INTRODUCTION

The term of paleopathology began to be widely used from the 20th century onwards. The earliest attempt to solve some biomedical problems was first recorded in the 19th century, when John Collins Warren (1778-1856), an American surgeon, spoke in 1822 about the artificial cranial lesion observed in a human skull of a native South American. In the early 20th century, Armand Ruffer (1910) described paleopathology as the study of the evidence of disease in human remains from several archaeological sites.
Human remains (skeletal remains and teeth) are considered to be as the primary source of evidence for past diseases and ancient medical practices, mainly during the prehistoric times, when there is a lack of written sources.

Stone age period covers a big timespan of the prehistory and is very important for human evolution and the emergence of civilization. It is divided into three periods, the Paleolithic period (2.6 Ma-10 ka), the Mesolithic (10.000-7.000 BC) and the Neolithic (7.000-3.200 BC)\(^2\). The Paleolithic period coincides with the onset of the Pleistocene at 2.6 million years, a period with extreme climatic events (alternations of glacial and interglacial periods), when human species had to cope with them and adapt to new life conditions. During the Paleolithic and Mesolithic period, the economy was based on foraging and hunting and changed to productive into the Neolithic period, when farming and cultivation were introduced.

These changes had great impact on dietary habits of populations, also affecting their health status and pathology. The Neolithic transition led to an overall deterioration in health, hence to the increase of exposure to disease agents, changes in diet and population aggregation in larger and denser settlements\(^4\). Various studies revealed an association between the advancement of agriculture and change in the health status of human populations. The most common changes reported are the pathological conditions which were induced by a combination of factors, including a higher rate of infection, a decline in the overall quality of nutrition, and an increase in physical stress\(^5,6\).

Last decades, several researches have been applied to skeletal remains from archaeological sites of the Stone age in Greece, aiming at highlighting the health status, the causes of death and hygiene level of past populations.

**PALEOPATHOLOGY**

Archaeologists can use paleopathology as a diagnostic tool for understanding the everyday life of ancient populations. During the analysis and interpretation of skeletal residues, three stages of data processing are performed. In the first stage, the bones are cleaned and sorted. In the second stage, it follows the gender and age determination, based on skeletal remains, such as the skull and pelvis, from which the morphological differences between men and women of each period emerge and in the third stage, the age of death is estimated due to the differences observed in the bones and the lesions they underwent\(^1\).

Paleopathology can be classified into three main categories of diseases: a) the infectious diseases, such as tuberculosis and syphilis; b) the metabolic disorders, like anemia and c) musculoskeletal diseases, such as arthropathies, osteoarthritis, osteoporosis and traumatic injuries (broken, malformed bones etc)\(^7\).

**Musculoskeletal Diseases**

The musculoskeletal disorders mainly concern the skeletal injuries. Injury is defined as any injury or damage to the bone, which in many cases may lead to a severe fracture (e.g. bone fracture), depending on the pressure exerted on the area or damage caused by sharp objects (axes, swords, arrows).

A special type of skeletal lesions are the so called ‘fatigue fractures’, which result from the constant strain on the bone, usually due to a repetitive movement which is usually caused by weakening of the bone. A common example is osteoarthritis, in which the connecting articular cartilage between the bones is gradually destroyed, resulting in the formation of a new bone, the so-called osteophyte. The osteophyte is considered as a bone extension of the already injured bone and its appearance tends to address the lack of connectivity. During its creation, the human body develops a mechanism of cell regeneration, which in the case of bones is called porosity\(^8\).

Another limitation regarding the reading of skeletal remains and the conclusions that can be drawn from them are the late complications of fractures, i.e those that are delayed in appearing in the bones, as in the case of a chronic disease. One such example is osteomyelitis, an inflammation of the bone that results from an infection, which is primarily associated with open fractures. This fact is the main reason that this type of inflammation is also included as a subcategory in infectious diseases.

Extreme traumatic lesions to the head, knees and hand with embedded stone projectiles recognized to a 10,000 year-old man in Turkana in Kenya, gave the earliest evidence of inter-group conflict between hunters-gatherers in the past\(^9\). Recent paleopathological studies to the skeletal remains of the...
Australopithecus afarensis (the well-known Lucy), proved that she died from traumatic injuries after falling from a tree10 (Fig. 1).

Periostitis is also very common in populations of the Upper Paleolithic. Periostitis is due to long-term walk on inaccessible ground and to painful living conditions.

Infectious diseases

The action of infectious diseases depends mainly on the infectious agent and its severity, the speed of infection and the resistance of the host. The two most common infectious diseases during the Stone Age were malaria and tuberculosis. Malaria comes from the mosquitoes, which are greatly affected by the change of wetlands, due to temperature increase and morphological changes. They are usually found in areas with stagnant water, where water is rapidly polluted due to stagnation, being a terrible carrier of pollution. The disease is thought to have originated in North Africa and the Middle East and has gradually spread to southern Europe11.

Tuberculosis is a deadly infectious disease, common in modern times, which is caused by the bacterium Mycobacterium tuberculosis. During the Neolithic period, tuberculosis most often affected the spine and the signs manifested by the formation of local cavities. This disease is estimated to be transmitted from domesticated cattle to humans. Mummies from ancient Egypt (4,000 BC) have been found suffering from this disease, as seen from their spine.

Metabolic diseases

A metabolic disorder can appear when abnormal chemical reactions in the body alter the normal metabolic process that take place in the cells of the human body. Because of this, the lack of one or more vitamins, trace elements and amino acids can lead to very severe diseases. The most common deficiency observed worldwide is that of iron, resulting to anemia, when the human body is unable to replenish the necessary number of red blood cells needed to function properly.

The main type of anemia found in skeletal remains is iron deficiency anemia and is manifested in two forms, as porotic hyperostosis and cribra orbitalia12,13. Porotic hyperostosis is the most common pathological abnormality during the Neolithic Age, with its morphology varying according to the archaeological sites. Porotic hyperostosis leads to thinning and almost to the total destruction of the outer solid tissue of the skull bones, due to the hypertrophy of the hematopoietic duplex, located between the outer and inner plate of the skull, in order to produce more red blood cells for the compensation of the lack of oxygen to the tissues. Porosities that are confined to the orbital roof (cribra orbitalia) called cribra orbitalia.

Teeth diseases

Teeth are the most durable anatomical formations of the human skeleton and their diseases are among the most common found in archaeological populations. They are directly related to diet, oral hygiene and stress levels of the body. The five main diseases are: caries, periodontal disease, calculus, dental abrasion and linear enamel hypoplasias14.

Caries is a multifactorial disease, characterized by the decalcification of dental tissues due to carbohydrates and sugars in the diet. It is placed in the teeth in the form of brown spots or cavities that have affected the tooth enamel, resulting in partial or total tooth loss.

Periodontitis is a chronic inflammation of the alveolar bone that surrounds the teeth. In the initial stages, it is undetectable and if the denture is left without care, then the gums are affected, the support lost, and the teeth fall out.

The calculus, or dental plaque, is a microbial dental plaque that is formed on the surface of the anterior teeth of the lower jaw and on the buccal surface of the first and second molars of the upper jaw. Depending on its location, it is divided into categories.

Dental abrasion involves the gradual wear and tear of the tooth surfaces during contact with each other during chewing. The result is the loss of enamel, a factor that predisposes to further pathological lesions in the teeth. Linear enamel hypoplasia is a disorder in the formation of the enamel, a possible sign of stress on the body, because of malnutrition.

Recently, scientists discovered the earliest direct evidence of milk consumption by humans. They
identified milk protein entombed in calcified dental plaque (calculus) on the teeth of prehistoric farmers from Britain. A milk protein called beta-lactoglobulin (BLG) was detected in the tartar of seven people from Britain. A milk protein called beta-lactoglobulin (BLG) was detected in the tartar of seven people from Britain.

**Discussion**

Within the framework of the traditional archaeological thought, with the distinct separation of the Paleolithic/ Mesolithic mobile hunter-gatherers and the permanently settled Neolithic and post-Neolithic farmers, the Paleolithic/ Mesolithic societies of hunter-gatherers show a low incidence of diseases due to the large consumption of animal protein and constant mobility. On the contrary, the Neolithic agricultural societies have higher incidence rates, hence the degradation of food quality and the sharp shift in their nutritional behaviors (from the consumption of animal protein to carbohydrates), combined also with the downgrading of the hygienic conditions. This pattern changes in the Bronze Age, which shows low rates of disease expression due to the improved economic and socio-cultural structures.

According to paleopathological studies, the life expectancy of people of the Paleolithic era was low. The main causes of death were accidents, lack of food and basic nutrients and some infectious diseases, although due to the fact that they lived in small groups and more isolated, the transmission of infectious-epidemic diseases was not favored. There is evidence of infectious zoonotic diseases before the permanent installation, during the nomadic stage. This is caused by the fact that the permanent installation contributed to the development of antibodies. Non-contagious diseases, such as hypertension, cancer, diabetes were almost non-existent.

In Homo erectus skeletons, exostosis or osteoma (a benign growth of new bone on top of existing bone) was a very common disease. A characteristic example of exostosis in the femur, is mentioned for the "Java Man" in Trinil.

In Neanderthals, arthritis and tuberculosis of the spine have been observed, with the characteristic kyphosis of the skeleton. Cases of congenital syphilis in Neanderthals skeletons from the British museum have been also observed, as the thinning and pitting of the occipital and parietal areas with the relative depression of the bridge of the nose ("saddle nose") supported a diagnosis of a generalized syphilitic osteomyelitis.

Recent research into Neanderthal baby teeth from the Rhone Valley in France (250,000 years old) has revealed the oldest environmental lead exposure. According to the research, the exposure occurred during the colder periods, possibly from the consumption of contaminated food or water or from the inhalation of smoke from fires containing lead.

Genetic mixtures between Homo Neanderthal and Homo sapiens resulted in the transmission of not just germs, but also genes that were predisposed to specific diseases. DNA studies on bones have shown that several diseases such as herpes, stomach ulcers, tuberculosis, etc. were transmitted by Homo sapiens who had been infected by contact with African hominids before leaving Africa, to Neanderthals, making them unable to respond immunologically. In fact, this has been suggested as one of the reasons for their disappearance.

Conversely, the transfer of Neanderthal genes to modern humans, given that we carry an average of 2% Neanderthal DNA, has resulted in the inheritance of genes that may be associated with type 2 diabetes, lupus erythematosus, and Crohn's disease, depression, smoking addiction, etc.

From dental studies, we can conclude that in general the populations showed relatively good oral health. There are cases of periodontitis, but caries is not so common, in contrast to the appearance of calculus, which is more related to the consumption of meat. The introduction of carbohydrates towards the end of the Paleolithic era and especially during the Neolithic era will increase the cases of caries and linear enamel hypoplasia.

For the Neolithic period, the paleopathological data are enough to be able to compose a picture of the diseases that usually affected the Neolithic populations. The new agro-bio-living conditions of housing, food, work, have resulted in the spread of several epidemic diseases, such as e.g. tuberculosis, smallpox, malaria.

Also, the technique of storage and preparation of food played a significant role in the spread of infections. The more potential carriers of a microorganism, the more likely it is that an infectious disease will survive. About 15,000 years ago, with the domestication of the dog, the first transmission of animal-to-human infection probably occurred. The effects of climate and geomorphological changes at the beginning of the Holocene could be associated with increased rates of malaria. The environmental changes raised the concentration of mosquitoes in coastal wetlands, resulting in increased rates of malaria in many parts of Europe. There is evidence that the malaria parasite *Plasmodium falciparum* appeared in southern Europe from North Africa and the Near East and settled in southern Europe, due to significant soil changes that coincided with the spread of the disease.

According to the latest research, the Egyptian king Tutankhamun died of malaria after an infection...
in his leg\textsuperscript{25}. The researchers believe that this is most likely due to intermarriage, which affects the transmission of deadly genes to the offspring, as the genetic analysis showed that the King’s parents were probably brothers.

From bone diseases, we have indications of fractures, arthritis, sinusitis, tuberculosis, etc. The richest information comes from the Egyptian mummies because the soft molecules have been preserved. Thus, the findings from the mummies include pneumonia, pleurisy, arteriosclerosis, appendicitis, stones, and even uterine prolapse and complications of childbirth, such as e.g. fetuses wedged in the pelvis\textsuperscript{26}.

The oldest preserved heart is from a mummmified rabbit of the Pleistocene epoch, over 20,000 years old. Cardiovascular diseases had been identified in human mummies from Alaska and Egypt, covering a big-time span, ranging from approximately 3,000 to 300 years ago\textsuperscript{27}.

Another interesting case is the finding of a skeleton in the region of South-Eastern Siberia, in the Lokomotiv cemetery. This cemetery goes back to the Early Neolithic period of Siberia and during its partial excavation 101 people were collected. An unprecedented discovery from this site was the skeleton of a woman who, according to the relevant research, died during the birth of her twins, 7,000 to 8,000 years ago. This finding was ranked in the international literature as the oldest of its kind. The analysis of the skeletal remains showed that the woman who was pregnant with the twins encountered serious complications in childbirth, during the expulsion, resulting in not only her own death but also that of the fetuses\textsuperscript{28}. According to the way she was buried, the remains of the embryos were found in the abdomen / pelvis up to the height of the thighs, which probably means that she was buried immediately after her death, without completely removing the deceased embryos.

Recently, scientists in Germany claim to have discovered the oldest known case of blood cancer, leukemia, in the bones of a woman skeleton, dating about 7,000 years ago and found in a Neolithic settlement in the southwest of the country\textsuperscript{29}.

Neolithic surgery was at a fairly-satisfactory level of technical ability, thanks to the various tools created by man. Skull drilling is the oldest evidence for which we have evidence\textsuperscript{30}. The reason for which trepanation took place has not been ascertained. Perhaps prehistoric doctors applied trepanation in order to remove bone remnants in cases of cranial injuries, or to release evil spirits for magical causes, which were thought to cause diseases of the brain, such as headaches or convulsions.

**Greek paleopathological studies**

Several paleopathological researches have been done in Neolithic sites of Greece, such as in Nea Nikomedia, in Makriyalos Pieria, in the cave of Alepotrypa in Mani, in the cave of Franchthi in Argolis, in the cave of Theopetra in Thessaly\textsuperscript{2,13,31-38} etc.

The introduction of agriculture brought changes in the diet of the Greek Neolithic populations, who consumed significantly less meat than their predecessor hunter-gatherers. Cereals are low in iron but high in fiber, which blocks the absorption of iron. Thus, the onset of iron deficiency anemia was one of the immediate effects.

Osteoarthritis, osteopenia and osteoporosis are also the most common joint diseases and occur more often in men due to the variation in agricultural activities depending on gender. Changes in physical stress in the skeleton, as well as nutritional deficiencies in calcium and vitamin D, contributed to the increase of these diseases\textsuperscript{39}.

Arthritis was very common. In Nea Nikomidia, Macedonia, in Alepotrypa cave and Skotini Cave in Evia the rates of osteoarthritis are very high. As studies of skeletal remains of the Neolithic period have shown arthropathies equally between men and women, it would therefore be relatively safe to say that there was no particular division of labor between men and women.

In addition, it should be mentioned that while the lesions in the joints develop because of aging, in Alepotrypa they occur in all age groups. This means that, from an early age, people were involved in the daily work of the settlement and played an important role in the production processes.

The presence of anemia in vulnerable groups of the population, such as infants (0-1 years old) and children (1-6 years old) is common and therefore child mortality is a key indicator of public health, hygiene and social conditions. During the Neolithic period, New Nicomedia constitutes a typical example of the occurrence of anemia, as the majority of the patients are newborns (0-1 years) and infants (1-6 years). Signs of anemia, such as porous hyperostosis and cribra orbitalia, were found in Alepotrypa, but no differences in the presence of anemia between the two sexes and age groups were recorded.

The next two diagrams (Fig. 3, 4) show in percentage the frequency of porotic hyperostosis and cribra orbitalia in the Greek Neolithic settlements. It is noted that the percentages in porous hyperostosis are very high for the cave of Alepotrypa and Nea Nikomidia, while in Makriyalos (Macedonia) it reached 100% of the studied samples. Unlike cribra orbitalia, the frequency in Makriyalos and Kefala.
(Kea) is negligible, however Franchthi cave and Alepotrypa show percentages, 50 and 60% respectively.34

**Conclusions**

Paleopathology is a scientific tool supported by history, archaeology, anthropology and medicine, which provides an integrated vision of diseases and lifestyle habits, helping to understand how populations lived and died in ancient times. The paleopathology of the Stone Age period is not well studied, although this period could be characterized as a landmark of human evolution and human paleopathology. The transition from the Paleolithic lifestyle to Neolithic period had great impact on dietary habits of populations, also affecting their health status and pathology. As seen above, the Neolithic everyday life led to health deterioration, hence to the increase of exposure to disease agents, changes in diet and activities and population accumulation in larger and denser settlements.40,41 More scientific studies from the skeletal remains of archaeological sites of the Stone Age period are needed in order to have an overview of health status and habits of prehistoric populations.
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K.T. conceived the original draft preparation. K.T. and M.K. were responsible for conception and design of the review. K.T. was responsible for the data acquisition. K.T and M.K. were responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. K.T., and M.K. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

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