presence or absence of chronic pain seemed to be a sufficiently clear clinical datum to be statistically analyzed; therefore, based on the presence or absence of pain, the patients were divided into two groups, *Pain*, and *No Pain*.

Total ALP

Among the laboratory analyses aimed at exploring bone metabolism, total ALP appears to be the most consistently performed examination, since only a few misses have been reported (11 individuals). The methods of assaying alkaline phosphatase, however, have not always been the same over the years. Therefore, for every patient we calculated the difference in percentage of the absolute datum with respect to the upper normal limit indicated by the laboratory, following this formula:

$$\frac{\text{Pts. ALP} - \text{Upper Normal Limit ALP}}{\text{Upper Normal Limit ALP}} \times 100$$

Treatment

Treatment of these patients varied according to the therapeutic trends of the different periods.

Before the 1980's the tendency was to check the disease's evolution but without administering any specific treatment. Alternatively, several patients were treated with calcitonin. Since the 1990's bisphosphonates have been the most commonly used drugs in our patients, whereas only a few patients have not received any treatment.

We divided our patients according to the treatment they received:

- *bisphosphonates* n. 18 (17%)
- *calcitonin* n. 27 (25%)
- *no-therapy* n. 62 (58%)

In the *bisphosphonates* group, 4 patients were treated with 400 mg orally per day of etidronate for six consecutive months, once a year for at least two years; 14 patients received 300 mg cycles of clondronate by infusion in 500 cc of physiological solution, once a day for 5 consecutive days, twice a year for at least two years. These bisphosphonates belong to the first generation and work in a very similar way (Burr 2001; Fleisch 1987; Nancollas *et al.* 2006). Furthermore, the protocol was applied correctly, even according to the most accepted guidelines (Selby 2002); we therefore put all these patients into one group.

The *calcitonin* group included patients who had undergone cycles of 50–100 IU i.v. a day of synthetic calcitonin for an average of thirty consecutive days, twice a year.

The *no-therapy* group consisted of patients who had not received any specific drugs for Paget's disease.

Statistical analysis

Pearson's chi–square test was used to evaluate the difference among the treatment groups in relation to the pain. The description of levels of total ALP within treatment groups was made in percentiles and the differences

were analysed by Kruskas Wallis Test, completed by post-hoc test (paired analysis by non-parametric Least Significance Difference test). The difference in the total ALP levels between the *Pain* and *No Pain* groups was analysed by non-parametric Mann-Whitney U Test.

RESULTS

We first assessed the frequency of pain in all the patients of our series and in relationship to the treatment *(Pain/ Therapy)*. We then analyzed the total ALP in relationship to the therapy administered (*total ALP / Therapy)*. Subsequently, the presence of the pain was considered in relationship to the levels of total ALP *(Pain / total ALP)*. Finally, we assessed the relationships between pain, levels of total ALP and the therapy received by the patients in the *Pain group* (*see tab. 4, Pain group: total ALP / Therapy*) and in *No Pain group* (*see Table 5, No Pain group: Total ALP / Therapy)*.

Description of the pain in the Pain and No Pain groups and comparison in relationship to therapy (see Table 1: Pain / Therapy)

Pain was present in most patients (n.91 = 85%); while relatively few patients (*No Pain)* did not report pain (n.16 = 15%).

With regard to the therapy performed, pain was present in 50% of patients belonging to the *bisphosphonate group*; in the *calcitonin group* pain was present in all the patients; while in the *no-therapy group* pain was reported in 88.7% of patients. The difference among the three groups of therapy was statistically significant.

Description of the total ALP levels and comparison in relationship to therapy (see Table 2: total ALP / Therapy)

The values of total ALP assayed on hospital admission exceeded normal levels in most cases (99 out of 107 = 92.5%). Nevertheless, values varied widely: mean 233.39 ± 416.39, ranging from 63.93 to 2635.2. Given the wide standard deviation, we described the values in percentiles for each treatment group.

The levels of total ALP were on average lower in the *bisphosphonate group* in comparison with the *calcitonin group* and the *no-therapy group*. The difference among the three groups was highly statistically significant (*see Table 2 A*). At "post hoc" pair analysis, the *bisphosphonate group* had significantly lower values of total ALP in comparison with the *calcitonin and no-therapy groups (see Table 2 B)*.

Description of the distribution of pain in relationship to total ALP level (see Table 3: Pain / Total ALP).

The descriptive analysis in percentiles highlighted how patients with pain always had higher than normal phosphatase values; in addition, in most cases values were double or triple in comparison with the normal upper limit. Instead, the patients without pain had values of total ALP on the whole lower than patients with pain and in 25% of cases the values were in the normal range.

Description of the total ALP levels according to pain and the therapy administered (see Table 4, Pain group: total ALP/Therapy and tab. 5, No Pain group: total ALP/ Therapy).

Finally, within the *Pain* and *No Pain groups* we analysed the distribution of total ALP values according to

Tab. 1. PAIN / THERAPY.

THERAPY	PAIN n. Pts	%	NO PAIN n. Pts	%	Pearson
Bisphosphonate	9	50	9	50	
Calcitonin	27	100	0	0	
No therapy	55	88.7	7	11.3	$p<0.0005$
Total	91	85	16	15	

Description of pain in the Pain and No-Pain groups and in the bisphosphonate, calcitonin, and no-therapy groups. Comparison in relation to therapy: the differences among the therapy groups are highly significant, according to Pearson's chi-square test.

Tab. 2. TOTAL ALP / THERAPY.

A

THERAPY	TOTAL ALP Diff. % from normal upper limit			K.W.
	Percentiles			
	25	Median 50	75	
Bisphosphonate	–2.87	26.75	130.6	
Calcitonin	125.2	231.7	384.7	$p<0.001$
No Therapy	8.8	45.0	225.8	

B

Paired analysis	L.S.D.
Bisphosphonate > No therapy	
Bisphosphonate > Calcitonin	$p<0.001$
Calcitonin > No therapy	

A: Difference in % from upper normal laboratory limit of total ALP.
Description in percentiles within therapy groups; highly significant difference among the groups according to the Kruskal Wallis Test.
B: Post-hoc test: paired analysis by non-parametric Least Significance Difference test;
the bisphosphonate group has significantly lower values compared to the other two groups.

Tab. 3. PAIN / TOTAL ALP.

PAIN	TOTAL ALP Diff. % from normal upper limit			U-test
	Percentiles			
	25	Median 50	75	
YES	32.65	107.15	293.65	$p<0.03$
NO	–13.75	30.15	124.85	

Difference in % from upper normal laboratory limit of total ALP. Description in percentiles within the Pain group (YES) and No-Pain group (NO); the differences between the groups are significant according to the non-parametric Mann-Whitney U test.

the treatment performed. We also observed how in each group the total ALP values tended to be higher in patients with pain *(see Table 4)* in comparison with those without pain (*see Table 5)*, which underlines the close relationship between metabolic hyperactivity and pain, despite the different therapies performed.

Nevertheless, in the *Pain group* statistical analysis showed how total ALP values were different in relationship to the treatment performed, the *bisphosphonate group* always having lower values; conversely, the *calcitonin group* always had higher values of total ALP compared with the *bisphosphonate* and *no therapy groups* (*see tab. 4*, *K.W. and L.S.D. tests*).

The trend also appeared similar in the *No Pain group*, where, however, differences did not appear significant, probably due to the lower number of cases.

DISCUSSION

The investigation into the existence or non-existence of primary pain in Paget's disease is not merely theoretical, it also has practical implications; recognising a primary origin of pain leads, in fact, to consider it appropriate to define a specific treatment for Paget's disease from the time of diagnosis, relegating pain relief therapy to the role of an additional symptomatic drug. The use of a purely analgesic drug in a situation in which pain is merely an expression of an active dysmetabolic process exposes the patient to all the well-known complications of Paget's disease.

Managing pain in Paget's disease requires an understanding of the pathogenesis of the pain. The most accredited cause of pain in Paget's disease is currently believed to be the mechanical incompetence of the tissue affected by the disease, i.e. the architectural disorganisation of the bone which leads to its inability to respond effectively to the mechanical stress and above all, for the lower limbs, to the load. It is highly probable that micro-fractures are the last effectors of pain in Paget's disease and that they are an integral part of the chaotic bone reabsorption and neoformation, the basis of the known alterations in this disorder: deformity, increase in volume, macro-fractures (Varenna *et al.* 2010). Some authors suggested that the pain in Paget's disease is caused by the typical hypervascularity of the bone tissue, with an increase in intermedullary bone pressure and stretching of the periosteum (Arlet & Mazieres 1975). In our opinion, this hypothesis is the least possible one, even if it would explain the presence of pain in the bone structures not subject to load.

Most authors now tend to recognise primary bone pain in Paget's disease as distinct from joint pain or pain due to compression of innervated structures close to the area affected by the disease. *Pain is attributed to bone if it is more severe at night and is neither precipitated by exercise nor relieved by rest*, according to criteria already described in the literature (Hamdy *et al.* 1993).

As regards the frequency of pain in Paget's disease, reports vary considerably (Davie *et al.* 1999; Harinck *et al.* 1986; Varenna *et al.* 2010; Ziegler *et al.* 1985) and depend on how the patients were recruited and how the symptoms were assessed. Although in our study we excluded all the known causes of secondary pain, the symptom was extremely common. We would like to stress that the pain was associated with high levels of alkaline phosphatase; the trend was always the same in all the groups: the patients with pain had high levels

Tab. 4. PAIN GROUP: TOTAL ALP/ THERAPY.

A

THERAPY	TOTAL ALP Diff. % from normal upper limit			K.W.
	Percentiles			
	25	Median 50	75	
Bisphosphonate	7.8	36.0	150.7	
Calcitonin	148.45	231.7	358.5	$p<0.001$
No Therapy	8.60	45.35	227.4	

B

Paired analysis	L.S.D.
Bisphosphonate > No therapy	
Bisphosphonate > Calcitonin	$p<0.01$
Calcitonin > No therapy	

A: Difference in % from upper normal laboratory limit of total ALP.
Description in percentiles within therapy groups; highly significant difference among the groups according to the Kruskal Wallis Test.
B: Post-hoc test; paired analysis by non-parametric Least Significance Difference test;
the bisphosphonate group has high significantly lower values compared to the calcitonin group.

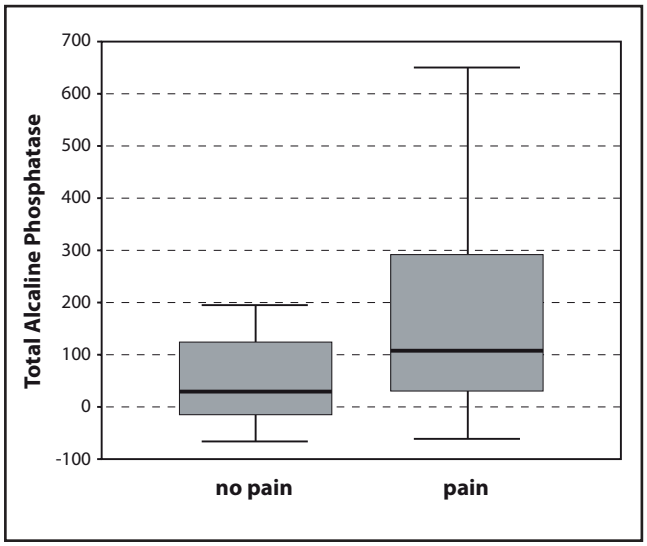

Fig. 1. Total ALP: Median and percentiles in the No-Pain and in Pain groups. In the No Pain group the values of total ALP are lower than the values in Pain group; the difference is significant ($p<0.03$) according Mann Whitney test.
The central line represents the median, the edges of the box represent the 25th and 75th percentiles; the edges of the whiskers represent the minimum and maximum values detected.

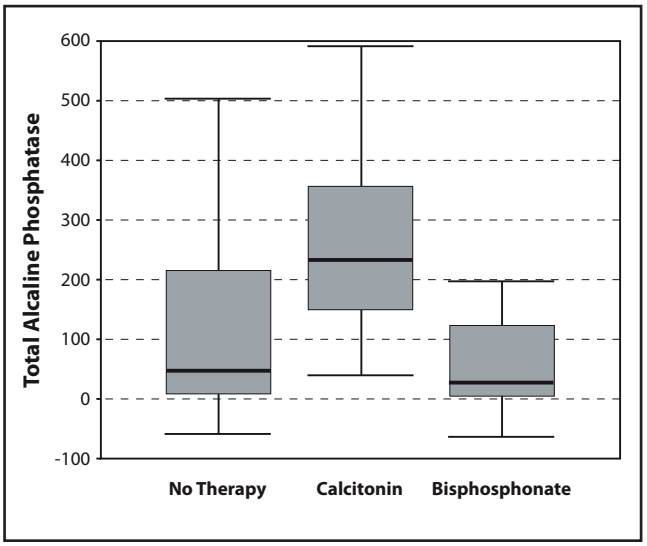

Fig. 2. Total ALP: Median and percentiles in the no therapy, calcitonin and bisphosphonate groups. In the bisphosphonate group the level of total ALP is lower than the value of the other two groups; the difference is highly significant ($p<0.001$) according to K.W. test and post hoc LSD paired analysis.

of ALP and vice versa (see Figure 1). This seems to confirm the close relationship that exists between pain and metabolic hyperactivity and indirectly indicates the measurement of ALP as a useful means for following the evolution of the disease.

As regards the efficacy of the treatment on the disease, we considered 2 items: *pain* and *bone dysmetabolism*.

For *pain* it appeared evident that only biphosphonates are able to have any effect on the symptom. The analgesic effect of biphosphonates seems complex: they inhibit the metabolic hyperactivity of the bone, being active both on osteoblasts and osteoclasts. They also have marked anti-inflammatory effects, inhibiting the release of mediators such as IL-6, IL-1 and TNF by the macrophages; this seems typical of non-amino-bisphosphonates (Corrado *et al.* 2007; Santini *et al.* 2004), i.e. the drugs used in our study.

On the contrary, *calcitonin* did not appear to have any effect on the pain in our patients, in contrast with the role attributed to this drug in the past. Unfortunately we do not know the exact extent of the pain suffered by our patients, we only know whether they had pain or not. Considering the great importance of calcitonin in the management of pain until the 1990s, we cannot therefore exclude the possibility that this drug was used in particularly symptomatic patients in our study. On the other hand, the frequency of pain in patients treated with calcitonin (100%) was very similar to the frequency in the no-therapy group (88%) and this certainly does not say much about the efficacy of the drug.

Tab. 5. NO-PAIN GROUP: TOTAL ALP / THERAPY.

THERAPY	TOTAL ALP Diff. % from normal upper limit			U test
	percentiles			
	25	Median 50	75	
Bisphosphonate	–35.7	17.5	101.7	
Calcitonin	–	–	–	n.s.
No therapy	17.6	33.9	128.6	

Difference in % from upper normal laboratory limit of total ALP. Description in percentiles within therapy groups; the differences are not significant according to the Mann Whitney U-test. The calcitonin group has no patients.

The *bone dysmetabolism* was very well controlled by biphosphonates: the group treated with biphosphonates had normal total ALP values in 25% of cases; slightly increased in 50% of cases and double with respect to normal values in only 25% of cases. In the other two groups (*calcitonin and No-therapy*), 75% of the patients had total ALP values much higher than normal, the worst values being found in the calcitonin group.

Finally, within the *biphosphonates group* the total ALP values were less scattered than in the other two groups; the data of the *biphosphonates group* appear, in fact, to be more compressed, as if the drug had homogenised the levels of total ALP of all the patients towards values closer to normal (see Figure 2).

CONCLUSIONS

Pain appears to be such a frequent symptom in Paget's disease that it can be considered an integral part of the same illness; pain seems to correlate to metabolic alteration.

Bisphosphonates seem to be the only drugs able to control both the pain and the levels of total ALP.

In the light of these historical data, we advocate bisphosphonate therapy in all patients affected by Paget's disease with pain and high levels of total ALP. In consideration of the same data, calcitonin therapy no longer seems to be an appropriate treatment for this disease.

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