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Evidence of tuberculosis among children in medieval (13th–15th century) Wrocław: A case study of hip joint tuberculosis in a juvenile skeleton excavated from the crypt of the St. Elizabeth church

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Abstract: Paleopathological examinations of the skeletal remains of people who died centuries ago are material source of knowledge about health and diseases in the past. In this article, a case of skeletal tuberculosis from historical (13th–15th c.) Wrocław, Poland has been presented. The juvenile skeleton excavated from grave No 93, from the crypt located under the church of St. Elizabeth, displayed pathological lesions within the right hip joint resulting from a chronic inflammation, which might have been assigned to signs typical for skeletal tuberculosis. The results of macroscopic and radiological analyses appeared to be consistent, and allowed to determine a reliable diagnosis of this paleopathological case.

Key words: *Mycobacterium tuberculosis*, hip joint tuberculosis, juvenile tuberculosis, paleopathology

Introduction

Tuberculosis is a disease described in paleopathological literature by many authors in a variety of ways. Some researchers focus on the shared history of humans and *Mycobacterium*, proving that tuberculosis has accompanied the humans for thousands of years (e.g. Donoghue et al. 2004; Hershkovitz et al. 2008). There are also many works on the paleopathological and molecular methodology of research on tuberculosis, which enable us to have a better understanding of the origin, pathways and demographic effects of the disease (e.g. Donoghue 2011; Roberts and Buikstra 2003). There are also descriptions of individual cases, which provide us with more efficient ways of detecting different forms of skeletal tuberculosis manifestation in archeological material (e.g. Bianucci et al. 2012; Pálfi and Molnár 2009; Holloway et al. 2011).

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The main goal of this paper is to present a probable case of the extrapulmonary skeletal tuberculosis which affected the right hip joint of a young individual, whose skeleton was excavated from a medieval grave located in the crypt under the St. Elizabeth church in Wrocław.

Currently, skeletal TB is seen in 1–2% of children (Cruz and Starke 2007).The development of the disease is caused by the movement of *Mycobacteria* in the blood stream from the initial focus, located usually in the lungs, lymph nodes or in the gastrointestinal tract to bones and joints. The result of the *Mycobacteria* spreading in bony tissue are small pathological lesions which tend to be located in the places characterized by the greatest blood flow and the greatest scarcity of phagocytic cells (Hopwell and Bloom 1994; Panek and Chyczewska 2001). A typical and most frequent in archaeological material form of the disease is spinal tuberculosis (Pott's disease) of the thoracic and lumbar vertebrae. Usually, only between one and four vertebrae are involved and neural arches are spared. Vertebral bodies are destroyed, potentially leading to angular kyphosis and fusion of vertebrae (Holloway et al. 2011) joints, hands, feet, which leads to severe disability.

The bodies of the thoracic vertebrae are the most common site of skeletal tuberculosis, mainly due to good blood supply (Malawski 2003) and large mass of the red marrow in trabecular bone that can be invaded by the bacilli. For the same reason in children, as in adults, the most frequently affected parts of the skeleton are epiphyseal parts of the long bones and large joints, such as the hip and knee. In general, tuberculosis may affect every element of the skeleton but in some areas, for example the metacarpals, pubic symphysis and bones of the cranial vault, tuberculous lesions occur with far less frequency (Gaździk 2010; Borejko and Dziak 1979). Solitary axial lesions are seen in immunocompetent hosts, whereas multifocal osseous involvement and associated systemic signs are more common in immunocompromised children (Vallejo et al. 1995; Morris et al. 2002; Cruz and Starke 2007).

While reports concerning skeletal tuberculosis in adult skeletons are often presented in paleopathological literature, cases involving descriptions of this form of the disease in children are published much less frequently (e.g. Dabernat and Crubézy 2010; Lewis 2011; Matos et al. 2011; Dawson and Brown 2012, Ioannou et al. 2015, Hlavenková et al. 2015, Sparacello et al. 2017). The reason is that the tuberculosis of bones and joints in children can take on a variety of less evident forms, which complicates the macroscopic evaluation. This is due to the specific nature of the juvenile skeleton, which is built mainly of cartilage (Daoud 1988) what modulates the duration of the inflammatory process. The main feature of the disease is the destruction of bone tissue, hence the frequent visible manifestations of the disease in archaeological material are different kinds of defects, erosions or focal tissue destruction.

In the paleopathological picture of skeletal TB, less specific morphological forms that can mimic other pathological conditions are also frequently observed, for example a single lytic lesion on the endocranial surface of the right parietal bone described by Dawson and Brown (2012) and differentiated from Langerhans cell histocytosis, eosinophilic granuloma and myofibromatosis. Hershkovitz et al. (2002) observed abnormal changes of porous type on the internal

surface of the cranial bones, which were given the name "serpentine engravings" (*serpes endocrania symmetrica*, SES). One of the diseases that these signs could be linked to is tuberculosis, although it is not a pathognomonic trait of the disease. However, it should be noted that there is an interaction between the incidence of SES with another pathological condition – the hypertrophic osteoarthropathy of long bones. (Lovejoy et al. 1977; Mensforth et al. 1978; Hershkovitz et al. 2002; Hershkovitz et al. 2008; Assis et al. 2011). All the factors that hinder the differentiation between the tuberculosis and other diseases may make the diagnosis of the skeletal TB based solely on the results of nonspecific macroscopic observations misleading. Thus it should be supported by other diagnostic methods, especially X-ray analysis and molecular techniques.

Material and methods

The archeological site at the St. Elizabeth church in Wrocław

The subject of the research – a juvenile skeleton from burial No 93 with pathological lesions – was unearthed from one of the brick lined tombs in the crypt localized under the church of St. Elizabeth in Wrocław. The temple was built in the 30s of the 13th century and served the residents of the western part of the city. It was a typical middle-class church, generously donated to by the rich patricians (Młynarska–Kaletynowa 1986; Wojcieszak 2012), so the residents of the city could count on burial within the walls of the parish church, which was previously reserved only for kings and priests. Within the walls of this late-Romanesque church, 61 inhumations were localzed in the presbytery and in the eastern part of the nave. The location of the burials in the heart of the temple may indicate the high socio-economic status of the people who were buried here. Under the presbytery, four brick tombs were also found, including one double tomb, containing a total of 13 burials (Wojcieszak 2012).

The skeleton unearthed from grave No 93

The skeleton is partially complete: the only preserved part of the skull is the right temporal bone and the postcranial elements are incomplete. The vertebrae are also incomplete – only 5 cervical, 7 thoracic, 5 lumbar and 3 sacral are present but in a good state of preservation. Components of the chest, in particular the ribs are preserved in fragments. Shoulder girdle and upper limbs: only a fragment of the right clavicle, right humerus (with damaged distal epiphysis), right radius and left humerus, ulna and radius preserved. From the skeleton of the right hand, only the hamate and capitate bone are present and elements of the left hand skeleton are missing. Pelvic girdle and lower limbs: hip, pubic and sciatic bones are preserved on both sides. Both femora (right with damaged distal epiphysis and left – complete), tibiae (right – complete and left – damaged proximal epiphysis) are also present. The skeleton of the right and left tarsus is complete; also the bones of the right metatarsus are present while most of the phalanges and bones of the left metatarsus are fragmentary.

Skeletal material explored from burial No 93 was cleaned from soil and segregated. Due to the incompleteness of the skeleton and young age of the individual, it was impossible to determine the

Table 1. Diaphyseal measurments of the well preserved long bones and estimated age at death of the individual

Bone measured	Value of the metric feature (mm)	Estimated age at death (in years)
Left ulna	258	14-15 (Maresh 1970 after Scheuer and Black 2009)
Left radius	186	10 (Gindhart 1973 after Scheuer and Black 2009)
Right femur	377	11-12 (Maresh 1970 after Scheuer and Black 2009)
Right tibia	340	11 (Maresh 1970 after Scheuer and Black 2009)

biological sex with certainty. Estimation of the age at death was also difficult, because teeth of the individual were not preserved, therefore, age could be determined only by an assessment of the degree of morphological development of the skeleton, based on the diaphyseal length measurements of the well-preserved long bones (Gindhart 1973; Maresh 1970; Scheuer et al. 2009). According to the metric features, the age at death of this juvenile can be estimated at approximately 10–15 years (Table 1)

Paleopathological evaluation

Pathological lesions were recorded during careful macroscopic examination and radiographic analysis. Attention was paid to the localization of the lesion in the skeleton and bony structures that were affected by the inflammatory process. Morphological features of the lesion were assessed according to the descriptions given by Aufderheide and Rodriguez-Martin (1998), Ortner (2003), Ortner (2008). In general, skeletal TB is characterized by the tendency to extensive destruction of bony structures composed primarily of trabecular bone, thus various types of bony defects and erosions that result from the accumulation of tuberculous granulomas are typical in the macroscopic picture. X-rays analysis gave an information regarding intensity of bone reactivity within the lesion, as well as the presence of sequestra and the type of bone remodeling resulting from the ongoing inflammatory process.

Results

Macroscopic and radiological picture of the disease

A single, large lesion was visible in the skeleton, in the proximal extremity of the right femur, which was distorted due to the pathological process (Fig. 1–2). The lesion in the form of an extensive erosion was located on the lower surface of the femoral neck (Fig. 3). As a result of ongoing inflammation, the size of the whole superior epiphysis was increased (it looks like it was "swollen") relative to the proximal extremity of the left femur, in which there was no visible signs of pathological lesions. The outline of the head was enlarged and distorted, and in the trochanter minor region massive bone formation of hypertrophic tissue could be seen. Signs of the disease were also apparent inside the acetabulum, on the inner surface of the ischium (Fig. 4), which indicates that the inflammatory process was actively spreading to other structures of the hip joint. Pathological lesions were located within the joint capsule, which must have become stretched due to the inflammatory process and the whole joint was probably swollen and painful.

The radiological picture of the disease can be considered as a typical example of

Fig. 1. Pathologically changed proximal metaphysis of the right femur in comparison to the left femur - without any visible signs of infection (anterior aspect)

Fig. 2. Comparison between pathologically changed proximal metaphysis of the right femur and free from lesions proximal epiphysis of the left femur (posterior aspect)

Fig. 3. Destructive lesion within the lower border of the right femoral neck

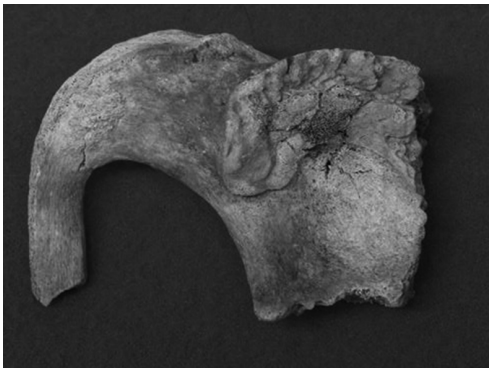

Fig. 4. The right ischium with pathological changes visible on the external surface

synovial tuberculosis with extensive erosions at the point of *synovium* attachment to the femoral neck (Fig. 5). During the individual's life, the gap of the hip joint was probably narrowed and the femoral head could have been overgrown (*coxa magna*) (Borejko and Dziak 1979).

Fig. 5. X-ray of the proximal metaphysis of the pathologically changed right femur

Inflammatory changes in the hip joint were clearly visible, but they were not the only skeletal signs of infection. In the thoracic vertebrae, evidence of hypervascularization, which is also connected to skeletal TB (Pálfi et al. 2012) could also be observed.

Discussion

Tuberculosis of bones and large joints (hip, knee) in paleopathological research is observed much less frequently than tuberculosis of the spine, moreover, this type of pathological changes are more often found in the skeletons of adults, for instance described by Jankauskas (1998), Molnár et al. (1998), Marcsik et al. (2006). In juvenile skeletons, this form of tuberculosis is observed very rarely due to the difficulties associated with the specificity of the immature skeleton, as well as diagnostic problems. Probably for these reasons, the common descriptions of juvenile skeletal TB refer to inflammation of the vertebrae, which is the most frequently occurring in archaeological material form of the disease (eg. Matos 2011; Lewis 2011).

Tuberculosis of the hip joint usually starts with the initial focus formation, which is situated in the roof of the acetabulum, femoral head or neck, or (less frequently) in the synovial membrane. In 10% of all cases, infection is restricted to the bone and takes the form of periarticular foci or breaks off the joint with periarticular abscesses and fistulae formation. In children's periarticular tuberculosis, swelling of the infected epiphysis may also be observed (Malawski 2003). In the first stage of infection, the primary focus forms in the bony tissue beneath the surface of the cartilage, then it expands to the articular cartilage and synovial membrane covering the whole joint. The pathological process, which leads to bone and articular structure degradation, involves formation of granulation tissue with foci of necrosis and caseation. They become fluid and break off from the synovial cavity with the formation of periarticular abscesses (Borejko and Dziak 1979; Hopwell and Bloom 1994).

The signs of tuberculous arthritis of the hip joint seems to be clearly identifiable in skeleton No 93, described here. In this case, it is most probable that the bacteria reached the joint cavity directly from the initial focus located in the femoral neck. *Tuberculous arthritis* is the second most common manifestation of tuberculosis in children (after the tuberculous spondylitis (spondylitis), and before tuberculous osteomyelitis. In the course of the disease, significant damage of the skeletal structures is usually inevitable and visible even in the macerated bony material, but due to the ambiguous morphological appearance of inflammatory diseases in historical skeletal material, initial diagnosis should be compared to paleopathological pictures of the diseases that leave signs in bones similar to skeletal tuberculosis.

Differential diagnosis

Taking into consideration the form and radiological signs of the disease observed in juvenile skeleton excavated from grave No 93, skeletal tuberculosis seems to be possible cause of hip joint pathology, although differential diagnosis is pivotal in paleopathology and needs to be performed. In Table No 2 three common inflammatory diseases that may cause lesions similar to skeletal TB lesions in the hip joint have been compared in terms of lesion localizations, skeletal manifestations and radiological pictures.

From the data presented in the Table No 2 it can be concluded that mainly due to the good conditions of blood supply, localizations of all types of infectious inflammatory processes within the skeleton are similar, however, the course of infection is dependent on the etiological factor and its impact on bony tissue.

Sarkar and coauthors (2016) demonstrated that some strains of *M. tuberculosis* may have inhibitory effects on osteoblasts, so it can be concluded that reactive changes observed in tuberculous arthritis may be poorly expressed, while *T. pallidum* infections produce strong bony reactions. In the examined case, well demarcated focus of osteolysis, as well as intense bone remodeling within the entire proximal epiphysis can be observed, which can be taken as a typical sign of chronic infection. Taking into consideration this observation, it is possible to exclude *T. pallidum* infection as the most probable cause of pathology within the hip joint.

The specific disease that seems to be the most similar to skeletal TB in terms

Table 2. Clinical and radiological features of joint infections in congenital syphilis, brucellosis and pyogenic arthritis

Disease	Frequent localizations	Clinical picture	Radiological features
Congenital syphilis	Epiphyseal cartilage and metaphyseal regions of the long bones; anterior surface of the tibia (sabre shins)	Usually symmetrical erosions within the metaphyseal regions of the long bones (Rasool and Govender, 1989); thickening of proximal regions of tibial shafts (Aufderheide and Rodriguez – Martin, 1998),	Diaphysitis and metaphyseal changes (eg. Wimberger's sign), metaphyseal serration, sawtooth – like appearance of the metaphysis; mild to severe periosteal reactions (Rasool and Govender, 1989), eg. lamellar periostitis within the anterior surface of the tibiae (sabre shins)
Brucellosis	Sacro-illiac joints and lumbar vertebrae (Mutolo et al., 2012; D'Anastasio, et al., 2011)large peripheral joints (hip and knee more frequently affected than sacroiliac joint and spine) (Alshaalan et al., 2014)	sacroiliitis or lumbar spondylitis (D'Anastasio et al., 2011); osteomyelitis in long bones and the pelvis, arthritis (Kelly et al., 1960; Ariza et al., 1985)54 years	epiphysitis of the anterosuperior angle of lumbar vertebrae (so-called sign of Pedro-Pons) (D'Anastasio et al., 2011)
Septic arthritis	Usually monoarticular; the most commonly involved joints in nongonococcal septic arthritis are the knee and hip, followed by the shoulder and ankle (Barton et al., 1987; Shirtliff and Mader, 2002)	Arthritis of the infected joint, osteomyelitis	Osteopenia, diffused joint space narrowing may evolve (García-Arias et al., 2012); features of osteomyelitis which in chronic and sub-chronic infections manifests in sequestra formation, which are visible as a focal area of sclerotic bone within an area of translucency (Christian et al., 2007)

of paleopathological and radiological observations is brucellosis, but in this case the localization of the pathological process would be rather unusual, as more advanced changes in the vertebrae should be expected, whereas in the examined case only traces of hypervascularization within the vertebral bodies were noted.

In paleopathological differential diagnosis, pyogenic arthritis of the hip joint should be also taken into consideration as a possible cause of the infection. It usually is monoarthritic and has radiological features simila to skeletal TB infection. However, in examined case any sequestra within pathologically changed superior epiphysis of the femur, which would be typical in chronic inflammatory process of the hip joint could be observed. Moreover, in late-stage TB of the large peripheral joints, besides periarticular osteopenia, Phemister's triad signs (peripheral osseous erosions, articular destruction with narrowing of the joint and juxta-articular osteoporosis) can be found (Garcia-Arias et al. 2012), which seems to be consistent with the macroscopic picture of the lesions observed in skeleton No 93.

In the differential diagnosis of tuberculosis of the hip joint also other diseases, e.g. sarcoidosis, rheumatoid arthritis, Sudeck's disease, some types of neoplasms (Hopwell and Bloom, 1994)

should be taken into consideration as a probable cause but due to the young age at death of the examined individual and quite clear macroscopic picture of the disease, they seem to be less probable.

Risk factors and socio-economic background of tuberculosis

As a separate issue, there remains the problem of the background of the TB spreading in the medieval Wrocław population. Young children (under 5th year of life) are very prone to pulmonary and other forms of tuberculosis (Maltezou et al. 2000; Marais et al. 2004; Cruz and Starke 2007; Newton et al. 2008) due to the immaturity of the immune system. As written above, the form of tuberculosis (intra or extrapulmonary and, in the case of skeletal TB, one or multifocal locations) is strongly related to the immune status. Jones et al. (1993) stated that extrapulmonary TB involvement tends to increase in frequency if immune function is lowered. Tuberculosis of the hip joint observed in the skeleton No 93 could suggest that immune status of this individual was low.

There are plenty of environmental conditions which strongly affect the immune system, and one of them is malnutrition, which is strongly linked to infectious diseases. Malnutrition can make a person more susceptible to infection, and infection also contributes to malnutrition, which causes a vicious cycle. An inadequate dietary intake leads to weight loss, lowered immunity, mucosal damage, invasion by pathogens, and impaired growth and development in children (Katona and Katona-Apte, 2008).

Malnutrition does not have to be severe – just a shortage of certain substances, especially protein can result in significant immunosuppression. Apart from deficiencies in single nutrients, such as vitamins, fatty acids, amino acids, iron, and trace elements, undernourishment based on PEM (protein energy malnutrition) greatly increases susceptibility to major human infectious diseases in low-income countries, particularly in children (Moret and Schmidt-Hempel 2000; Scrimshaw and SanGiovanni 1997; Ambrus and Ambrus 2004; Schaible and Kaufmann 2007). The main reason is that malnutrition causes impairment of both acquired immunity and innate host defense mechanisms.

In TB infection, the interaction between macrophage and *Mycobacterium tuberculosis* plays a main role. *Mycobacterium* is an intracellular microorganism, so it has to penetrate inside the macrophage through one of the numerous trans-membrane receptors which enable internalization of the bacteria (Mason and Ali 2004). Macrophage is, in fact, the first line of defense against intracellular microbial pathogens. It has been proved (Rivadeneira et al. 2001) on a cellular level that malnutrition can induce macrophage apoptosis, which is crucial in immuno-resistance to infectious diseases, particularly in the mechanism of TB infection.

Skeleton No 93 was unearthed in the crypt located under the St. Elizabeth Church in Wrocław and this burial site indicates that this individual could belong to a wealthy middle class. None of visible physiological stress markers (*cribra orbitalia*, *enamel hypoplasia*) could have been observed on preserved bones in the macroscopic examination, mainly due to the bad state of preservation of the skeletal material, but it does not mean that the child did not suffer from any nutritional deficiencies.

Another factor contributing to infection risk, could have been life in the crowded big city environment, which is inextricably linked to continuous exposure to infectious agents. A child living among adults suffering from active pulmonary tuberculosis, might have become infected, even though the overall health and nutrition were satisfactory.

A combination of different environmental conditions, especially poverty, overcrowding and malnutrition (Millet et al. 2013) that have a negative influence on human health is the perfect background for the development and spread of infectious diseases.

Conclusion

In a skeleton of a juvenile who died centuries ago, traces of the disease, which was (and still is a serious medical problem) were revealed. In a pre-antibiotic era, the only protection against the development of tuberculosis was an efficient immune system and its functioning was dependent on many factors affecting the immunological status of the individuals. In the past, tuberculosis was thought to be a disease of the poor and the highest morbidity was among children and young adults, which reflected the high prevalence of the disease in historical populations. This situation is similar to the pattern of the incidence of tuberculosis in the societies of developing countries, which indicates that there is significant association between socio-economic status and the risk of developing tuberculosis (Millet et al. 2013). However, in medieval times, the disease was not restricted only to the poor strata of the community and, as shown by the example of the young individual, who was buried in the crypt under the church of St. Elizabeth in Wrocław, even wealthy patricians of Wrocław were under the risk of infection caused by *Mycobacterium tuberculosi*s.

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References

Alshaalan, MA, Alalola SA, Almuneef MA, Albanyan EA, Balkhy HH, AlShahrani DA, Aljohani S. 2014. Brucellosis in children: Prevention, diagnosis and management guidelines for general pediatricians endorsed by the Saudi Pediatric Infectious Diseases Society (SPIDS). IJAMH 1(1):40–46.

Ambrus JL Sr, Ambrus JL Jr. 2004. Nutrition and infectious diseases in developing countries and problems of acquired immunodeficiency syndrome. Exp Biol Med 229:464–72.

Ariza J, Gudiol F, Valverde J, Pallares R., Fernandez-Viladrich P, Rufi G, Fernandez-Nogues F. 1985. Brucellar spondylitis: a detailed analysis based on current findings. Rev Infect Dis 7(5):656–64.

Assis S, Santos AL, Roberts CA. 2011. Evidence of hypertrophic osteoarthropathy in individuals from the Coimbra Skele-

tal Identified Collection (Portugal). Int J Paleopathol 1(3–4):155–63.

Aufderheide AC, Rodriguez-Martin CR. 1998. Infectious diseases. In: AC Aufderheide, C Rodriguez-Martin and O Langsjoen. Cambridge Encyclopedia of Paleopathology. Cambridge: Cambridge University Press. 118–69.

Barton LL, Dunkle LM, Habib FH. 1987. Septic arthritis in childhood. A 13-year review. Am J Dis Child 141(8):898–900.

Bianucci R, Giuffra V, Bachmeier BE, Ball M, Pusch CM, Fornaciari G, Nerlich AG. 2012. Eleonora of Toledo (1522–1562): Evidence for tuberculosis and leishmaniasis co-infection in Renaissance Italy. Int J Paleopathol 2(4):231–35.

Borejko M, Dziak A. 1979. Badanie radiologiczne w ortopedii. Warszawa:Państwowy Zakład Wydawnictw Lekarskich.

Christian S, Kraas J, Conway WF. 2007. Musculoskeletal Infections. Semin Roentgenol 42(2):92–101.

Cruz AT, Starke JR. 2007. Clinical manifestations of tuberculosis in children. Paediatr Respir Rev 8(2):107–17.

D'Anastasio R, Staniscia T, Milia ML, Manzoli L, Capasso L. 2011. Origin, evolution and paleoepidemiology of brucellosis. Epidemiol Infect 139(1):149–56.

Dabernat H, Crubézy É. 2010. Multiple bone tuberculosis in a child from predynastic Upper Egypt (3200 BC). Int J Osteoarchaeol 20(6):719–30.

Dawson H, Robson Brown K. 2012. Childhood tuberculosis: A probable case from late mediaeval Somerset, England. Int J Paleopathol 2(1):31–35.

Donoghue HD. 2011. Insights gained from palaeomicrobiology into ancient and modern tuberculosis. Clin Microbiol Infec 17(6):821–29.

Donoghue HD, Spigelman M, Greenblatt CL, Lev-Maor G, Bar-Gal GK, Vernon, K., Nehrlich A.G, Zink, A. R. (2004). Review Tuberculosis and ancient DNA Tuberculosis : from prehistory to Robert Koch , as revealed by ancient DNA. Lancet Infect Dis 4(9):584–92.

García-Arias M, Pérez-Esteban S, Castañeda S. 2012. Septic Arthritis and Tuberculosis Arthritis. Journal of Arthritis 1(1):1–10

Gaździk TS. 2010. Zapalenia narządu ruchu. In: TS Gaździk, ed. Ortopedia i traumatologia. 3rd edition. Warszawa: Wydawnictwa Lekarskie PZWL. 495–531.

Gindhart P. 1973. Growth standards for the tibia and radius in children aged one month through eighteen years. Am J Phys Anthropol 39:41–48.

Hershkovitz I, Donoghue HD, Minnikin DE, Besra GS, Lee OY-C, Gernaey AM, Galili E, Eshed V, Greenblatt CL, Lemma E, Bar-Gal GK, Spigelman M. 2008. Detection and molecular characterization of 9,000-year-old Mycobacterium tuberculosis from a Neolithic settlement in the Eastern Mediterranean. PloS One 3(10):e3426.

Hershkovitz I, Greenwald CM, Latimer B, Jellema LM, Wish-Baratz S, Eshed V, Dotour O, Rothschild BM. 2002. Serpens endocrania symmetrica (SES): a new term and a possible clue for identifying intrathoracic disease in skeletal populations. Am J Phys Anthropol 118(3):201–16.

Hlavenková L, Teasdale MD, Gábor O, Nagy G, Beňuš R, Marcsik A, Hajdu T. 2015. Childhood bone tuberculosis from Roman Pécs, Hungary. HOMO 66(1):27–37.

Holloway KL, Henneberg RJ, de Barros Lopes M, Henneberg M. 2011. Evolution of human tuberculosis: a systematic review and meta-analysis of paleopathological evidence. HOMO 62(6):402–58.

Hopwell PC, Bloom BR. 1994. Tuberculosis and other mycobacterial diseases. In: JA Murray and JF Nadel, eds. Textbook of Respiratory Medicine. Philadelphia: W.B. Saunders Corp. 1094 – 1160.

Ioannou S, Henneberg M, Henneberg RJ, Anson T. 2015. Diagnosis of mercurial teeth in a possible case of congenital syphilis and tuberculosis in a 19th century child skeleton. Journal of Anthropology. Article ID 103842. doi.org/10.1155/2015/103842.

Jankauskas R. 1998. History of human tuberculosis in Lithuania : possibilities and

limitations of paleoosteological evidences. Bulletins et Memoires de La Societe D'anthropologie de Paris 10(3–4):357–74.
Jones BE, Young SM, Antoniskis D, Davidson PT, Kramer F, Barnes PF. 1993. Relationship of the Manifestations of Tuberculosis to CD4 Cell Counts in Patients with Human Immunodeficiency Virus Infection. Am Rev Respir Dis 148:1292–97.
Katona P, Katona-Apte J. 2008. The interaction between nutrition and infection. Clin Infect Dis 46(10):1582–88.
Kelly PJ, Martin WJ, Schirger A, Weed LA. 1960. Brucellosis of the bones and joints experience with thirty-six patients. JAMA 174(4):347–53.
Lovejoy CO, Meindl RS, Pryzbeck TR, Barton TS, Heiple KG, Kotting D. 1977. Paleodemography of the libben site, Ottawa County, Ohio. Science 198(4314):291–93.
Malawski S. 2003. Gruźlica kości i stawów. In: W Maciniak and A Szulc, eds. Wiktora Degi ortopedia i rehabilitacja. Warszawa: Wydawnictwa Lekarskie PZWL. 247–59.
Maltezou HC, Spyridis P, Kafetzis DA. 2000. Extra-pulmonary tuberculosis in children. Arch Dis Child 83:342–46.
Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Obihara CC, Starke JJ, Beyers N. 2004. The natural history of childhood intra-thoracic tuberculosis: A critical review of literature from the pre-chemotherapy era. Int J Tuberc Lung D 8(4):392–402.
Marcsik A, Molnár E, Szathmary L. 2006. The antiquity of tuberculosis in Hungary: the skeletal evidence. Mem Inst Oswaldo Cruz 101(Suppl. 2): 67–71.
Maresh MM. 1970. Measurements from roentgenograms. In: RW McCammon, ed. Human growth and development. Springfield IL: C.C. Thomas. 157–200.
Mason CM, Ali J. 2004. Immunity against Mycobacteria. Semin Respir Crit Care Med 25(1): 53–61.
Mensforth RP, Lovejoy CO, Lallo JW, Armelagos GJ. 1978. Part two: the role of constitutional factors, diet, and infectious disease in the etiology of porotic hyperostosis and periosteal reactions in prehistoric infants and children. Med Anthropol 2: 1–59.
Millet JP, Moreno A., Fina L., del Bano L., Orcau A., Garcia de Olalla P., Cayla JA. 2013. Factors that influence current tuberculosis epidemiology. Eur Spine J (2013) 22 (Suppl 4):S539–S548
Molnár E, Marcsik A, Dutour O, Bérato J, Pálfi G. 1998. Skeletal tuberculosis in Hungarian and French Medieval anthropological material. In: A Guerci, ed. Treating illnesses: historical routes. Genova: Erga Edizioni. 87–99.
Moret Y, Schmid-Hempel P. 2000. Survival for immunity: the price of immune system activation for bumblebee workers. Science 10:290(5494):1166–68.
Morris BS, Varma R, Garg A, Awasthi M, Maheshwari M. 2002. Multifocal musculoskeletal tuberculosis in children: appearances on computed tomography. Skeletal Radiol 31(1):1–8.
Mutolo MJ, Jenny LL, Buszek AR, Fenton TW, Foran DR. 2012. Osteological and molecular identification of brucellosis in ancient Butrint, Albania. Am J Phys Anthropol 147(2):254–63.
Newton SM, Brent AJ, Anderson S, Whittaker E, Kampmann B. 2008. Paediatric tuberculosis. Lancet Infect Dis 8(8):498–510.
Ortner DJ. 2003. Infection diseases: tuberculosis and leprosy. In: Identification of pathological conditions in human skeletal remains. Elsevier. 191–215.
Ortner D J. 2008. Differential diagnosis of skeletal lesions in infectious diseases. In: R Pinhasi and S Mays, eds. Advances in human paleopathology. John Wiley & Sons, Ltd. 191–215.
Pálfi G, Molnár E. 2009. The Paleopathology of specific infectious diseases from Southeastern Hungary : a brief overview. Acta Biologica Szegediensis 53(2):111–16.
Panek B, Chyczewska E. 2001. Gruźlicze zapalenie kości. Pneumonol Alergol Pol: 69(11–12):673–76.
Rasool MN, Govender S. 1989. The skeletal manifestations of congenital syphilis.

A review of 197 cases. J Bone Joint Surg Br 71–B(5):752–55.

Rivadeneira DE, Grobmyer SR, Naama HA, Mackrell PJ, Mestre JR, Stapleton PP, Daly JM. 2001. Malnutrition-induced macrophage apoptosis. Surgery 129(5):617–25.

Roberts CA, Buikstra J. 2003. The bioarchaeology of Tuberculosis: a global view on a reemerging disease. Florida: University Press of Florida.

Sarkar S, Dlamini MG, Bhattacharya D, Ashiru OT, Sturm AW, Moodley P. 2016. Strains of Mycobacterium tuberculosis differ in affinity for human osteoblasts and alveolar cells in vitro. SpringerPlus 5(1):163.

Schaefer M, Black S, Scheuer L. 2009. Juvenile osteology a laboratory and field manual. Elsevier Academic Press.

Schaible UE, Kaufmann SHE. 2007. Malnutrition and infection: Complex mechanisms and global impacts. PLoS Med 4(5):0806–12.

Scrimshaw NS, SanGiovanni JP. 1997. Synergism of nutrition, infection, and immunity: An overview. Am J Clin Nutr 66(2):464S–477S.

Shirtliff ME, Mader JT. 2002. Acute septic arthritis. Clin Microbiol Rev 15(4):527–44.

Sparacello VS, CA Roberts, Kerudin A, Müller R. 2017. A 6500-year-old Middle Neolithic child from Pollera Cave (Liguria, Italy) with probable multifocal osteoarticular tuberculosis. In J Paleopathol 17:67–74.

Vallejo JG, Ong LT, Starke JR. 1995. Tuberculous osteomyelitis of the long bones in children. Pediatr Infect Dis J 14(6):542–46.

Wojcieszak M. 2012. Nekropole średniowiecznego i wczesnonowożytnego Wrocławia. Wratislavia Antiqua 15:39–41.