The role of bone histomorphometry in the management of metabolic bone disease

Nicolau R[1*], Pereira L[2], Terroso G[3], Vaz C[2,3], Brito I[2,4], Frazão J[2,5]

[1] Rheumatology Department, Unidade de Saúde Viseu Dão Lafões, Viseu, Portugal

[2] Faculty of Medicine, University of Porto, Porto, Portugal

[3] Rheumatology Department, Centro Hospitalar e Universitário de São João, Porto, Portugal

[4] Pediatrics and young adult Rheumatology Unit, Centro Hospitalar Universitário de São João, Porto, Portugal

[5] Nephrology Department, Centro Hospitalar Universitário de São João, Porto, Portugal

*ORCID ID: 0000-0001-6410-0121

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Correspondence to

Rafaela Nicolau

E-mail: 8511@ulsvdl.min-saude.pt

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Abstract

Purpose: Bone biopsy is the only technique capable of comprehensively assessing all bone parameters, including turnover, microarchitecture, and mineralization, yet its clinical utility is debated. This study evaluates its role in routine diagnostic and therapeutic applications.
Methods: A retrospective analysis was conducted on 22 horizontal transiliac bone biopsies from 20 patients referred for rheumatology consultation between August 2016 and May 2022. Diagnoses included osteoporosis, adynamic bone disease, hyperparathyroidism-related bone disease, and osteomalacia.
Results: Histopathological findings led to therapeutic strategies differing from standard anti-osteoporotic treatment in over one-third of cases. In certain cases, bone biopsy provided critical diagnostic insights that guided therapeutic decisions.
Conclusion: Although advancements in non-invasive diagnostics exist, bone biopsy remains indispensable for a subset of patients, offering essential diagnostic and therapeutic insights that significantly influence clinical management.

Keywords: Osteomalacia; Treatment response; Osteoporosis; Antiosteoporotic treatments; Bone.

Introduction

Bone biopsy with bone histomorphometric analysis remains the most reliable method for comprehensively assessing bone health and diagnosing Metabolic Bone Diseases (MBD)[1]. This method evaluates bone quality by assessing factors such as the degree of mineralization and microarchitecture, and it also analyzes bone turnover mechanisms to guide treatment decisions and measure therapeutic efficacy. Currently, bone biopsy is primarily used to diagnose osteomalacia, characterize renal osteodystrophy, and to investigate cases of bone fragility that do not respond to conventional osteoporotic treatments[2].

Although Dual Energy X-ray Absorptiometry (DEXA) scans are widely used to diagnose osteoporosis, they primarily measure bone mineral density (BMD), potentially overlooking abnormalities in bone mass or mineralization. As a result, individuals with seemingly normal BMD may still be vulnerable to fractures due to underlying issues with bone structure.

Additionally, DEXA scans may not accurately reflect bone strength, especially in individuals with degenerative conditions or those undergoing specific medical treatments[3-6].

Traditionally, a bone biopsy is recommended in CKD stages 4–5 for suspected osteomalacia, unexplained discordance in bone-related biomarkers and severe calcium or phosphate imbalances. Despite improvements in hormone level testing methods, they still lack the specificity, sensitivity, or reliability needed to accurately predict bone histology. Although fracture risk prediction can rely on bone mineral density measurements in CKD stages 1–3, it becomes more complex in stages 4–5 due to various subtypes of renal osteodystrophy resulting in low bone mineral density. Precise diagnosis of renal osteodystrophy subtypes through histomorphometric analysis is crucial for guiding effective prevention and treatment strategies. This analysis serves as a fundamental tool in identifying patients who could benefit from antiresorptive therapy, enabling a personalized and targeted approach to selecting treatments[7-9].

Despite its clinical value, bone biopsy and histomorphometry are often underutilized due to concerns about invasiveness, the need for specialized technical expertise and the lack of individuals trained in performing the histomorphometric analysis.

However, transiliac bone biopsy is a well-tolerated procedure with minimal morbidity and no mortality risk. While bone histomorphometry has traditionally focused on trabecular bone, the significance of cortical bone quality is increasingly recognized, particularly in patients with CKD, where cortical abnormalities such as increased porosity and reduced thickness are prevalent. Recent studies have underscored the importance of analyzing cortical bone to better understand bone health in various clinical contexts[10-12].

In this paper, the authors report on a decade of experience with clinical bone biopsies requested by the Rheumatology department, in collaboration with the Bone Histomorphometry Unit and the Nephrology Department. This long-term study provides valuable insights that can serve as a helpful reference for clinical practice.

Patients and methods

A retrospective cohort study was conducted between August 2016 and May 2022, involving 20 patients who underwent a total of 22 horizontal transiliac bone biopsies, which were subsequently analyzed for diagnostic purposes. Bone biopsies were performed by the Nephrology Department of São João Hospital Centre and analyzed in collaboration with the Bone Histomorphometry Unit at the Faculty of Medicine of Porto.

All patients were submitted to a transiliac bone biopsy using a modified Bordier trephine, horizontal approach, under local anesthesia with lidocaine 2% and conscious sedation with

intravenous midazolam. Bone biopsy was performed 3–5 days after a double course of tetracycline-doxycycline 100 mg twice daily for 3 days, repeated after an interval of 12 days[13]. Doxycycline was the only tetracycline available in our country at the time of this study. Biopsy specimens were 5–7 mm in diameter by 10 mm in length. Bone was dehydrated in alcohol, cleared with xylene, and embedded in methyl methacrylate. Undecalcified 5-µm sections were cut and stained with modified Masson-Goldner trichrome for static histomorphometric evaluation. Unstained 10-µm sections were prepared for fluorescent microscopy analysis of dynamic parameters. All histomorphometric analyses were performed by a single operator. Samples were considered suitable for histomorphometric evaluation only if it was possible to read without artifacts 30 fields under magnification x200. According to KDIGO guidelines, MBD was classified by analyzing turnover, mineralization, and volume (TMV classification) in osteomalacia (low turnover, abnormal mineralization); adynamic bone (low turnover, normal mineralization); mixed uremic osteodystrophy (high turnover, abnormal mineralization); and hyperparathyroid-related bone disease (high turnover, normal mineralization). In line with the framework proposed by Ott and recognizing the importance of bone volume, patients with low bone volume with normal turnover and mineralization were grouped within the diagnosis of osteoporosis and patients with normal turnover, volume, and mineralization were classified as having normal bone[14]. Bone volume was considered normal if bone volume/tissue volume (BV/TV) >20%; normal turnover range was considered when bone formation rate/bone surface (BFR/BS) was between 18 and 38 $\mu m^3/\mu m^2$/year. Mineralization was abnormal when mineralization lag time (MLT) was higher than 100 days[15].

The evaluation of bone biopsies involved examination of six key aspects:

1. Indications for bone biopsy: Reasons prompting the need for bone biopsy;
2. Quality of bone specimens: Assessment of the bone samples by the osteopathologist;
3. Histopathological diagnosis: Findings and conclusions provided by the osteopathologist;
4. Change of diagnosis: Any changes in diagnosis provided by bone biopsy;
5. Therapeutic strategy implications: Documentation of any changes in medical treatment for bone health, including initiation or avoidance of specific anti-osteoporotic treatments.
6. Complications: Identification and documentation of any complications arising from the bone biopsy procedure.

Results

Twenty patients underwent bone biopsy, as detailed in Table I, which presents an overview of their demographic and clinical characteristics. Two patients were rebiopsied during the follow-up. One patient's bone sample did not meet the criteria for satisfactory histomorphometric analysis.

Fragility fracture and CKD stage 4-5 (n=13, 59.1%) were the most common indications for biopsy, followed by suspicion of osteomalacia (n=6, 27.3%), atypical femoral fracture (n=2, 9%), and refractory osteoporosis (patients who had a fragility fracture under osteoporosis treatment) (n=1, 4.6%), as detailed in Table II.

Histomorphometric parameters and histopathological diagnoses, categorized according to TMV classification, are presented in Table III. The most frequently diagnosed pattern was adynamic bone disease (n=9; 40.9%), followed by osteomalacia (n=6; 27.3%), osteoporosis (n=4; 18.2%), and hyperparathyroidism bone disease secondary to CKD (n=3; 13.6%). Table IV delineates analytical parameters corresponding to different histopathological diagnoses.

After histopathological diagnosis, following histopathological diagnosis, 70% of patients (n=14) were not prescribed any anti-osteoporotic treatment, and 10% (n=2) discontinued ongoing treatment. There were no reported complications associated with the procedure.

In the following section of results, we examined the data by categorizing patients based on their diagnosis.

Adynamic bone disease

Nine patients were diagnosed with adynamic bone disease (Figure 1), eight of them associated with CKD stages 4-5. Notably, one patient presented an atypical fracture following 20 years of bisphosphonate treatment. In this case, teriparatide therapy was initiated, and a follow-up bone biopsy performed two years later indicated a slight improvement in cortical thickness. For the remaining 8 cases, modifications were implemented in vitamin D and calcium supplementation, alongside a reduction in secondary hyperparathyroidism treatment. One patient stopped denosumab.

One patient with CKD underwent follow-up biopsy procedure two years later due to a new fragility fracture. The biopsy results showed similarities with the previous findings, leading to the continuation of the existing therapeutic strategy.

Osteomalacia

Six patients were diagnosed with osteomalacia (Figure 2), and distinctive underlying causes were identified for each individual. These included a patient with Rendu Oslo Weber syndrome treated with ferric carboxymaltose, another with hypophosphatemic rickets, and one with oncogenic hypophosphatemic osteomalacia. In the remaining 4 patients, inadequate levels of vitamin D were identified as the primary cause. Consequently, a personalized approach was implemented, with adjustments made to calcium, vitamin D, and phosphorus supplementation tailored to each individual's underlying cause. Additionally, one patient discontinued bisphosphonate treatment.

Osteoporosis

Four patients were diagnosed with Osteoporosis - three with fragility fractures and CKD stage 4, and one with refractory osteoporosis. Following bone biopsy, denosumab treatment was initiated for the three patients with CKD, while zoledronic acid was prescribed for the remaining patient.

Hyperparathyroidism bone disease

Three patients were diagnosed with bone disease associated with hyperparathyroidism secondary to CKD. In all cases, treatment with denosumab was started.

Follow-up

Patients were followed for an average follow-up period of 3.6 years. Three (15%) patients suffered a new fragility fracture and 4 (20%) died from infectious diseases.

Among those who sustained fractures, two were female, and one was male. The male patient, aged 36, was diagnosed with osteomalacia and treated with vitamin D and calcium supplementation. One female patient, aged 62, had refractory osteoporosis and was treated with zoledronic acid, while the other, aged 73, was diagnosed with adynamic bone disease and received vitamin D and calcium supplementation. Of these, only the patient with adynamic bone disease underwent a repeat biopsy, and the results closely resembled the initial findings, supporting the continuation of the existing therapeutic strategy.

Discussion

Our study analyzed bone biopsy procedures in 20 patients, complemented by histomorphometric analysis, with the explicit aim of unraveling the intricate relationship between bone histology and therapeutic interventions. This patient cohort, predominantly comprising postmenopausal females aged 36 to 88, was deliberately selected based on the manifestation of atypical symptoms indicative of osteoporosis or metabolic bone disease.

In instances where histopathological assessments uncovered adynamic bone disease alongside CKD stages 4-5, our recommendation leaned towards the supplementation of active vitamin D (1,25-dihydroxycholecalciferol) as opposed to conventional antiresorptive therapy. Conversely, for patients exhibiting secondary hyperparathyroidism bone disease, denosumab therapy emerged as the preferred modality. Remarkably, the divergence from standard anti-osteoporotic treatments often stemmed from insights gleaned through histopathological analysis.

The remarkably high prevalence of prior fragility fractures, 95% in our cohort, highlights the critical need for early fracture risk assessment to enhance patient outcomes. Early risk assessment, alongside advanced diagnostic techniques, can provide a more detailed understanding of bone health and help tailor more effective treatment strategies. Moreover, integrating early fracture risk assessment with advanced diagnostic tools could potentially reduce the incidence of fractures, improving quality of life and reducing healthcare costs associated with fracture treatment and management[16-18].

Kann *et al.* have demonstrated the utility of bone biopsies in cases of atypical clinical or biochemical profiles or instances of treatment failure, aligning closely with our findings. Furthermore, biopsies aimed at assessing bone quality, encompassing microarchitecture and mineral quality, offer invaluable insights into bone fragility, thereby paving the way for enhanced therapeutic strategies[19].

Chavassieux *et al.* and Dempster *et al.* have highlighted the pivotal role of bone biopsy samples in assessing the long-term efficacy and safety of osteoporosis medications. Their research emphasizes how bone biopsies provide detailed insights into bone tissue responses, including changes in bone microarchitecture and turnover rates, which are crucial for understanding the comprehensive impact of treatments over time. By examining bone biopsy samples, these studies have contributed to a deeper understanding of how osteoporosis medications impact bone quality, including changes in bone microarchitecture and turnover rates. This level of detailed analysis is essential for determining not only the effectiveness of these medications in

increasing bone density but also their ability to enhance overall bone strength and reduce fracture risk[20,21].

Despite its advantages, the routine use of bone biopsy in osteoporosis management remains controversial. Non-invasive tools such as dual-energy X-ray absorptiometry, high-resolution peripheral quantitative computed tomography, and biochemical markers provide valuable insights into bone density and turnover. However, they fail to directly assess bone microarchitecture, mineralization, and cellular activity - critical factors in bone fragility. This limitation becomes particularly relevant in cases of unexplained fractures, atypical treatment responses, or complex metabolic bone disorders, where conventional imaging and laboratory tests may be insufficient for precise diagnosis and treatment planning.

While the ultimate objective remains the development of non-invasive predictors for bone health, current clinical practices often necessitate bone biopsies to unravel underlying pathogenic mechanisms, transcending mere documentation of therapy outcomes. To address the limitations inherent in bone biopsy as a diagnostic tool, we advocate for augmenting physician proficiency in biopsy procedures, fostering a deeper understanding of biopsy insights, and establishing proficient laboratories for histological assessments. A comprehensive evaluation of the repercussions and complications associated with transiliac bone biopsies holds particular significance. Fortunately, reported low complication rates bolster the safety of this procedure, especially when conducted by experienced clinicians, allaying concerns regarding its perceived invasiveness and risks. Previous studies analyzing 99 cases over 14 years and 101 cases in one year reported only rare and mild complications, further supporting its safety and tolerability[22-23].

Moreover, we emphasize the advantages of interdisciplinary collaboration between Nephrology and Rheumatology in managing these patients, advocating for standardized protocols for bone biopsy procedures to enhance utilization and improve patient outcomes.

However, it is crucial to acknowledge several limitations inherent in this study, primarily stemming from its retrospective design and limited sample size. Retrospective studies rely on existing records, which may lack comprehensiveness or systematic documentation, potentially introducing inaccuracies. Future research endeavors should aim to mitigate these limitations by expanding sample sizes, encompassing more diverse populations, and conducting long-term, prospective studies to furnish a more nuanced understanding of the role of bone biopsies in managing osteoporosis.

Conclusion

The integration of bone biopsy and histomorphometry into conventional diagnostic methods stands as a valuable tool in osteoporosis assessment. By providing detailed information on bone microarchitecture and turnover, these techniques empower clinicians to tailor treatments to individual needs, elevating the precision of clinical decisions. Embracing these methodologies has the potential to improve osteoporosis management, optimizing patient care and contributing to a reduction in fracture prevalence. However, larger studies are needed to confirm these findings and fully assess their impact on clinical practice.

Tables and Figures

Table I. Demographic and clinical characteristics of patients.

Female, n (%)	15 (75)
Premenopausal	1 (6.5)
Median age, years	64.5 (20)
BMI (kg/m2)	26.2 (3.2)
Median lumbar spine BMD (g/cm2)	0.851 (0.321)
Median total hip BMD (g/cm2)	0.644 (0.274)
Median FRAX, %	
Major fracture risk	18 (11)
Hip fracture risk	11 (8)
Comorbidities, n (%)	
Previous fragility fracture	19 (33.3)
Diabetes Mellitus	7 (38.9)
Chronic kidney disease	12 (66.7)
Corticotherapy	6 (33.3)
Laboratory parameters	
Ionized Calcium (mg/dL)	2.5 (0.1)
Inorganic phosphate (mg/dL)	2.7 (1.3)
25-OH-Vitamin D (ng/mL)	24.5 (26)
PTH (pg/mL)	93.9 (191)
CTX (ng/L)	0.8 (1.3)
Osteocalcin (µg/L)	26 (106)
ALP (UI/L)	101 (100)

Data is presented as median (range) for non-normal distribution variables.
ALP = alkaline phosphatase, CTX C-terminal telopeptide of type I collagen, PTH = Parathormone.

Table II. Indications for bone biopsy.

Indications for bone biopsy	N (%)
Fragility fracture and stage 4-5 CKD	13 (59.1)
Suspicion of osteomalacia	6 (27.3)
Atypical femoral fracture	2 (9)
Refractory osteoporosis	1 (4.6)

Table III. Histomorphometric analysis.

Histomorphometric parameters	Correlation with reference values (n/total)[1]		
	Reduced	**Normal**	**Increased**
Cortex			
Thickness	19/21	2/21	-
Porosity	2/21	7/21	12/21
Osteoid volume	3/22	10/22	9/22
Trabecular volume	19/22	2/22	1/22
Erosion surface	11/22	8/22	3/22
Osteoblastic surface	20/22	1/22	1/22
Osteoclastic surface	3/22	16/22	3/22
Turnover	16 (72.7%)	3 (13.6%)	3 (13.6%)
Mineralization: normal n (%) / abnormal n (%)	6 (27.3%) / 16 (72.7%)		
Volume	20 (90.9)	1 (4.5)	1 (4.5)
Fluorescent microscopy			
Mineralized surface	16/22	3/22	3/22
Double labelled (n/total)	4/22		
Single labelled (n/total)	18/22		
Peritrabecular fibrosis (n/total)	5/22		

[1] n (%) in case of turnover, mineralization and volume parameters; Mineralization distinction only between normal and abnormal; double labelled, single labelled and peritrabecular fibrosis only with absolute values in relation with total.

Table IV. Laboratory parameters according to histopathological diagnoses.

Histopathological diagnoses	Ionized Calcium (mg/dL)	Inorganic phosphate (mg/dL)	25-OH-Vitamin D (ng/mL)	PTH (pg/mL)	CTX (ng/L)	Osteocalcin (ng/L)	ALP (UI/L)
Adynamic bone disease (n=9)	2.5 (0.1)	3.9 (1)	29.9 (20.8)	114.2 (133.9)	1.2 (1.3)	51 (56.5)	100.6 (37.5)
Osteomalacia (n=6)	2.5 (0.1)	1.8 (0.7)	24.2 (5.4)	135.6 (167.2)	4.7 (0.1)	13.8 (22.5)	192.8 (144)
Osteoporosis (n=4)	2.6 (0.2)	3.2 (0.5)	38.3 (9)	113.9 (50.20)	1.1 (0.7)	115.4 (96.8)	94.3 (12)
Hyperparathyrodism bone disease (n=3)	2.4 (0.1)	4 (1.2)	27.3	251.9 (133.7)	1.9 (0.6)	196.9 (1.35)	184 (128)
	8.5–10.5	3.5–5.5	20–50	12–60	0.185-0.427	14-46	46-120

Data are expressed as median and interquartile range (IQR). The respective reference values are in the last line of the table. ALP: Alkaline Phosphatase, CTX: C-terminal telopeptide of type I collagen, PTH: Parathormone.

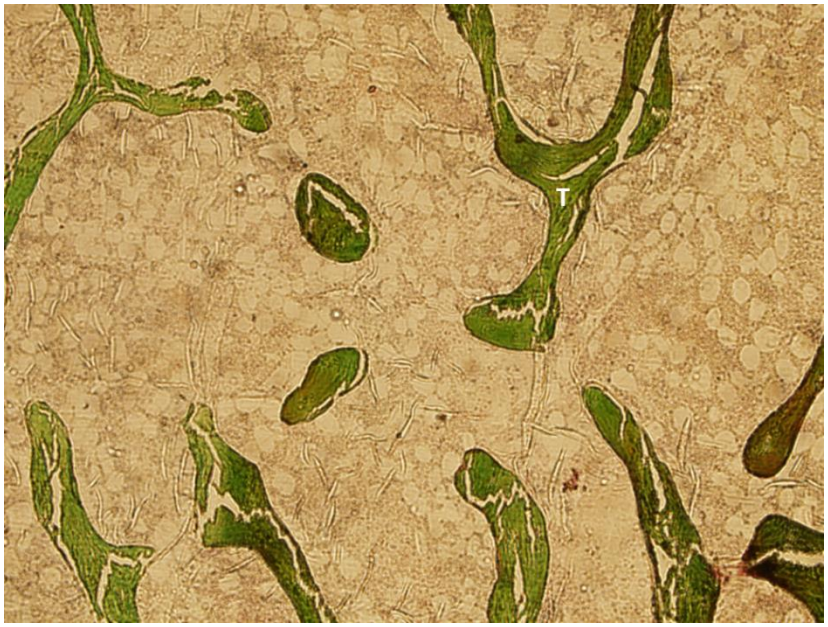

Figure 1. Adynamic bone disease showing marked reduction of bone volume and trabecular connectivity and absence of osteoid. (T: trabeculae)

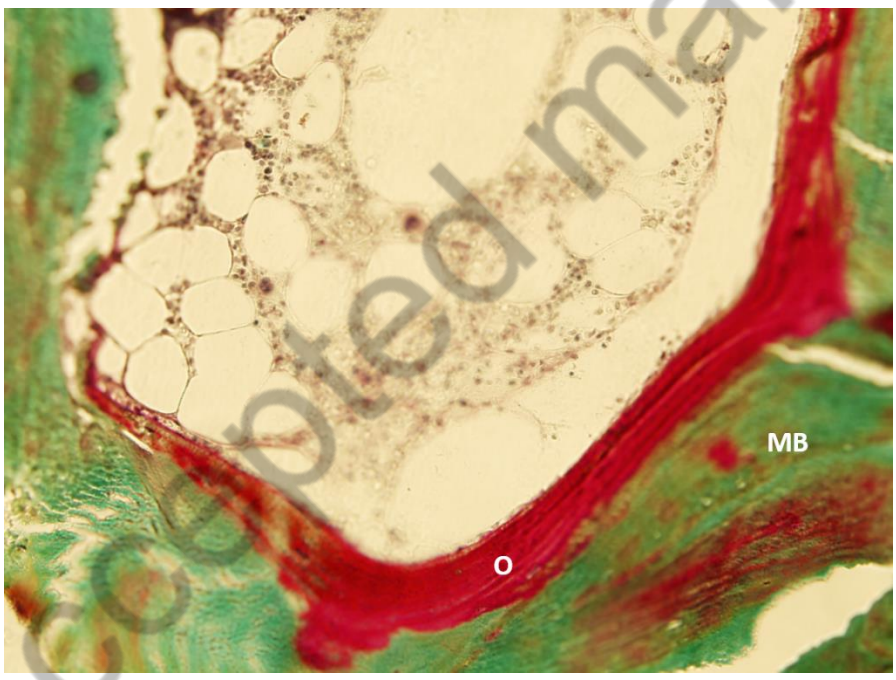

Figure 2. Osteomalacia showing increased extent and thickness of osteoid seams, without active bone cells (MB: mineralized bone; O: osteoid)

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