



Tuberculosis origin: The Neolithic scenario



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This paper follows the dramatic changes in scientific research during the last 20 years regarding the relationship between the *Mycobacterium tuberculosis* complex and its hosts – bovids and/or humans. Once the *M. tuberculosis* and *Mycobacterium bovis* genomes were sequenced, it became obvious that the old story of *M. bovis* evolving into the human pathogen should be reversed, as *M. tuberculosis* is more ancestral than *M. bovis*. Nevertheless, the timescale and geographical origin remained an enigma.

In the current study human and cattle bone samples were examined for evidence of tuberculosis from the site of Atlit-Yam in the Eastern Mediterranean, dating from 9250 to 8160 (calibrated) years ago. Strict precautions were used to prevent contamination in the DNA analysis, and independent centers used to confirm authenticity of findings. DNA from five *M. tuberculosis* genetic loci was detected and had characteristics consistent with extant genetic lineages. High performance liquid chromatography was used as an independent method of verification and it directly detected mycolic acid lipid biomarkers, specific for the *M. tuberculosis* complex. These, together with pathological changes detected in some of the bones, confirm the presence of the disease in the Levantine populations during the Pre-pottery Neolithic C period, more than 8000 years ago.

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1. Introduction

Human tuberculosis (TB) persists as a global epidemic with disproportionate effects on low-income populations. Modern genetic data supported by the archaeological evidence indicate that

the *Mycobacterium tuberculosis* complex (MTBC) may have co-existed with humans for at least 15,000 years since the Neolithic [1,2]. The disease reached near-epidemic proportions in the rapidly urbanizing and industrializing societies of Europe and North America in the 18th and 19th centuries [3].

Despite extensive research over period of more than 100 years, the timing, cause and geographical origin of TB in humans is still under debate. Until the end of the previous century, it was commonly believed that animals, especially bovine, transmitted the ancestral *Mycobacterium* to humans – divergent evolution. As infection with tuberculosis spreads in two major ways, by the respiratory route directly from another infected person (e.g., *M. tuberculosis*) or by the gastrointestinal route mainly by drinking milk infected or milk products with the bovine tubercle bacillus (*Mycobacterium bovis*) [4], the notion that newly domesticated

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cattle, sheep or goats in the Eastern Mediterranean region during the agricultural revolution (ca. 8300–5500 BC), is the source of the disease in humans, became common [5]. Even when this idea of zoonotic transmission of *M. bovis* to Early Neolithic farmers was widespread, we pointed out the following criticisms [6]: 1) It was unclear when and how the *M. bovis* spread among domesticated cattle; 2) The oldest known human skeletal evidence of TB from the Mediterranean region, other than those of the Pre-Pottery Neolithic (PPN) C site of Ain Gaazal [7], were all roughly dated to a much later period – the fourth millennium BC or later [6,8]. Also, this later date was reflected by pathological and molecular findings reported for Egyptian mummies (some dating back to the XXIst Dynasty) and skeletons (the oldest dated to 3300 BC) that were reported to have tuberculosis pathology [9,10]; 3) The spread of TB from cattle to human occurs largely by drinking infected milk, yet milk consumption did not start until the “Secondary Products Revolution” in the fifth-fourth millennium BC [11]. Furthermore, according to Keusch et al. [12], by two years of age virtually all Neolithic children were lactase-deficient, i.e., they lacked the ability to metabolize milk. Biological tolerance of adult populations to bovine milk and milk products only began in the Neolithic period [13]. In this case only infants would have consumed milk and thus contracted bovine TB; 4) When considering TB infection, herd size is of greater relevance than human population size [14]. With few exceptions, the harsh unpredictable Mediterranean environmental conditions, including large arid zones and hilly topography, are suitable for goats but not for raising large herds of cattle. Based on the above arguments, at that time we rejected the ‘domesticated-bovine-hypothesis’ for TB and concluded that the appearance of human TB was probably associated with the beginning of urbanization in the Fertile Crescent region during the fifth-fourth millennium BC, during the Chalcolithic-Early Bronze Age c. 3.500 BC.

In the last decade of the 20th century it was shown that the identification of *M. tuberculosis* DNA in ancient bones is possible [15]. Less than 10 years later, the plethora of molecular studies of the MTBC – both ancient and modern – showed that there is no direct evolutionary relationship between *M. bovis* and *M. tuberculosis* but these were divergent evolutionary lineages, with *M. tuberculosis* being more ancestral [16]. Genetic analysis of the pathogen from a Pleistocene bison bone (17,000 years) showing tubercular-like infection indicated greater similarity to *M. tuberculosis* and *Mycobacterium africanum* rather than to *M. bovis* [17]. Furthermore, the overwhelming majority of studies that have examined MTBC complex aDNA by spoligotyping [17,18] demonstrate that the organisms are not *M. bovis*. The sole exception to date is the detection of *M. bovis* in a group of Iron Age semi-nomadic pastoralists from Siberia dating from the 4th century BC to 4th century AD [19]. Further genetic studies, based on coalescence analysis have even suggested the possibility of human to bovine transmission of TB, whereby the most ancestral human MTBC may have infected livestock and through a parallel evolutionary process established tuberculosis in cattle (*M. bovis*) and goats (*Mycobacterium caprae*) [20]. Nonetheless, this and other DNA studies adhered to two basic notions: the first that the origin of the disease in humans is within the Fertile Crescent; the second that the transition from human to domesticated animal hosts is linked to the development of agriculture some 13,000 years ago [1,16,20].

As TB is still one of the leading infectious diseases worldwide, with an estimated 1.4 million deaths in 2011 [21] the questions of the time and conditions surrounding the emergence of *M. tuberculosis* are important. The primary aim of the current research was to present both the published and later findings from the Pre-pottery Neolithic C site of Atlit-Yam in an attempt to answer those questions.

1.1. Background on the site and its inhabitants

Atlit-Yam is one of the major submerged sites discovered and studied during the 1980s and 1990s. Hershkovitz et al. (2008) [22] gives the full bibliography that describes the site, its structures and occupation. The site is located 300–500 m offshore and 8–12 m below sea level in the North Bay of Atlit, 10 km south of Haifa (34°56′ E, 32°42.5′ N). Stone foundations of several rectangular structures, paved floors, long straight walls, hearths, round megalithic structures, storage and production installations, and water wells have been discovered, all embedded in dark clay. The structures and installations are sparsely scattered over the site with wide-open spaces between them. The site was dated to the end of the Pre-Pottery Neolithic period (PPNC). Radiocarbon dates on charcoal and waterlogged plant remains range from 8180 to 7250 years BP (9250–8160 BP calibrated). The rich, well-preserved finds of Atlit-Yam include botanical and faunal remains, stone, flint and bone tool assemblages, and human bones. The site is one of the earliest prehistoric Mediterranean fishing villages ever excavated. Human bones were revealed in ninety-one different locations at the site, of which forty-six were recognized as graves dug into the clay. Most burials (70%) were located in specific areas, adjacent to walls or installations. No grave showed evidence of stone construction, or surface marking. Burials were mainly primary, containing mostly (75%) single interments, situated around the rectangular structures and rarely in within them. In some cases, grave goods were added to the graves. Secondary burials were rare. Grave goods were found in fifteen burials.

The health status of the Atlit-Yam population was relatively good, as attested by the life span of the population. The pathologies identified are mainly associated with infectious diseases, such as ear infections due to diving (auditory exostosis), spondylolysis due to intensive rowing activities, anemia due to the marshy environment and probably tuberculosis following cattle domestication [22]. Dental wear associated with weaving fishing nets and dental diseases was also identified.

2. Materials and methods

The remains of 64 individuals from Atlit-Yam were examined for TB lesions. All human bones are housed at Tel Aviv University. Identification of TB was based on both morphological (macro and micro) and molecular analyses. All cases with bony lesions indicative of TB were sampled for MTBC aDNA, either directly from the lesion itself or from a bony area with a rich blood supply.

2.1. Morphological analysis

Osseous criteria for TB: As many infectious diseases tend to produce similar bone changes, osseous criteria alone are not sufficient to reach a definite diagnosis of TB.

2.1.1. Osseous criteria for the presence of TB in infants, children and adolescents

All skeletons were inspected for the following gross osseous changes, all of which are indicative for potential presence of tuberculosis in sub adult and children: (a) convoluted engraving on the inner aspect of the cranial bones, a phenomenon termed ‘*Serpens Endocrania Symmetrica*’ (SES) [23]; (b) periosteal reactive bone of tubular bones characterized by destruction of the cortex and formation of an expanded shell of periosteal reactive bone [24]; (c) growth deficit and/or intrauterine growth retardation; (d) deformity of long bones (due to foci destroying a growth plate) [25]; (e) presence of multiple lesions throughout the skeleton.

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