The paleopathological evidence on the origins of human tuberculosis: a review

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Summary

Tuberculosis (TB) has been one of the most important infectious diseases affecting mankind and still represents a plague on a global scale. In this narrative review the origins of tuberculosis are outlined, according to the evidence of paleopathology. In particular the first cases of human TB in ancient skeletal remains are presented, together with the most recent discoveries resulting from the paleomicrobiology of the tubercle bacillus, which provide innovative information on the history of TB. The paleopathological evidence of TB attests the presence of the disease starting from Neolithic times. Traditionally, it was thought that TB has a zoonotic origin, being acquired by humans from cattle during the Neolithic revolution. However, the biomolecular studies proposed a new evolutionary scenario demonstrating that human TB has a human origin. The researches show that the disease was present in the early human populations of Africa at least 70000 years ago and that it expanded following the migrations of Homo sapiens out of Africa, adapting to the different human groups. The demographic success of TB during the Neolithic period was due to the growth of density and size of the human host population, and not the zoonotic transfer from cattle, as previously hypothesized. These data demonstrate a long coevolution of the disease and its human host. Understanding the changes of TB through time thanks to the advances in the field of paleopathology can help to solve the present problems and understand the future evolution of TB.

Introduction

Tuberculosis (TB) is an infectious disease caused by bacteria of the *Mycobacterium tuberculosis* complex (MTBC), which includes *M. tuberculosis*, *M. bovis*, *M. canettii*, *M. africanum*, *M. pinnipedii*, *M. microti*, *M. caprae*, *M. mungi* and *M. orygis*. The first two strains are most frequently responsible for TB in humans [1]. Despite the efforts to reduce the burden of TB worldwide and the progress in care and prevention, it is still a major global cause of disease and death [2].

Starting from the industrial era, TB became particularly diffused, favoured by the increased population density and the poor living conditions. Thanks to the improvement of health status, alimentation and hygiene during the 20th century in developed countries, the disease began to decrease its incidence; the introduction of the BCG (Bacillus Calmette-Guérin) vaccine in 1921 and the use of chemotherapeutic drugs efficacious against the infection, such as streptomycin and isoniazid in 1943 and 1952 respectively, further decreased the incidence. However, despite being considered in the 80s of the 20th century as a conquered infection [3], TB still remains a plague on a global scale and is the top infectious killer globally by being present today in both developed and developing countries; it is estimated that a quarter of the world population (1.7 billion people) is infected with *M. tuberculosis*, 5-15% of which will develop the TB disease during their lifetime [4]. Statistics show that in 2016 TB was the underlying cause of 1.3 million deaths among HIV-negative people and furthermore was a contributing cause of 374,000 deaths among people with HIV [4]. Due to historical, social and geopolitical determinants, the regions with the highest rates of TB are Sub-Saharan Africa, South-East Asia and East Europe [5, 6]. The only available vaccine (BCG) is obtained from attenuated strains of *M. bovis*, but is not extensively effective; no other vaccines had been produced in the meantime [7]. Finally, the appearance of TB-strains that are resistant to antibiotics, in particular multi-drug and even totally drug-resistant strains, represents a real challenge in the struggle against the disease [8].

Paleopathology, the interdisciplinary field of research that focuses on the development of ancient diseases and their impact and distribution in past populations, together with ancient DNA analyses, can provide important contributions to our knowledge of this major pathogen through the study of how TB evolved through time.

Early paleopathological and biomolecular evidences for TB in ancient skeletal remains

The paleopathological evidence for TB is based on primary sources, such as the analysis of skeletal remains and mummified soft tissues. The diagnosis of TB can be considered reliable on the basis of specific skeletal fea-

tures; these include characteristic changes to the spine, consisting in lytic lesions affecting the vertebral bodies with resulting ankylosis, body collapse and kyphosis (Pott's disease); extraspinal unifocal lytic lesions with absence of new bone formation; single joint ankylosis, specially localised in the hip, knee and wrist; and new bone formation on the internal surface of the ribs [9, 10].
In the last decades, the development of the new field of palaeomicrobiology permitted in several cases further corroboration of the diagnosis through the detection of TB ancient DNA (aDNA); the latest technologies of high-throughput sequencing and metagenomics allowed us to obtain a complete picture of the pathogen in ancient human remains [10].
However, modern clinical data demonstrated that only 1-5% of patients with pulmonary TB develops skeletal lesions [11]; therefore, it should be considered that the detection of TB in paleopathology is largely underestimated [12].
The earliest human skeletal remains with paleopathological changes of TB date back to 8000-10000 years ago, corresponding to the Neolithic revolution, and come from the Near East. Before this period, a single controversial diagnosis of Leptomeningitis tuberculosa, in relation to non specific endocranial changes of the frontal bone of a fossil, has been attributed to a Homo erectus from Turkey dating from the middle Pleistocene (490000–510000 years BP) [13]; this could represent the most ancient example of TB in a human fossil, but this interpretation was questioned by other authors [14].
The most ancient animal case, which was confirmed by morphological and biomolecular analyses, is represented by a ca. 17000-year-old late Pleistocene long-horned extinct bison (*Bison antiquus*) enclosed in sediments from the Natural Trap Cave from Wyoming (United States). This fossil documents that TB was present in North America at least 20000 years BP, long before the domestication [15].
The most notable of the first TB traces in human skeletal remains are concentrated in the Near East and Europe.
As for the Near East, five cases from two sites located in the Fertile Crescent belonging to the Pre-Pottery Neolithic B (PPNB) period provide evidence for the presence of human TB. Four individuals with lesions consistent with TB were brought to light from Dja'de el Mughara, situated on the Euphrates river in Northern Syria and dating to the pre-domestication phase (8800-8300 BC). An individual from Tell Aswad from Southern Syria, belonging to the early domestication phase (8200-7600 BC), displayed features typical of Hypertrophic Pulmonary Osteoarthropathy (HPOA), that is caused by chronic pulmonary diseases such as TB. In addition to the morphological features, multidisciplinary analyses such as morphological examination, MicroCT scan, lipid biomarkers and molecular analyses were also performed with positive diagnostic results on selected specimens from these archaeological sites, confirming the presence of human TB in the pre-domestication and early domestication phases of the Neolithic [16].
Another three cases evoking skeletal human TB were reported in the Neolithic village of Ain Ghazal in Jordan, dated to 7250 BC and also located in the cradle of agriculture; these cases, whose diagnosis was only morphological as no molecular analyses were performed, suggest the presence of human TB before and/or during the introduction of agriculture and animal domestication [17].
From the same geographical area, in the ancient Levantine village of Atlit-Yam now submerged (Israel), there is a report of two cases of TB on the basis of scarce paleopathological changes involving an adult individual and an adolescent, presumed to be mother and son, as they were buried together. The site is dated from 6200-5500 BC, corresponding to the last phase of the Pre-Pottery Neolithic period, when the transition to agriculture and animal domestication was fully accomplished. Lipid biomarkers and molecular analyses confirmed the presence of TB in the two individuals [18, 19]. Lipid biomarkers examination consists in the extraction, derivatisation and high-performance liquid chromatography (HPLC) analysis of mycobacterial cell wall mycolic acids [18, 19].
As for Europe, among the earliest cases of TB in skeletal evidence there are cases of tuberculous spondylitis (Pott's disease) in two individuals from the Early Neolithic belonging to the Linear Pottery culture (5400–4800 BC) from three sites (Halberstadt, Derenburg and Karsdorf) from Saxony-Anhalt in central Germany. Molecular analyses detected the presence of pathogens belonging to the MTC in skeletal remains from all the three sites taken in examination [20].
Other cases with morphological evidences of TB were unearthed from several Neolithic sites dated back to 5000 BC, including Heidelberg, Germany [22], Zlota, Poland [20], Hódmezővásárhely-Gorzsa, Hungary (confirmed by lipid biomarker analyses and ancient DNA analysis) [23], Alsónyék-Bátaszék, Hungary (confirmed by molecular analyses) [24, 25], attesting to the diffusion of the infection in different areas of Europe.
A particular concentration of TB was observed in the Finalese area in Liguria (Northwestern Italy) belonging to the Middle Neolithic period (4000-3500 BC), where three cases were discovered in three important caves that are in close proximity to each other: Arene Candide [26], Arma dell'Aquila [27], and Pollera [28] caves. The diagnosis was based on typical skeletal lesions; biomolecular analyses using polymerase chain reaction (PCR) were performed on the Pollera case, but did not confirm the presence of the MTBC ancient DNA.
As for Africa, 13 cases from the Upper Egyptian site of Nagada (4500-3000 BC) suggest that the earliest evidence of TB in Egypt could be dated back to 4500 BC [3]. The first Egyptian cases of TB confirmed by molecular analyses date back to the predynastic period (3500-2650 BC) and suggest that infection with *M. tuberculosis* was relatively recurrent in this period [29-33].
Outside the European landscape, a possible Neolithic case of TB was observed in an adult individual from Shanghai, China, associated with the Songze culture

(3900-3200 BC), at the beginning of the wet rice agriculture [34].
From the late Neolithic onward the paleopathological evidence of TB becomes more frequent.
Finally, in the prehistoric New World, macroscopic and molecular analyses suggest that the earliest evidence of human TB in skeletal remains and mummified soft tissues is attested in prehistoric South America in Peru by 700 AD, while in North America it is attested by 900 AD in the Southwest, where large permanent agricultural settlements are concentrated [35, 36].

The biomolecular advancements on the origins of TB

As highlighted in the previous section, the paleopathological evidence of human TB attests the presence of the disease starting from Neolithic times; no sure skeletal cases are dated before this period [37]. However, absence of evidence does not mean evidence of absence. Did TB affect humans in more ancient times? When did TB become a human pathogen? Did human TB originate from animal TB? The new next-generation sequencing technologies tried to answer these questions [38, 39].
According to the traditional theory, formulated before the advent of the biomolecular studies, humans acquired TB from cattle during the Neolithic revolution due to the zoonotic transfer from the newly domesticated animals [40-42]. As several infectious diseases have a zoonotic origin, it was thought that TB was also transferred to humans from animals; in particular, *M. bovis* would have infected humans, then adapting and evolving into *M. tuberculosis*. This theory was supported by the fact that the oldest human remains presenting paleopathological changes of TB were found in the Neolithic period, while the findings in animal remains have suggested a more ancestral existence of TB in cattle [15].
The evolutionary history of TB was dramatically changed by recent biomolecular studies that challenged the old theory, proposing an African origin for the MTBC long pre-dating the Neolithic [43, 44].
Phylogenetic studies have clarified that within MTB seven lineages, associated with different areas of the world, can be identified [46]: the Lineage 1 (East Africa, Philippines), the modern Euroasian lineages 2 (which includes the Beijing family), 3, 4 that are in close phylogenetic relationship, African lineages 5 and 6 with *M. africanum* phylogeographically distributed in West Africa, and finally, the newly described lineage 7 [47] collected from patients with TB from Ethiopia. Animal species, including *M. bovis*, *M. microti* and *M. pinnipedii*, represent monophyletic lineages, and *M. canettii* has an ancestral position in the MTBC. The chronological positions of the lineages are determined by the presence or absence of an MTB-specific deletion (TbD1); the presence makes them ancestral ($TbD1^+$), the absence makes them modern ($TbD1^-$) [48, 49]. On this basis, lineages 1, 5, and 6, the animal lineages and *M. canettii* represent the ancestral MTBC group, whereas lineages 2, 3 and 4 are defined as modern from an evolutionary point of view, because they are thought to have diffused more recently; lineage 7 resulted as intermediate between ancient and modern MTB lineages. These findings suggest that the animal lineages and *M. africanum* have diverged from the progenitor of the ancestral MTB lineages and that the tubercle bacillus was originally a human pathogen [49], confirming previous studies which suggested that animal adapted MTBC strains diverged from the major MTBC strains [48, 43-45]. Therefore, the new evolutionary scenario proposed that the human TB did not derive from *M. bovis*, but that, on the contrary, MTB has a human origin.
Furthermore, a recent work seems to confirm this theory with phylogenetic studies based on whole-genome data of MTCB. This study is based on the sequencing of a global collection of 259 MTBC modern clinical strains representative of the diversity of the global MTBC for reconstructing the phylogenetic relationship between them [50]. The overall results of three independent phylogenetic analyses for the determination of the most recent common ancestor of TB using a Bayesian approach suggested East and West Africa as the most probable geographic origin of MTBC. The results of this research would show the common origin in Africa of Homo sapiens and MTBC and that TB was present in the early human populations of Africa at least 70000 years ago, then infecting humans for thousands of years [50].
The study of Comas and colleagues [50] also would demonstrate that MTBC evolved in parallel with its human host. The disease expanded in correspondence with the migrations of *Homo sapiens* out of Africa. It has been hypothesized that the two *M. africanum* lineages, *M. canettii* and lineage 7 might have remained in Africa, whereas the others could have reached Europe and Asia, following the colonization of these areas, and finally becoming endemic worldwide. This work would suggest that the different lineages have adapted to different human groups. On the basis of this study a correlation between the divergence of the Lineage 1 of MTBC about 67000 years ago and the first human wave of migration out of Africa that was directed around the Indian Ocean was observed. Another split of MTBC that would have occurred 46000 years ago corresponds instead to the second great migration of *Homo sapiens* from Africa, which was directed to Eurasia [50]. With the rise of Neolithic Demographic Transition 10000 ± 2000 years ago, TB raised its rate of diffusion together with the increase in the human population density following the advance of agriculture and animal domestication. These results would suggest that the demographic success of TB during the Neolithic period was due to the growth of density and size of the human host population, and not to the zoonotic transfer from cattle, as previously hypothesized [50].
Also, of interest is the study of the dispersal of the modern Lineage 2, which includes the "Bejing" strains that have an increased virulence and transmission potential, a shorter latency phase than ancient lineages, furthermore being particularly successful in geographical dif-

fusion, and are associated with antibiotic resistance [8]. The study has evidenced that the dating of Lineage 2 in Asia coincides with the arrival of the anatomically modern humans in East Asia about 42000-32000 years ago confirmed by the archaeological evidence. This lineage presents a first expansion about 11000-6000 years ago corresponding to the development of agriculture in China about 8000 years ago and, later, a further expansion about 5000-3000 years ago, when agriculture was introduced in the regions near China [50]. These results seem to show that tuberculosis had various moments of expansion other than the increase during the Neolithic in the Mediterranean region.

Furthermore, these data could explain why TB presents an adaptation to both low and high host population densities. In fact, the high level of asymptomatic latency that allows reactivation of TB and the slow progression to disease are an indication of adaptation to low host population density that is consistent with the ancestral emergence of MTBC in Africa before the Neolithic revolution. On the other hand, the modality of aerosol transmission and the high virulence in order to guarantee the maximum level of transmission are typical of a high-density population environment. This double adaptation would have ensured to the bacterium a large diffusion in both high- and low-density areas, resulting in the fact that one-third of the human population is infected but remains asymptomatic, representing an extraordinary reservoir for the bacterium [8].

The study of the origins and patterns of change in the evolution of MTBC would demonstrate that migration and demography of the anatomically modern humans affected the evolution and spread of TB. The major recent molecular studies on the evaluation of its demography and timing of propagation seem to show a long coevolution of the disease and its human host, demonstrating that TB represents an exemplary model of adaptation to humans [8]. They also suggest that the palaeomicrobiology of TB can be fully understood through an integrated approach in correlation-association with the human host genome sequencing, considering the relation between the evolution of TB genomes and their human hosts.

Conclusions

TB was traditionally thought to be a zoonosis, but the advancements of biomolecular analyses performed by various teams of researchers seem to suggest that *M. tuberculosis* did not evolve from *M. bovis*, but has a complex evolutionary history that reflects human evolution. In order to understand the evolution of the bacterium and the current epidemiology of TB it is necessary to investigate the history of the disease in parallel with that of humans. In fact, MTBC has evolved with humans during thousands of years, influencing reciprocally their evolution. Understanding the changes of TB through time thanks to the advent of the next-generation sequencing technology can aid the problems of the present and future evolution of TB in relationship with its human host.

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Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

IB performed the bibliographic research and wrote the text; VG conceived the design, partially wrote the text and revised the manuscript. All authors critically revised the manuscript. All authors have read and approved the latest version of the manuscript.

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