What Do Mummies Tell Us About Atherosclerosis?☆

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Why do humans develop atherosclerosis? Is the human genome hardwired to develop atherosclerosis? Can atherosclerosis be entirely prevented? Is atherosclerosis fundamental to the aging process? Have the risk factors that have contributed to the development of atherosclerosis been the same all along human evolution? An excellent collection of original investigations and review articles in this issue of *Global Heart* traces the antiquity of this noncommunicable disease through the study of mummies from all continents except Australia and Antarctica.

Using x-ray computed tomography (CT), the investigators contributing to this issue of *Global Heart* have yet to find a culture that did not have pre-clinical atherosclerosis. Thompson et al. [1] had previously reported atherosclerosis in 4 ancient cultures from different parts of the world, including ancient Egyptians, ancient Peruvians, ancient Native Americans in the American Southwest, and Aleutian Island hunter gatherers [2], and have now reported the evidence of atherosclerosis in the fifth culture. They describe atherosclerosis in a nomad who lived in the Gobi desert of Mongolia circa 1450 CE. Gaeta et al. [3] have recently also reported atherosclerosis on autopsy examination of a Renaissance king who reigned over the city state of Naples during the same time. The pioneering early work of Zimmerman et al. [4–6] had recorded atherosclerosis in 3 ancient indigenous persons of modern day Alaska. Comparing the CT scans of 178 current-day Egyptians to those of 76 ancient Egyptians in this issue of *Global Heart,* Allam et al. [7] found a similar prevalence of atherosclerosis in the 2 cultures despite a temporal separation of 2,000 to 3,500 years. Unlike in the modern day, they observed a trend toward more atherosclerosis in women. As women did the cooking in those times and did so over an open fire, the smoke exposure might explain this paradox. Analogous to the work of Wong et al. [8,9] in the MESA population, Allam reported that atherosclerosis occurred first in the iliac, femoral, and aortic beds. This was followed by the involvement, roughly a decade later, of carotids and coronaries, the vascular beds that are most often associated with major adverse events [7]. Whereas the presence of vascular calcification in these many vascular beds infers that clinical atherosclerosis occurred in these ancient people similar to its prevalence in contemporary society, limited direct evidence exists that events such as myocardial infarction and stroke occurred in these populations. CT detection of vascular calcification in mummies is relatively robust, whereas preservation of soft tissue sufficient to detect clinical manifestations of atherosclerosis such as myocardial and brain necrosis is unusual.

The remarkable preservation of Ötzi the Iceman from 5,300 years ago allowed Zink et al. [10] and Murphy et al. [11] to evaluate not only phenotype but also genotype of this naturally preserved mummy. Despite Ötzi's active lifestyle as an alpine hunter-gatherer, atherosclerosis developed in his carotids, aorta, and an iliac artery [10]. Using the ancient deoxyribonucleic acid facility, Zink et al. [10] identified that Ötzi, a man of the Neolithic (New Stone) age, harbored many of the alleles that predispose to atherosclerosis during the present day. Ötzi died of trauma (an arrowhead lodged in his right subclavian artery) between 40 and 50 years of age—what would be described today as mid-life. Ötzi, like most other mummies, died before his atherosclerosis could have become clinically manifest.

Miyamoto et al. [12], on the other hand, explored the hypothesis of a possible relationship between the process of atherosclerosis with the accelerated aging as seen in the rare Hutchinson-Gilford progeria syndrome (HGPS) (12). HGPS is caused by an autosomal dominant mutation in the gene coding for lamin A, a nuclear structural protein [13,14]. The abnormal protein, called progerin, can be detected in negligible amounts in subjects without HGPS and increases with age in non-HGPS humans. These observations raise intriguing questions around whether age-dependent variation in the level of this and other related proteins might have influenced vascular and overall aging.

An understanding of the varied cultures of Peru who mummified their dead is particularly difficult given the lack of written language prior to the arrival of the Spanish in 1528. With the adoption of Catholicism, mummification, and the written or oral memories of the rationale for its use, vanished. Sutherland et al. [15] use CT evaluation of funerary objects in the bundles in which the mummies were wrapped to better understand these cultures. The living provided a remarkable number of these grave goods to their dead. Over 750 objects were found in 51 mummy bundles, a mean of 15 per bundle. As 45% of the bundles contained foodstuffs for nourishment, a belief in the afterlife was likely. In ancient Egypt, it was predominately the elite who were mummified, but it seems that common men or women were mummified in ancient Peru. The efforts of Sutherland et al. [15] also add to the anthropology literature examining these ancient cultures, apparently representing the largest evaluation of mummy bundles to date. Their technique of examining the full range of Hounsfield units (HU) by windowing through the entire HU range yielded low HU items such as baskets and wood that would be missed when examining higher HU items such as bone and metal. Other customs remain a mystery: children are often accompanied by an adult man or woman in the mummy bundle. It is inconclusive whether they were related and how they perished at the same time.

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Thomas et al. [16] posit that chronic inflammation produced by poor hygiene, frequent and persistent infections, and/or chronic exposure to smoke could represent ancient pre-disposing factors for atherosclerosis. They question as well whether other as yet undiscovered factors, present both then and now, could result in the ancients developing atherosclerosis despite an active lifestyle without tobacco and a broad diet likely much closer to what we currently accept as ideal. However, it is more likely that the modern risk factors were already emerging with the changes in agriculture and animal husbandry, which led to the development of atherosclerosis. Thomas et al. [16] suggest that the CT imaging findings might be more consistent with a gene-environment interplay as causal for atherosclerosis. Human genes have probably evolved (in a protective attempt) to become more susceptible to atherosclerosis, and our environment and the choices determined its speed and severity.

Wann et al. [17], in the concluding article, call for a continued multidisciplinary evaluation of atherosclerosis. The melding of archeology, anthropology, paleopathology, and medical science teams has created the opportunity to develop new insights into atherosclerosis. Cross fertilization of other seemly unrelated disciplines and reexamination of common and uncommon diseases in the light of new data and capabilities from such disciplines harbors great potential for new discoveries across the field of medicine.

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