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The most ancient evidence of a diseased lagomorph: Infectious paleopathology in a tibiofibular bone (Middle Miocene, Germany)

L'évidence la plus ancienne d'un lagomorphe malade : paléopathologie infectieuse dans un os tibiofibulaire (Miocène moyen, Allemagne)

Blanca Moncunill-Solé [a,b,*], Albert Isidro [c], Alejandro Blanco [b,d], Chiara Angelone [a,e,f], Gertrud E. Rössner [d,g], Xavier Jordana [h]

[a] *Dipartimento di Scienze, Università degli Studi Roma Tre, Largo S. Leonardo Murialdo 1, 00146 Roma, Italy*
[b] *Centro de Investigacións Científicas Avanzadas (CICA), As Carballeiras s/n, Campus de Elviña, Universidade da Coruña, 15071 A Coruña, Spain*
[c] *Department of Orthopedics, Hospital Universitari Sagrat Cor, 08029 Barcelona, España*
[d] *SNSB - Bayerische Staatssammlung für Paläontologie und Geologie (BSPG), Richard-Wagner-Str. 10, 80333 München, Germany*
[e] *Institut Català de Paleontologia Miquel Crusafont (ICP), Edifici Z ICTA-ICP, Carrer de les Columnes s/n, Campus de la Universitat Autònoma de Barcelona, 08193 Cerdanyola del Vallès, Barcelona, Spain*
[f] *Key Laboratory of Vertebrate Evolution and Human Origins, Institute of Vertebrate Paleontology and Palaeoanthropology, Chinese Academy of Sciences, 142 Xi Zhi Men Wai Da Jie, 100044 Beijing, China*
[g] *Department of Earth and Environmental Sciences, Paleontology & Geobiology, Ludwig-Maximilians-Universität München, Richard-Wagner-Str. 10, 80333 München, Germany*
[h] *Unitat d'Antropologia, Departament de Biologia Animal, Biologia Vegetal i Ecologia, Edifici C Facultat de Biociències, Universitat Autònoma de Barcelona, 08193 Cerdanyola del Vallès, Barcelona, Spain*

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ABSTRACT

Few pathological cases have been identified in fossils of small mammals. Here we report the most ancient paleopathological evidence identified in a lagomorph (Ochotonidae, middle Miocene). The tibiofibular bone was macro- and microscopically (μCT) inspected to provide a diagnosis, an etiology, and its possible relationship with the individual's cause of death. Osteogenesis (reactive bone growth) and osteolysis, processes related with neoplasms and infections, are identified in the abnormal bony region. Its location (juxta-articular) and morphology allow us to identify it as a joint infection (septic arthritis) consequential of a violent mechanism, such as a bite. Both the origin of bone accumulation (avian pellets) and the poor vital state of the specimen (with a joint infection) point to predation as the most probable cause of death. Up to now, lagomorph paleopathologies had only been described in insular populations, and the present one is the first evidence in a mainland specimen.

* Corresponding author at: Universidade da Coruña, Centro de Investigacións Científicas Avanzadas (CICA), Departamento de Física e Ciencias da Terra, As Carballeiras s/n, Campus de Elviña, 15071 A Coruña, Spain.
E-mail addresses: blanca.moncunill@udc.es, blanca.moncunill@gmail.com (B. Moncunill-Solé), aisidro.cot@gmail.com (A. Isidro), alejandro.blancoc@udc.es (A. Blanco), chiara.angelone@uniroma3.it (C. Angelone), roessner@snsb.de (G.E. Rössner), xavier.jordana@uab.cat (X. Jordana).

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R É S U M É

Peu de cas pathologiques ont été identifiés dans des fossiles de petits mammifères. Nous rapportons ici les preuves paléopathologiques les plus anciennes identifiées chez un lagomorphe (Ochotonidae, Miocène moyen). L'os tibiofibulaire a fait l'objet d'une inspection macroscopique et microscopique (μCT) afin de fournir un diagnostic, son étiologie et sa relation possible avec la cause de décès de l'individu. L'ostéogenèse (croissance osseuse réactive) et l'ostéolyse, processus liés aux néoplasmes et aux infections, sont identifiés dans la région anormale de l'os. Sa localisation (juxta-articulaire) et sa morphologie permettent de l'identifier comme une infection articulaire (arthrite septique) consécutive à un mécanisme violent, tel qu'une morsure. L'origine de l'accumulation osseuse (granulés aviaires) et le mauvais état vital du spécimen (avec une infection articulaire) indiquent que la prédation est la cause de décès la plus probable. Jusqu'à présent, les paléopathologies lagomorphes n'avaient été décrites que dans des populations insulaires, et celle-ci est la première preuve sur un spécimen du continent.

Mots clés :
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Ostéolyse
Arthrite septique
Petits mammifères

1. Introduction

Occasionally, biological remains of extinct species show pathological conditions (Rothschild and Martin, 2006). Developmental disorders, stress marks, tumors, infections or traumas are among the most common. Because these abnormalities are comparable to those observed in extant living beings, paleontologists can provide an accurate diagnosis and can investigate their etiology (Rothschild and Martin, 2006; Shufeldt, 1893). Paleopathological investigations can unveil many biological aspects of extinct species, *inter alia* traits of their immunology, physiology, life history, behavior, and of inter- and intraspecific interactions (Anné et al., 2016; Böhmer and Rössner, 2018; Hone and Tanke, 2015; Rothschild and Martin, 2006; Waldron, 2009). In this regard, non-lethal pathologies that leave a trace in bones or teeth over time are of special significance (Foth et al., 2015). The big boom of paleopathological studies is relatively recent, coinciding with the improvement of non-invasive diagnostic techniques (Mariani-Costantini et al., 1996; Shaffer and Baker, 1997). Pathological abnormalities have been described in a wide range of fossils, including plants, invertebrates (mainly trilobites), and vertebrates (such as fishes, amphibians, reptiles, carnivorans, several odd-toed and even-toed ungulates, and primates) (Anné et al., 2016; Böhmer and Rössner, 2018; Dieguez et al., 1996; Flynn et al., 2013; Foth et al., 2015; Haridy et al., 2019; Lyras et al., 2016, 2019; Pawłowska et al., 2014; Petit and Khalloufi, 2012; Rooney, 1997; Rothschild and Laub, 2013). Only a few paleopathological conditions have been described in small mammals, mainly in rodents. Luna et al. (2017) noted the presence of fractures, enthesial changes, osteoarthroses, and other abnormal conditions in several species of rodents (Cueva Tixi, middle to late Holocene, Argentina). The paleoparasitological analysis in rodent coprolites carried out by Sardella and Fugassa (2009) detected the presence of nematodes (Cerro Casa de Piedra, Holocene, Argentina). In fossil lagomorphs, Zoboli (2003) and Zoboli et al. (2018) described several abnormal conditions (arthrosis, periostitis, osteomalacia, fractures, osteosarcoma, osteonecrosis, etc.) of remains in *Prolagus sardus* (Wagner, 1829), a middlePleistocene–Holocene endemic insular ochotonid from Sardinia (Italy). Paleopathologies reported in continental lagomorphs are completely lacking, in spite of the fact that the members of this order are extremely common, widespread and abundant in the fossil record, especially since the Neogene onwards.

In the present research, we report on the most ancient known paleopathology in the order Lagomorpha up to now (middle Miocene, MN6), and the first ever documented on a mainland taxon. The aims of this study are: (1) to describe and assess this bony abnormality macro- and microscopically (μCT); and (2) to provide a diagnosis and to determine its etiology as well as the cause of death of the individual.

2. Material and methods

2.1. Geological setting

The examined pathological tibiofibular bone comes from the Goldberg site, a fossiliferous locality of the Nördlinger Ries, Bavaria, southern Germany (Fig. 1). Nördlinger Ries is a circular, shallow depression (22–24 km in diameter), formed by one of the cosmic impacts of a binary stony meteorite, at approximately 14–15 Ma (Abdul Aziz et al., 2008; Arp, 1995, 2006; Buchner et al., 2013; Göhlich and Ballmann, 2013). The depression was filled with an enclosed evaporitic soda shallow-water lake, which probably existed for a time span of 0.3 to 2 Ma (Jankowski, 1981). The Goldberg site (among other coeval, neighboring sites as Steinberg-Spitzberg or Wallerstein) is a spring mound of calcareous cool-water tufa ("travertine" hills) that rose at the level of a sublacustrine spring water source (Arp, 1995, 2006; Göhlich and Ballmann, 2013). It is assumed that, during certain periods, the spring mounds emerged from the soda crater lake as little islands. Fissures and pockets were formed in the sediments in the subaerial medium, and birds of prey used their crevices for resting or nesting. Their regurgitated pellets were accumulated in the late freshwater stages, forming the fossil vertebrate assemblages. *Miotyto montispetrosi* Göhlich and Ballmann, 2013, the barn owl described from Steinberg, was the main

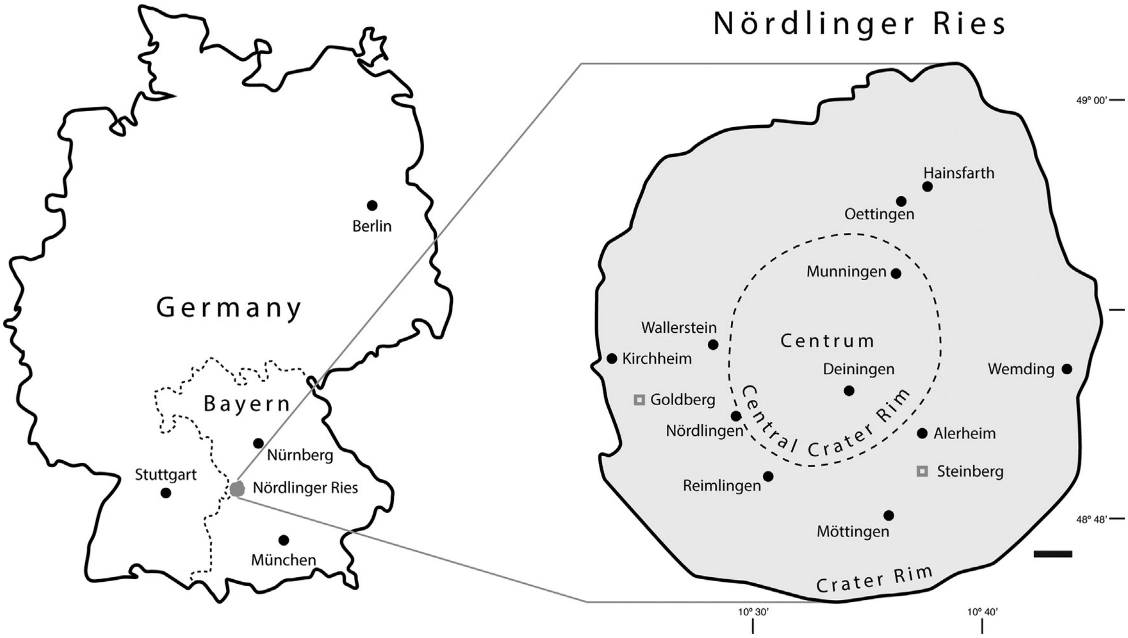

Fig. 1. Schematic map of Germany and detail of the Nördlinger Ries (Bayern, southern Germany). The position of the meteorite crater and its limits is highlighted in light grey. The black dots indicate towns and cities, whereas the dark grey squares indicate fossil localities with middle Miocene faunas (Goldberg and Steinberg). The data is from the Bayerisches Geologisches Landesamt (2004). The scale bar represents 2 km.

Fig. 1. Plan schématique de l'Allemagne et détail de la localité de Nördlinger Ries (Bavière, Sud de l'Allemagne). La position du cratère de météorite et de ses limites est surlignée en gris clair. Les points noirs indiquent les villes et les cités, tandis que les carrés gris foncé indiquent les localités fossilifères avec des faunes du Miocène moyen (Goldberg et Steinberg). Données : Bayerisches Geologisches Landesamt (2004). L'échelle représente 2 km.

agent of accumulation (Göhlich and Ballmann, 2013). The vertebrate assemblages contain mostly small vertebrates, including fishes, amphibians, reptiles, birds, and small mammals (Arp, 2006; Heizmann and Fahlbusch, 1983; Rachl, 1983; Ziegler, 1983). The state of preservation of these fossil remains is excellent (Göhlich and Ballmann, 2013; Heizmann and Fahlbusch, 1983).

The age of the Goldberg site dates back to the Early Astaracian (middle Miocene, MN6), younger than 14.7 Ma (Bolten, 1977; Lindsay et al., 1989). The paleoclimate of this region at that moment has been interpreted as semi-arid with a mean annual rainfall of 584 ± 252 mm (Böhme et al., 2006; Heizmann and Fahlbusch, 1983).

2.2. Specimen

A lagomorph right tibiofibular bone is described and examined (Figs. 2A–B, 3A; Appendix S1). It is curated at the fossil mammal collection of the Staatliche Naturwissenschaftliche Sammlungen Bayerns–Bayerische Staatssammlung für Paläontologie und Geologie (SNSB–BSPG) in Munich (Germany) under number 1966XXXIV 3340. The specimen, as the other fossil remains from Goldberg, was gained from subjecting the blocks of calcareous tufa to dilute acetic acid (Göhlich and Ballmann, 2013).

The specimen was assigned to an adult individual based on the fusion state of its epiphyses. Although the proximal ones are impossible to evaluate due to the abnormal condition, the distal one is completely fused. In *Oryctolagus cuniculus* Linnaeus, 1758, the growth plate of this latter fuses between the 16th and 28th weeks after birth (Kaweblum et al., 1994; Masoud et al., 1986), whereas no data is available for ochotonids. The examined specimen is attributed to the family Ochotonidae. Its geological age (middle Miocene, MN6), body size and morphology exclude its classification as a leporid. Actually, leporids settled definitively in Europe only in the latest Miocene (7 Ma), and their presence in European sites before 11 Ma is a matter of debate (Flynn et al., 2014; López Martínez, 2008). Moreover, the tibiofibula from Goldberg has a total length of 35 mm, and a weight of 126 g based on the transversal diameter of the distal epiphysis (allometric models in Moncunill-Solé et al., 2015). Both dimensions fit with its taxonomic placement among ochotonids (Moncunill-Solé et al., 2016a, fig. 3; Smith et al., 2018). Indeed, in the coeval, neighboring site of Steinberg (Fig. 1), Heizmann and Fahlbusch (1983) reported the presence of two ochotonids: *Prolagus oeningensis* König, 1825 and *Lagopsis verus* Hensel, 1856, the latter in larger quantities (Prieto et al., 2009). It is very likely that the pathological specimen from Goldberg pertains to one of these two species. However, as detailed studies and statistics about the postcranial bones of fossil ochotonids are lacking, we refrain to assess a generic taxonomic attribution of the tibiofibula.

2.3. Analytical tools

The most common methodology for studying paleopathological conditions is the histological analysis (D'Anastasio, 2004; Lyras et al., 2016, 2019). Due to its destructive base, however, it is not recommended when

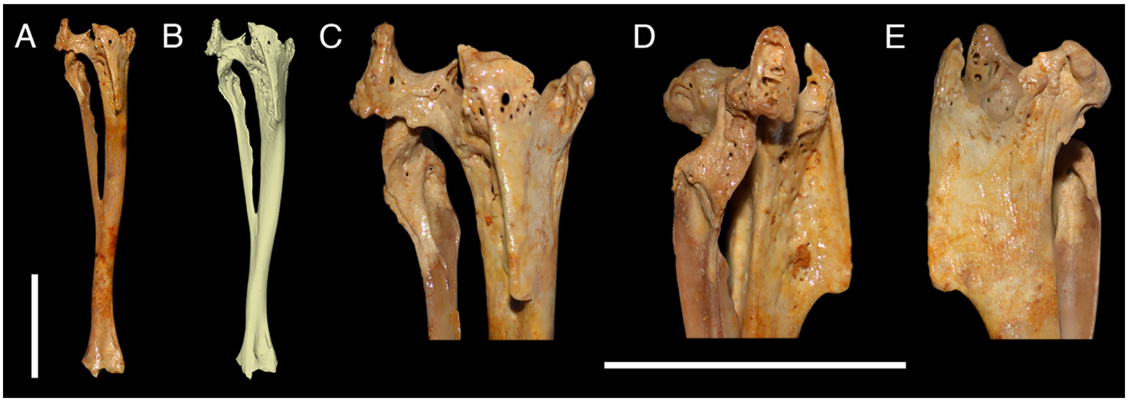

Fig. 2. Paleopathological tibiofibular bone of ochotonid from the Goldberg site (middle Miocene, MN6). A. Complete bone. B. 3D Reconstruction of the complete bone. C. Anterior view. D. Lateral view. E. Medial view of the proximal end of the bone. The scale bar represents 10 mm.

Fig. 2. Os tibiofibulaire paléopathologique du gisement de Goldberg (Miocène moyen, MN6). A. Os complet. B. Reconstruction 3D de l'os complet. C. Vue antérieure. D. Vue latérale. E. Vue médiale de l'extrémité proximale de l'os. L'échelle représente 10 mm.

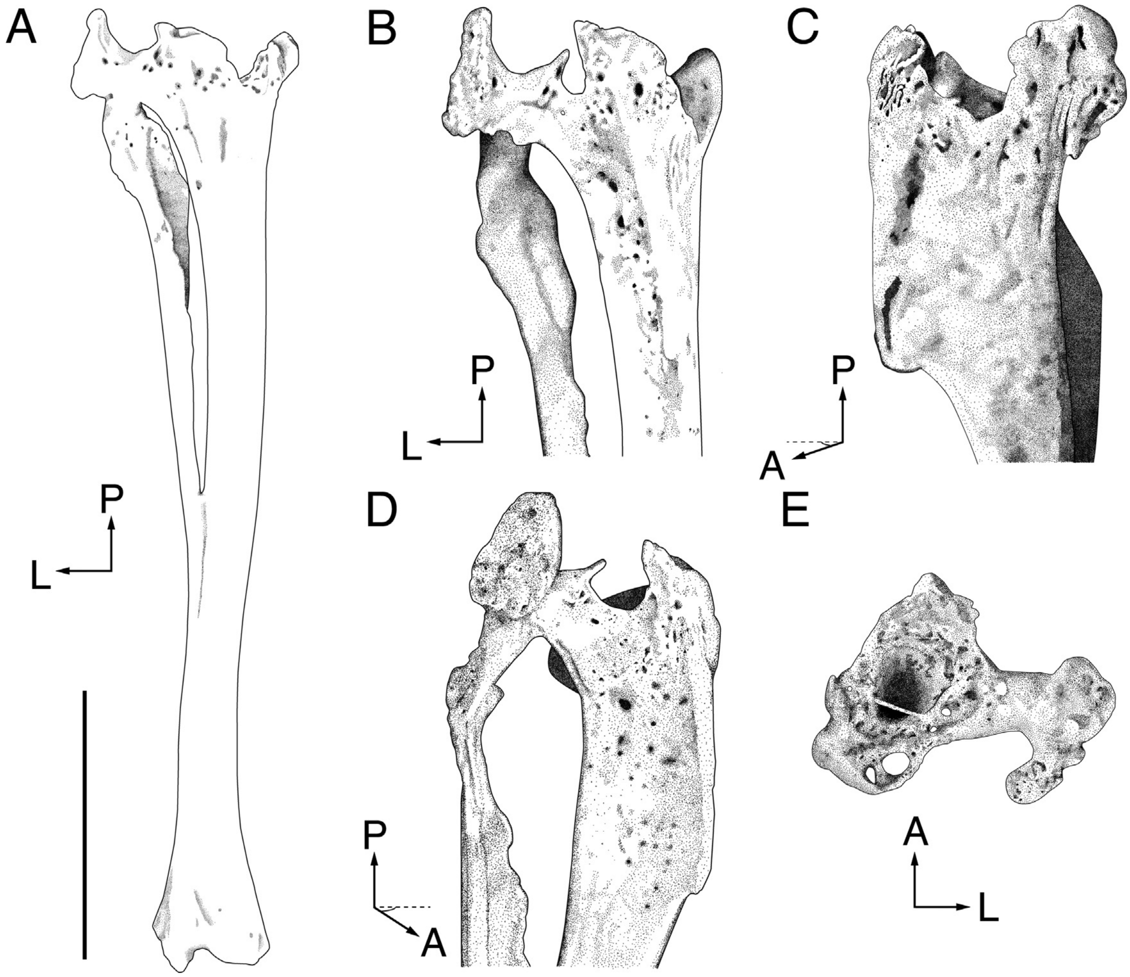

Fig. 3. Detailed drawings of the paleopathological region of the tibiofibular bone of the ochotonid (Goldberg site, MN6). A. Scheme of the complete bone. B. Anterior view. C. Antero-Medial view. D. Antero-Lateral view. E. Proximal view. A: anterior; L: lateral; P: proximal. The scale bar represents 10 mm.

Fig. 3. Dessins détaillés de la région paléopathologique de l'os tibiofibulaire de l'ochotonidé (gisement de Goldberg, MN6). A. Schéma de l'os complet. B. Vue antérieure. C. Vue antéromédiale. D. Vue antérolatérale. E. Vue proximale. A : antérieure ; L : latérale ; P : proximale. L'échelle représente 10 mm.

the sample size is very small (Anné et al., 2016). Recently, other non-destructive analytical tools (μCT or electron microscopes) allow one to explore paleopathologies without damaging the remains (Anné et al., 2016; Böhmer and Rössner, 2018; Flynn et al., 2013; Foth et al., 2015; Rothschild and Martin, 2006). Because of the small size of our sample, we decided to evaluate the paleopathology macroscopically and via X-ray microtomography (μCT). The first methodology allows us to identify broadly the main important abnormalities of the bone, whereas the latter provides valuable data about the inner structure of the bone and the microstructural changes. The paleopathological bone was scanned using a phoenix|x-ray nanotom® m (GE Sensing & Inspection Techonologies GmbH, Wunstorf/Hannover, Germany) at the Staatliche Naturwissenschaftliche Sammlungen Bayerns, in Munich. The complete bone was scanned at a voxel size of 0.0164 μm with a voltage of 120 kV and current of 70 μA and a 0.2-mm copper filter (dimensions 566 × 547 × 2326 bytes). A high-resolution μCT of the proximal part of the bone was also conducted (voxel size 0.0053 μm, voltage of 120 kV, current of 60 μA, 0.2 mm copper filter, dimensions 1548 × 2001 × 2364 bytes). Visualization, processing, and analysis of data were performed with software Amira 5.2.0 (Build 531) (Property of 1995–2008 Konrad-Zuse-Zentrum Berlin [ZIB] and 1999–2008 Visage Imaging, Inc.) and Avizo Standard Edition 7.1.0 (Property of 1995–2012 Konrad-Zuse-Zentrum Berlin [ZIB] and 1999–2012 Visualization Sciences Group [VSG], SAS).

For creating the interactive 3D model (Appendix S1), the segmentation tool of AMIRA 5.2.0 was used to differentiate the tibiofibular bone from the modelling clay (used to mount the bone in the chamber of the μCT during scanning). The bone material selected from all slices was converted into a surface component (polygon mesh). Using Avizo 7.1.0, the number of faces of the model was reduced (polygon reduction tool). The surface was saved in Wavefront Format (OBJ). MeshLab v2016.12 (Property 2005–2017 Paolo Cignoni, Visual Computing Lab, and ISTI–CNR) allowed the conversion of OBJ Format into U3D File Format (U3D). This latter file was embedded into a PDF using Adobe Acrobat XI tools (Property 1984–2012 Adobe Systems Incorporated, 2003–2011 Solid Documents, LLC, and 1987–2012 IRIS SA). The protocols described by Ruthensteiner and Heß (2008) and van de Kamp et al. (2014) were followed.

2.4. Pathologies in extant lagomorphs

In order to achieve an accurate diagnosis of the studied pathology, comparison with pathologies of extant individuals is paramount. Extant lagomorphs are prone to a large spectrum of diseases and disorders caused by multiple factors (Varga, 2014). They have been mainly described in domestic and farmed specimens of the European rabbit *O. cuniculus* (Quesenberry and Carpenter, 2004; Richardson, 2000; Varga, 2014). The most frequent are abscesses (e.g., mandibular abscesses, ulcerative pododermatitis or hock joint infection), ophthalmic, skin, and dental diseases, digestive, neurological and locomotor disorders, as well as cardiorespiratory and urogenital pathologies (Quesenberry and Carpenter, 2004; Varga, 2014).

Lagomorphs have a very fragile skeleton, which represents only 7–8% of their total weight (Raftery, 2014; Richardson, 2000). Even though this offers advantages for a rapid escape, the lagomorphs also become more prone to skeletal problems. The most common affections of their musculoskeletal system are dysplastic and degenerative diseases, neoplasia, trauma (leg and vertebral fractures), infection, and pathologies with a nutritional base (Quesenberry and Carpenter, 2004; Richardson, 2000; Turner et al., 2018). In addition, this mammalian group is distinguished by two immunological conditions: lymphopenia and low production of neutrophils (Varga, 2014). This makes them more susceptible to developing infectious diseases and to a high probability of hematogenous spread (Langley-Hobbs and Harcourt-Brown, 2014).

Particularly, wild lagomorphs have fewer dental diseases (feeding on buds and young leaves of bushes), skin diseases (benefits of grooming), and weight problems (not overweight) (Quesenberry and Carpenter, 2004; Varga, 2014). On the other hand, their natural habitat fosters a range of pathologies that are not common (or have a lower incidence) in domestic individuals (e.g., paratuberculosis, intestinal worms, myxomatosis, or other viral diseases) (Smith et al., 2018; Varga, 2014). Disabled wild lagomorphs (e.g., as consequence of a chronic diseases or a trauma) have higher probabilities to be caught by a predator (Varga, 2014), whereas most of the domestic animals survive. That explains why literature provides a smaller number of documented medical cases of pathologies in wild lagomorphs, and a large amount in those that are kept in laboratories or private homes.

We compiled and listed in Table 1 data (description, incidence and prognosis) of known pathologies of extant lagomorphs related with osteogenesis and osteolysis.

3. Results

3.1. Macroscopic description

In the studied specimen, the tibia head (from the tibial plateaus to below the tibial crest, approximately 10 mm) and the most proximal part of the fibula, including the tibiofibular syndesmosis (Figs. 2C–E, 3), are the regions affected by the pathology. A local disease affects the metaphysis (the narrow portion between the epiphysis and diaphysis formed mainly by cancellous bone) of the proximal epiphysis and it does not continue along the diaphysis (cortical bone).

A macroscopic examination allows us to identify two differentiated structures in the abnormal region: (1) a jagged-like contour of the metaphyseal border of the tibia (mainly); and (2) a complete rarefaction of the proximal third of tibia and fibula, with the presence of pit holes of different sizes. The proximal margin of the tibia is brittle and discontinuous, full of notches (osteolysis) and projections (osteogenesis) (Fig. 3B–D). In addition to osteophytes and protuberances, an important suprafibular bony projection is located in the most proximal and lateral area of the tibia (Fig. 3B). It ends in a more lateral position than

Table 1
Skeletal pathologies in extant lagomorphs related with lysis and formation of bone tissue. A brief description, incidence, and prognosis are provided. Information has been taken from Richardson (2000), Ishikawa et al. (2012), Oglesbee (2012), Suckow et al. (2012), Harcourt-Brown and Langley-Hobbs (2014), Varga (2014), Meuten (2017), Azadian et al. (2018), and Turner et al. (2018).
Tableau 1
Pathologies squelettiques chez les lagomorphes actuels liés à la lyse et à la formation de tissu osseux. Une brève description, l'incidence et les pronostics sont fournis. Informations de Richardson (2000), Ishikawa et al. (2012), Oglesbee (2012), Suckow et al. (2012), Harcourt-Brown and Langley-Hobbs (2014), Varga (2014), Meuten (2017), Azadian et al. (2018), et Turner et al. (2018).

Condition	Description	Incidence	Prognosis
Infectious disease	Osteomyelitis: bacterial infection of the bone, characterized by an osteolysis (bone porosity) and secondary new bone production adjacent to the infected area (periosteal reaction, thicken of compact bone and cortex), resulting in osteitis, periostitis, and spongiosclerosis. Drainage tracts appear in severe cases. Primary or secondary (contamination of wounds, open fractures or ulcerative pododermatitis)	Common (chronic in some cases)	Fair–Poor[a]
	Tuberculosis: macro and microscopical lesions, including granulomatous inflammation of bone, with caseous necrosis (osteolytic process, from cancellous to cortical bone, leading to osteoporosis) and little areas of osseous proliferation (absence or little periosteal reaction, sequestra are rare, and cloacae are not formed). Bacilli reach skeleton via the bloodstream. In long bones, it is localized in the metaphyseal or epiphyseal region	Rare	No data[b]
	Septic arthritis: infection (bacterial, viral or fungal) of the synovial fluid of the limb joints. It is characterized by a rapidly destruction of bone, osteonecrosis, considerable proliferation of new bone, and (partial or complete) bony ankylosis. Primary (penetrating injury, wound) or secondary (hematogenous spread, contamination of traumatic injuries, or extension of a primary osteomyelitis [metaphyseal spread] or an infection of soft tissues)	Rare	Poor[c]
Neoplasia	Osteosarcoma: bone lysis and hyperplasia (periosteal and endosteal new bone growth and production of tumor bone, "spicular" form). Generally, they are centered in the metaphysis and they rarely cross joints (adjacent bones are not involved). "Sunburst" appearance in X-ray images	Rare[d]	Poor[e]
	Osteochondroma: pedunculated lesions (globular "bath-sponge" form) located in the cortical surface (metaphyseal and diaphysis region, not involving the epiphysis), generally in the direction of muscle traction. There is neither osteolysis nor periosteal reaction. The cortex of the bone and the overlying tumorous mass are continuous. Their projection is opaque on X-ray images	Rare	Fair[f]
Osteonecrosis	Necrotic region (osteolysis) in bones as a result of the loss of blood supply. It could be the consequence of a trauma, fracture or dislocation. Located mainly on the femoral head, the proximal humerus, the femoral condyles, and the carpal and tarsal bones	No data[g]	Fair[h]

[a] Extremely difficult to treat. Prolonged therapy of systemic antibiotics and surgical debridement or amputation of the infected region.
[b] No information, few cases diagnosed.
[c] Initial acute diagnoses and an aggressive treatment may lead to a fair prognosis. Long-term antibiotic therapy, surgical debridement, and in last instance amputation. Recurrences are common.
[d] In dogs, large-sized breeds or individuals are at higher risk of developing an osteosarcoma (unclear relationship in rabbits). The lifespan of laboratory and domestic rabbits have been prolonged, entailing an increase of the neoplastic incidence in the last period.
[e] Generally, it is associated with metastasis to thoracic organs, abdomen or subcutaneous tissue. Even with an early proper diagnosis and a small size of tumor, the prognosis is poor.
[f] They stop growing once the individual has reached skeletal maturity. In some occasions, the lesion resorbed or was incorporated into the metaphysis later.
[g] No information available.
[h] Successful treatment.
[a] Extrêmement difficile à traiter. Antibiothérapie systémique prolongée, chirurgie ou amputation de la région infectée.
[b] Aucune information, peu de cas diagnostiqués.
[c] Les diagnostics aigus initiaux et un traitement agressif peuvent conduire à un pronostic correct. Antibiothérapie à long terme, débridement chirurgical et amputation de dernière minute. Les récidives sont courantes.
[d] Chez les chiens, les races ou les individus de grande taille présentent un risque plus élevé de développer un ostéosarcome (relation incertaine chez le lapin). La durée de vie des lapins de laboratoire et domestiques a été prolongée, entraînant une augmentation de l'incidence néoplasique au cours de la dernière période.
[e] En général, il est associé à des métastases aux organes thoraciques, à l'abdomen ou aux tissus sous-cutanés. Même avec un diagnostic correct précoce et une petite taille de la tumeur, le pronostic est mauvais.
[f] Ils cessent de croître une fois que l'individu a atteint la maturité squelettique. Dans certaines occasions, la lésion résorbée ou incorporée à la métaphyse plus tard.
[g] Pas d'information disponible.
[h] Traitement couronné de succès.

tibia and fibula heads and, over its course from medial to lateral region, it increases in size. In lateral view (Fig. 3D), the projection is oval (measuring approx. 3.5×1.75 mm) and very porous. The smooth surface of the proximal part of this projection and the curvature in anterior view point to a possible facet joint, which would accommodate the lateral condyle of the femur. The complete absence of tibial plateaus (osteolysis) exposes the medullary cavity (Fig. 3E). Cancellous bone in the abnormal metaphysis is almost destroyed. Medullary cavity houses an incipient mesh of large bony fibers; one of them is crossing the cavity halfway (Fig. 3E). Externally, the compact bone has a fragile and very porous appearance, with the presence of rounded holes of little to middle size (range: < 0.04 mm–0.4 mm), principally located on the lateral and central region of the tibial head (Fig. 3B–D). In contrast, those of the suprafibular bony projection display elliptic outlines (Fig. 2D). At first glance, the surrounding areas of all these pit holes shows an increase of periosteal bone (periostitis).

Overall, the fibula does not present a major destruction of bone. The proximal epiphysis and diaphysis are complete (Fig. 3B and D). Externally, it has a smooth surface with the presence of a few pores at the posterior and lateral side (Figs. 2C–D, 3D). Under normal conditions, tibia and fibula are connected by a syndesmosis at the proximal end (Grove and Whitehouse, 1941). The abnormal condition has a strong ankylosis of the two bones, with a reactive bone tissue that covers the most proximal end of the fibula (Fig. 3D). From the lateral view, fibula and tibia are arranged in parallel, and an uncommon curvature is present in the most proximal region (Figs. 2D, 3D). The cause of this abnormal morphology is impossible to identify at simple sight, but it could be consequence of the strong ankylosis (reactive bone growth), a fracture, or both.

3.2. μCT examination

The examination of the slices of the μCT reveals the presence of periosteal growth (reactive bone growth, osteogenesis) throughout the pathological region (Figs. 4 and 5). This growth of new bone is distributed irregularly, showing lacunar-like spots of different size (Fig. 4A–C). These spots or foramina, located inside of new bone formation, could either be a new vascular supply inside the periosteal bone (what is very uncommon) or a cystic-like structure in the cortical new bone layers (what is the most probable, as a secondary phenomenon of a septic process). Periosteal growth is conspicuous in coronal slices of the tibia (Fig. 5A–C), which shows clearly the apposition of two different layers of periosteal bone. The medial bone wall shows only a vertical line, but the lateral one has a different and more complex pattern, full of irregularities and cystic-like structures. Some isolated fragments (Fig. 5A–C) are considered bony micro-sequestra, without the presence of fistulous tracts and cloacae. The presence of periosteal reaction is also evidenced around the regions of the pit holes of the cortical (at different levels) (Figs. 4 and 5), confirming the macroscopic examination (periostitis). The ankylosis (osteogenesis) of the proximal articulation between tibia and fibula show both bones in a continuum (Fig. 5E). This abnormal adhesion is a common and unspecific reaction of the joint, which is produced after different types of aggressions, including post-traumatic, degenerative, rheumatic or infectious pathologies (Venes, 2001).

On the other hand, there are evidences of different radiological density (rarefaction) between several regions of the metaphyseal pathology (but not present in the diaphysis). Particularly in coronal slices, this effect is marked comparing the medial and lateral cortical bones of the metaphyseal area (Fig. 5A–C). These differences could be related with an overloading of the medial side or with differences between the distribution of the abnormal condition.

Finally, other microstructural changes have been noticed in the pathology. From transversal slices, in the union of the first quarter proximal region of the tibia with the rest, it is drawn a first step of a fistula (abnormal channel that connects internal organs among them or one of them to the outside surface of the body) from in to out (Fig. 4B). Besides, the images allow us to observe several lines related with traumas or fractures. The first one is a healed fracture oblique line in the upper fibula, which is observed in coronal and sagittal slices (Fig. 5D, F–G). The second one is located at the level of the fibula too, following a proximo-distal axis, but its outline and surrounding bone highlight that, with all likelihood, it occurred post-mortem (Fig. 5F). The slices of the inner region of the tibial diaphysis show the appearance of the cancellous bone with porosity (Fig. 5A–C). However, it is much less specific than the injuries that are present in the cortical bone.

4. Discussion

4.1. Diagnosis

In the studied specimen, osteogenesis and osteolysis are the two principal processes observed in the abnormal bony region. Infectious diseases (bacterial, viral or fungal) and neoplastic disorders (osteosarcoma or osteochondroma) are the two main conditions that show both processes, whereas osteonecrosis solely related to osteolysis is excluded (Table 1). *In vivo*, the differentiation between the first two pathological groups is problematic (Raftery, 2014). It is obtained combining histopathological examinations and biopsies, assessment of growth patterns, consistency, exudations, and X-ray images (Harcourt-Brown and Chitty, 2014). In our case, we will try to have to rely on evidences to exclude one of the two possible causes.

Neoplasias are uncommon in rabbits and hares (particularly in juveniles and young adults), especially those that affect the limbs (Tinkey et al., 2012; Varga, 2014). Osteochondromas are generally pedunculated injuries, not associated with bone destruction, and with a very low incidence in lagomorphs (Meuten, 2017; Suckow et al., 2012). Osteosarcomas mainly affect maxilla and mandible in lagomorphs (Manning et al., 1994). They have a distinguishable morphology (spicular) and generally never cross joints (adjacent bones are not affected) (Meuten, 2017). These specific traits (morphology, location, etc.) and their low incidence (Table 1) allow us to rule out neoplastic conditions as the cause of the examined tibiofibular abnormality.

As for infectious diseases, epithelial and dermic abscesses are frequent in lagomorphs. The diagnosis *in vivo* of the affected limbs includes the observation of palpable masses, lameness, hair loss, and cellulitis (Oglesbee, 2012). When an infectious disease affects bones, osteolysis and periosteal reaction are observed (Richardson, 2000). Osteomyelitis, tuberculosis, and septic arthritis are the most common bony infections in lagomorphs (Table 1). The first two entail an inflammation of the bone, whereas the latter is an infection of the joint (Oglesbee, 2012;

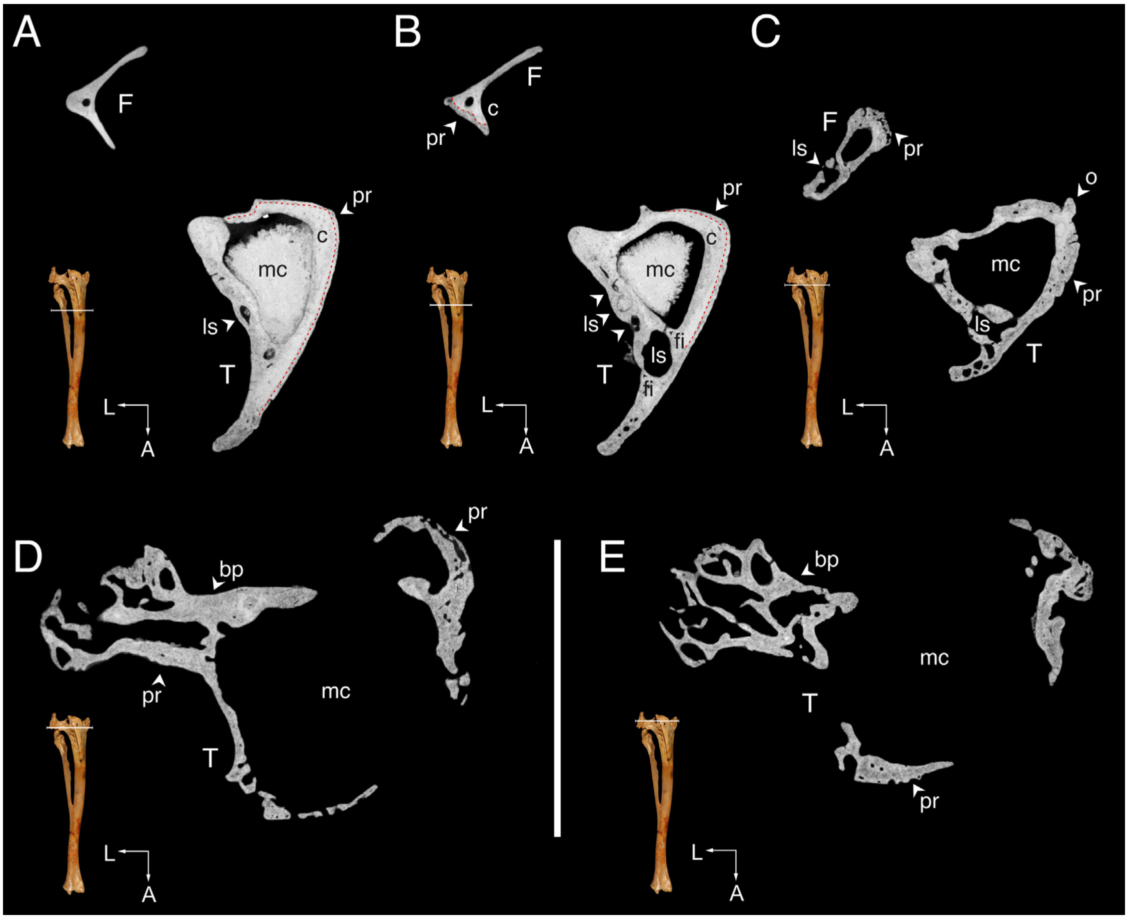

Fig. 4. μCT images of paleopathological region of the tibiofibular bone (1966XXXIV 3340) in transverse views. A–E. Slices at different levels (see cutting line in each case), from distal to proximal. The red dashed lines split the cortical bone from the periosteal reaction. A: anterior; bp: bony projection; c: cortical bone; F: fibula; fi: fistula; L: lateral; ls: lacunar-like spot; mc: medullary cavity; o: osteophyte; T: tibia; pr: periosteal reaction. The scale bar represents 5 mm.

Fig. 4. Images μCT de la région paléopathologique de l'os tibiofibulaire (1966XXXIV 3340) en vues transversales. A–E. Coupes à différents niveaux (voir les lignes de coupe dans chaque cas), de distal à proximal. Les lignes pointillées rouges séparent l'os cortical de la réaction périostée. A : antérieure ; bp : projection osseuse ; c : corticale ; F : fibule ; fi : fistule ; L : latérale ; ls : tache lacunaire ; mc : cavité médullaire ; o : ostéophyte ; T : tibia ; pr : réaction périostée. L'échelle représente 5 mm.

Richardson, 2000). Tuberculosis can be excluded because it has a low incidence and it is not associated with a periosteal reaction (Table 1), a process observed in the examined tibiofibula (Barthold et al., 2016; Rogers and Waldron, 1989). In addition, the origin of the *Mycobacterium tuberculosis* complex (the group of bacteria that includes *Mycobateriun bovis*, the main agent of tuberculosis in rabbits), is dated back to only 40,000 years ago (Manning et al., 1994; Wirth et al., 2008).

Osteomyelitis and septic arthritis affect different bony regions, although they are often difficult to distinguish, because one can trigger the other. Osteomyelitis, related with bone lysis and periosteal reaction, causes a heat, swollen, and painful limb. Septic arthritis is an inflammatory disease characterized by ticked periarticular tissues, synovial effusion, osteolysis, irregular joint space, erosions and periarticular osteophytes, and is associated with lameness, decreased range motion of the joint, soft tissue swelling, heat, and pain (Oglesbee, 2012). In the examined specimen, the macroscopic and radiologic analyses (periosteal reaction, ankylosis and lysis) and the local affection of the juxta-articular region are consistent with the diagnosis of a septic arthritis of the knee (Table 1). We cannot evaluate the kind of affection that would be presented in the femoral condyles, but the radiological patterns of the studied individual put aside the diagnosis of degenerative joint disease (progressive deterioration of the articular cartilage) and post-traumatic joint disease.

4.2. Etiology

In septic arthritis, the bacterium reaches the synovium of the bone/joint using two possible ways: (1) direct, primary (infection of the bone, joint or surrounding soft tissues, e.g., an osteomyelitis in the metaphysis of a long bone), and (2) indirect, secondary (hematogenous spread, bacteremia or septicemia, from a primary focus of infection). In the former case, several conditions can be

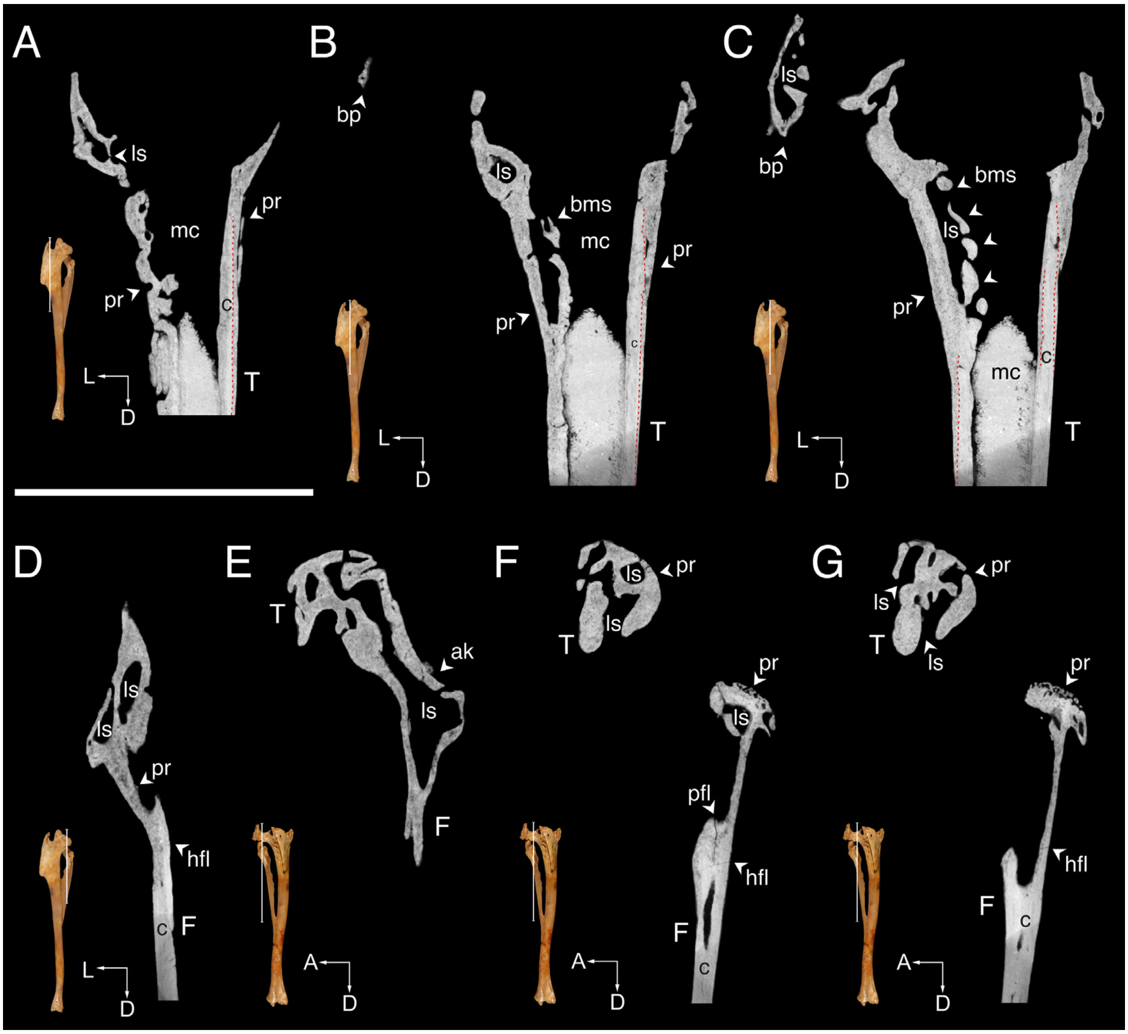

Fig. 5. μCT images of paleopathological region of the tibiofibular bone (1966XXXIV 3340). A–D. Coronal views. E–G. Sagittal views. Cutting lines indicate the level of the slices. The red dashed lines split the cortical bone from the periosteal reaction. A: anterior; ak: ankylosis; bms: bony micro-sequestra; bp: bony projection; c: cortical bone; D: distal; F: fibula; hfl: healed fracture line; L: lateral; ls: lacunar-like spot; mc: medullary cavity; pfl: postmortem fracture line; T: tibia; pr: periosteal reaction. The scale bar represents 5 mm.

Fig. 5. Images μCT de la région paléopathologique de l'os tibiofibulaire (1966XXXIV 3340). A–D. Vues coronales. E–G. Vues sagittales. Les lignes de coupe indiquent le niveau des images. Les lignes pointillées rouges séparent l'os cortical de la réaction périostée. A : antérieure ; ak : ankylose ; bms : micro-séquestre de l'os ; bp : projection osseuse ; c : corticale ; D : distale ; F : fibule ; hfl : ligne de fracture guérie ; L : latérale ; ls : tache lacunaire ; mc : cavité médullaire ; pfl : ligne de fracture post-mortem ; T : tibia ; pr : réaction du périoste. L'échelle représente 5 mm.

susceptible of bone infection: trauma (fracture or fissure), puncture/penetrating wounds (seeds or pieces of hay that penetrate the skin), or bite wounds (fights with other rabbits or predators) (Oglesbee, 2012; Varga, 2014). Moreover, skin infections (ulcerative pododermatitis, nail-bed infection, abrasions or furunculosis) can extend to underlying soft tissues, bones or joints (Oglesbee, 2012; Richardson, 2000). It is also known that primary infections could spread via bloodstream or lymph causing secondary infections in any other organ system (especially on thoracic cavity or abdomen) (Varga, 2014).

The assessment of the patterns of the injury, the microscopical analysis of the abnormal area, as well as the affected body region (hindleg) allow us to consider that, with all likelihood, the septic arthritis was a peri-articular joint reaction to a violent mechanism as a bite. Thus, the entrance of the bacterium was direct (primary focus of infection). Bite wounds in lagomorphs could be consequential of combats among different individuals (intraspecific competition, especially among males) or could be inflicted by predators when lagomorphs try to escape or avoid their attack (e.g., carnivoran such as canids) (Varga, 2014). For the moment, we cannot identify the potential causative species.

The bacteria related with septic arthritis in lagomorphs are pyogenic ones, including staphylococci (e.g., *Staphylococcus aureus*), *Pasteurella multocida*, *Pseudomonas*, *Fusiformis*, and anaerobic ones (Nade, 2003; Oglesbee, 2012). Varga (2014) described that the most common bacterium isolated from infected bite wounds in lagomorphs is *P. multocida*, a Gram-negative coccobacillus of small size.

4.3. Cause of death of the individual

The strong necrotic and osteogenic changes observed in the tibiofibular bone highlight that the pathology certainly had a large impact on the life of the individual, affecting locomotion, feeding or predator escaping, among other vital activities. Abscessed joints are swollen and very painful, and the individual limps and keeps immobile, avoiding moving (Oglesbee, 2012; van Praag et al., 2010; Varga, 2014). The infection can lead to a permanent disability of the articular movement, preventing feeding or safeguarding. Additionally, the locomotive reduction entails a poor blood circulation, and consequently a decrease of the vital conditions (van Praag et al., 2010). Infections have a very poor prognosis in this mammalian group (Table 1), and a generalized spread of the infection (septicemia) can cause a rapid death (Richardson, 2000; Suckow et al., 2012).

In natural environments, the decreased mobility and the poor vital conditions of individuals with septic arthritis make them easy targets for predators (Varga, 2014). Indeed, the vertebrate assemblages from Goldberg are mainly the result of the piling of pellets regurgitated by birds of prey (Göhlich and Ballmann, 2013). In this regard, the cause of death of the concerned ochotonid is probably related to predation, and not a direct consequence of the infection (e.g., septicemia).

4.4. Paleopathology in lagomorphs

The study of paleopathologies is indeed a quite new field of research. However, there is an important scarcity of evidences of paleopathological conditions in lagomorphs and other small mammals compared with large ones. This fact may be consequence of several reasons. The study of small mammals is based on dental remains, which are the most numerous and best preserved parts of small mammals as fossils (sometimes the only to be preserved). Skeletal elements are less likely to be preserved and are less studied, as taxonomy is based mainly on teeth. In addition, dental diseases have a minor incidence in wild animals (Varga, 2014). On the other hand, extinct and extant lagomorphs are considered small/medium mammal species (70–300 g) (Smith, 2008). Their little dimensions could be a factor that hampers the observation, assessment, and diagnosis of abnormal bony conditions (Luna et al., 2017). Moreover, lagomorphs show a fast life history (marked by an earlier reproduction maturity, large litter size, and short lifespan, some of them do not live more than one or two years) (Promislow and Harvey, 1990; Smith, 2008). Thus, their interaction period with the environment is lesser than in large mammals, as well as the probability of suffering some pathological disorders. In the wild, injured or sick individuals are at increased risk of predation (Varga, 2014). Although they could survive, this will depend on their ability as individual (for feeding and avoiding predators) and the biological traits of their species (social behavior). In general, the presence of paleopathological changes (e.g., fused fracture or chronic pathologies) highlights survival of the individual for a certain time period (Luna et al., 2017; Mariani-Costantini et al., 1996). Accordingly, Mariani-Costantini et al. (1996) proposed that paleopathologies will be more frequent in large powerful species, with a complex social behavior and remarkable defensive abilities (Adams, 1990), conditions quite contrary to the biology of lagomorphs (Smith et al., 2018).

Studies of paleopathological dental or maxilla/jaw remains of lagomorphs are not available in the literature. Instead, there are citations of probable abnormal conditions. Crusafont et al. (1955) erected the species *Heterolagus albaredae* Crusafont et al., 1955 (Molí Calopa, Spain, MN3b) based on an unnoticed pathological specimen of *Lagopsis penai* Royo, 1928 with "wrongly" inclined lower molars (López Martínez, 1989). Berzi (1967) described an unusual possible pathological condition (a diastema between the third and fourth lower premolars) in *Prolagus savagei* Berzi, 1967 (Italy, late Pliocene, MN16a). López Martínez and Thaler (1975) argued that this condition was consequence of anomalous fossilization. López Martínez and Thaler (1975) noticed that, in the material of *Prolagus crusafonti* López Martínez, 1975 (in López Martínez and Thaler, 1975) from Can Poncic (Spain, early late Miocene, MN9), there is a high incidence of teeth with an irregular occlusal surface. They associated this condition on teeth with a necrotic process affecting the mandibular condyle. That part of the jaw is not preserved in the mentioned material. López López Martínez (1989, p. 108), p. 108) refers to a high number of pathological teeth of *Titanomys calmaensis* Tobien, 1974 from La Chaux-de-Fonds (Switzerland, MN2a) (Tobien, 1974, figs. 81, 84, 85, 87) supposedly characterized by divergent axes of the tooth shafts. However, the figures in Tobien (1974, figs. 81, 87) show a minimally inclined shaft that makes us refrain to define it as pathological. At any rate, the incidence of lagomorph paleopathological teeth is minimal in Eurasian collections and they have been limited mainly to fractures or growth out of axis probably due to feeding accidents and wrong position during eruption respectively. The evidence for those conditions is a bizarre or unusual occlusal surface pattern. The individuals in which those conditions were observed were adults and apparently lived with the pathological condition without being seriously affected (CA, pers. obs.).

The first attempt to diagnose pathological conditions in fossil lagomorphs was based on postcranial elements of *P. sardus*, the middle Pleistocene–Holocene endemic ochotonid of Corsica and Sardinia. Zoboli (2003) and Zoboli et al. (2018) reported abnormal conditions in Sardinian materials, mainly related to traumas and infections, but secondarily to tumors and malnutrition conditions. Congenital diseases, on the other hand, were completely excluded. The authors also noticed that the incidence of diseased remains was less than 2%. Their results are in line with the several studies focused on the description of abnormal conditions in insular mammals (Adrover, 1972; Dermitzakis et al., 2006; Jordana et al., 2011; Lyras et al., 2016, 2019; Maempel, 1993; Palombo and Zedda, 2016). Also, in those cases, pathological conditions are mainly related to nutritional (long-term malnutrition, deficiency of some elements or vitamins) or environmental (traumatic or degenerative) causes. The prevalence of pathological specimens in those samples ranges from 0.2 to 10%.

Insular environments are characterized by a lower predation pressure than in mainland ones (Sondaar, 1977). Specially in small mammals, this different selective pressure entails a modification of the life history, such as a longer lifespan (Palkovacs, 2003). In this regard, Moncunill-Solé et al. (2015, 2016a) noticed a longer lifespan in *Prolagus apricenicus* Mazza, 1987 than in mainland extant ochotonids. As bigger animals live longer, it is possible that also the insular endemic Sardinian chronospecies *Prolagus figaro* López Martínez, 1975 (in López Martínez and Thaler, 1975) and *P. sardus*, which weighed almost double than coeval congeneric species (Moncunill-Solé et al., 2016b), had a longer lifespan, in spite of the fact that it coexisted with the Sardinian dhole *Cynotherium sardoum* Studiati, 1857, which was a small prey hunter (Lyras et al., 2006). Thus, due to the longer lifespan of insular lagomorphs, it is not surprising that most of the evidence of paleopathological conditions in lagomorphs have been recorded in insular forms (Zoboli, 2003; Zoboli et al., 2018).

To sum up, the finding of an extinct mainland ochotonid showing a pathological condition is a rarity. Thus, the abnormal tibiofibular bone from Goldberg site is exceptional. The diagnosis, etiology, and cause of death of the individual that are provided here give us clues about the paleobiological traits of mainland lagomorph species (e.g., survival capacity or circumstances of death) and their role in the ecological habitats (e.g., interaction between species and environments). Although lacking detailed statistical studies, the prevalence of paleopathological conditions in mainland ochotonids is lower than in populations of insular endemics.

5. Conclusions

Paleopathologies in small mammals are of major scientific interest. Their description and assessment allow us to improve their biological knowledge, but also to approach the history and evolution of diseases scientifically. Publications that deal about abnormal conditions in small fossil mammals are extremely few. We try to start filling this gap in lagomorphs, an order of small mammals extremely common and widespread in the Neogene of Europe. The present paper reports the most ancient evidence of a pathology in an extinct lagomorph (Goldberg site, middle Miocene, MN6). The abnormal condition of the tibiofibula is the result of a septic arthritis caused by a violent mechanism such as a bite. As a consequence, the individual became an easy target for birds of prey. The abnormal tibiofibular bone from the Goldberg site is the only pathology documented in a mainland fossil lagomorph up to now. The paleontological research focused in fossil dental remains exclusively; the small dimensions of the skeletal elements and the specific biology (e.g., short life) of lagomorphs are the main factors that may explain the low prevalence of pathologies in the fossil lagomorph record, especially in mainland environments.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.crpv.2019.10.007.

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