Circulation

ON MY MIND

Possible Evolutionary Origins of Atherosclerosis: Suggestive Evidence From Ancient to Modern Populations

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The nameplate on the glass-cased mummy of the Egyptian Pharoah Merneptah—13th son of and successor to Pharoah Ramses the Great, who reigned from 1213 through 1203 BC—stated that he died at ≈60 years of age, and had dental disease, arthritis, and arteriosclerosis (Figure). Greg Thomas walked out of the Royal Mummy Room of the Egyptian Museum of Antiquities in Cairo, Egypt, to find his host, Adel Allam. Allam had just returned from Friday noon prayers. As cardiologists, they were puzzled about and skeptical of the reported diagnosis of arteriosclerosis, which they interpreted as atherosclerosis. The Pharoah lived 3200 years ago, long before modern risk factors were present; why would he have atherosclerosis? How would the museum curators know if he had atherosclerosis? He was a mummy in a glass case.

Thomas and Allam had an idea. The year was 2008 and cardiologists were finding coronary calcium scoring to be a useful tool. Perhaps vascular atherosclerotic calcification could be seen in mummified remains. If they could scan Merneptah, they could determine whether he had atherosclerosis. Allam excitedly brought Thomas around to the side of the museum. On his way to find a prayer room he had spotted a 6-slice computed tomography scanner on museum premises that had been donated by Siemens and National Geographic and previously used to scan Pharoah Tutankhamun.

With colleagues, they developed a plan that initially seemed preposterous: they would scan Merneptah and other mummies in the museum to see if they had atherosclerosis. A year later, after obtaining funding, and permission from the Egyptian Supreme Council of Antiquities, they returned with a team of cardiologists and local Egyptologists, scanning 22 outwardly well-preserved mummies who lived between 1981 BC and 334 AD. They identified vascular tissue in 16; 5 had definite atherosclerosis, defined as calcification in the wall of an artery, which often appeared identical to atherosclerotic calcifications in modern patients; and 4 had probable atherosclerosis (calcification along the expected course of an artery).[1] Thus, 9 of 16 (56%) of those with identifiable vessels had definite or probable atherosclerosis. Ancient Egyptians did have atherosclerosis.

These mummies were from elite individuals, who may have had diets and lifestyles conducive to atherosclerosis. To establish whether atherosclerosis was present in ancient commoners, the investigators, referred to as the Horus Team, broadened the study of mummified remains to include ancestral Puebloans from the southwestern United States, ancient fisherman–farmers from the shores of Peru, ancient Andean farmer–pastoralists of Peru and Bolivia, Middle-Ages Mongolian Gobi Desert nomads, and hunter–gathers from the shores of Greenland and the Aleutian Islands. Individuals from every culture had atherosclerosis. In total, the database assembled included 237 adult mummies (mean age, 40±11.6 years) from 7 diverse cultures spanning 5 continents. Definite or probable atherosclerosis was present in all cultures and in 89 (38%) of the individuals.[2] Atherosclerosis was typically mild, involving 1 or 2 vessel beds.

Key Words: apolipoproteins E ■ atherosclerosis ■ biological evolution ■ genetic predisposition to disease ■ mummies ■ pleiotropy

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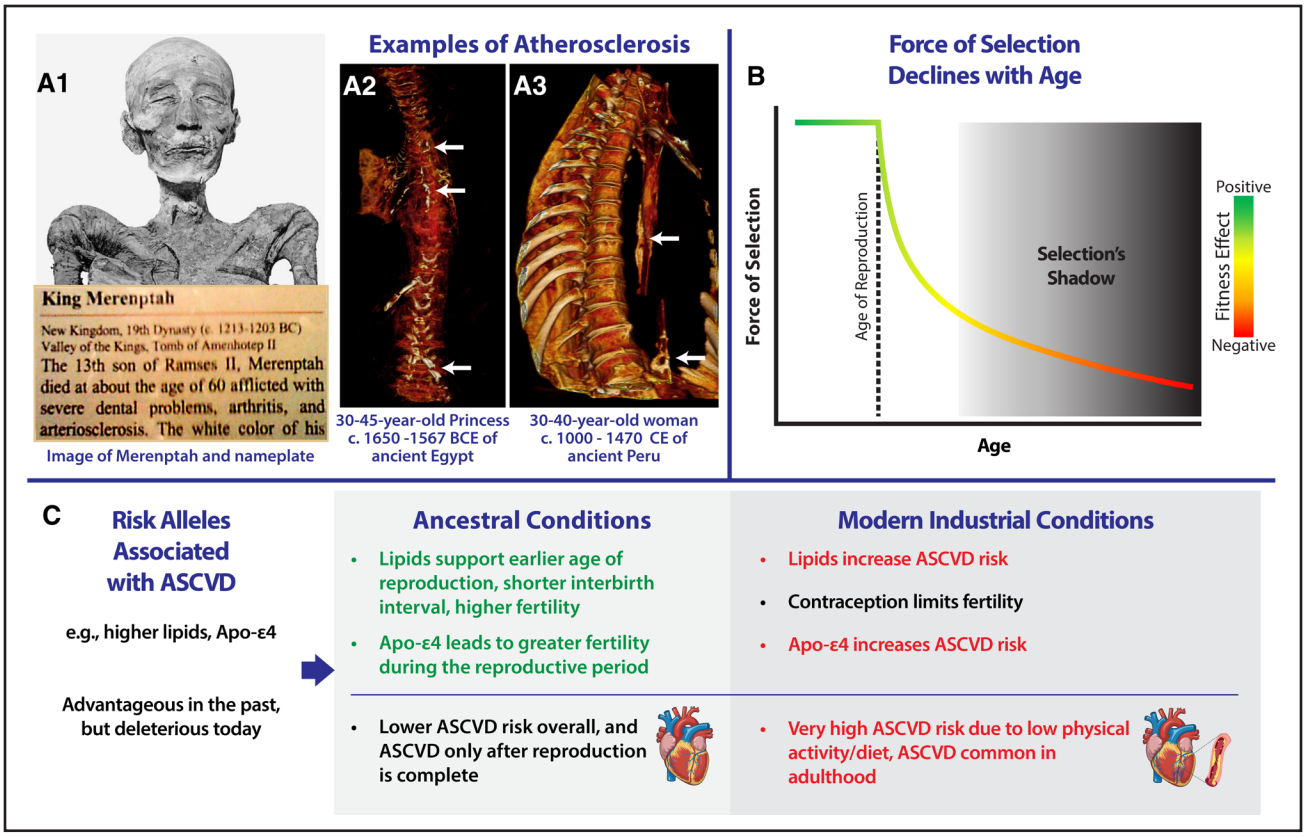

Figure. Potential impact of evolutionary pressures on atherosclerosis.
A1, Image of Pharoah (King) Merneptah and his nameplate at the Museum of Egyptian Antiquities, Cairo, Egypt. (Image of Pharoah: G. Elliot Smith, Wikimedia Commons). **A2**, Volume-rendered 3-dimensional computed tomographic image from a 30- to 45-year-old princess of the Second Intermediate Period of Ancient Egypt (≈1650 through 1567 BCE). Aortic atherosclerosis appears white–yellow in this color scheme. The arrows point to atherosclerosis of the thoracic aorta, right and left anterior descending coronaries, and bilateral iliac arteries (Egyptian Museum of Antiquities, JE26206[b]). **A3**, Volume-rendered 3-dimensional computed tomographic image of a 30- to 40-year-old woman of the Chanchay culture of ancient Peru (≈1000 through 1470 CE). In the modern day, she is known as Rosita. The aorta is fractured. Arrows point to atherosclerosis in the mid-aorta and distal aorta, where a ring of calcification is seen (Huando Archaeological Museum, Huaral District, Peru.) **B**, The force of evolutionary selections declines after the age of reproduction. Selective pressures decrease once an individual has produced and raised offspring, and thus it is difficult for natural selection to diminish the genetic influence of conditions that occur late in life. This is especially true in the case of antagonistic pleiotropy: if a gene has multiple functions and provides a benefit for reproduction or survival until reproduction, but has an adverse effect in late life. **C**, Risk alleles associated with atherosclerotic cardiovascular disease (ASCVD) have been suggested as an example of antagonistic pleiotropy. For >99% of human history, we lived as hunter-gathers. Under those physically active subsistence conditions, there could have been selection for genes that benefit early-life survival or reproduction, with minimal increased risk of cardiovascular disease due to ancestral diets and physical activity. In sedentary industrialized populations today, those same genes could be increasing the risk of cardiovascular disease in sedentary urban populations. Figure partially created with BioRender.

The Horus team and other mummy research teams have been unable to find an ancient culture that did not have atherosclerosis.

Why would these ancient individuals from cultures with such diverse lifestyles and diets have atherosclerosis? A genetic predisposition seemed likely, and recent evidence is consistent with this hypothesis. Zink and colleagues[3] analyzed the DNA of Ötzi, a natural (non-embalmed) mummy frozen in an Alpine glacier for 5300 years. They examined 163 genetic variants in Ötzi previously linked to atherosclerotic cardiovascular disease. Ötzi was homozygous for 58 and heterozygous for 46 of the risk variants. In total, Ötzi had the risk allele in 104 out of the 162 covered loci (64%).

Why would Ötzi carry so many variants that predisposed to atherosclerosis? Could there be an evolutionary advantage to some of these variants? George C. Williams pioneered the concept of antagonistic pleiotropy, proposing that a gene that has a beneficial effect at one life stage, such as enhancing either fertility or one's chance of reaching maturity, could have a harmful effect at another life stage, such as increasing risk of disease later in life.

Evolution optimizes reproduction, not health, so benefits to fertility would be favored even if they result in death at older ages, particularly if the deleterious effects occurred after reproduction and after offspring reached maturity. It is difficult for natural selection to

act on diseases that occur in "selection's shadow": after one has already had offspring, seen them through childhood, and successfully passed on genes to the next generation.

Byars and colleagues[4] investigated this potential in 76 genetic variants associated with atherosclerotic cardiovascular disease within 12 worldwide populations. Fifty-one of the 76 were significantly associated with lifetime reproductive success. Their analyses suggested that these variants have been under positive selection. They concluded that antagonistic pleiotropy likely plays a key role in the maintenance and high prevalence of atherosclerotic cardiovascular disease in modern humans.

A candidate allele for antagonistic pleiotropy is *APOE* ε4, a commonplace variant known to increase risk for Alzheimer disease and myocardial infarction. Early work in small populations suggested that *APOE* ε4 enhanced fertility. We examined the effects of *APOE* ε4 in the Tsimane, a natural fertility population of Bolivian forager–horticulturalists. Among 795 women, those with at least 1 *APOE* ε4 allele had ≈0.5 more children than ε3/ε3 homozygotes, and those with 2 ε4 alleles gave birth to ≈1.7 more children.[5]

Returning to Merneptah, the museum curators were correct. A section of his aorta had been sent to the Royal College of Surgeons in London in 1908. Histopathologic examination confirmed substantial calcific atherosclerosis.

These findings raise the potential that antagonistic pleiotropy played a role in the genetic predisposition to and consequent phenotypic expression of atherosclerosis observed in Merneptah, Ötzi, and mummied individuals from 7 different cultures. The potential fitness benefits of these genes that promote atherosclerosis could have allowed them to spread over the past millennia when physically active lifestyles and low-fat diets reduced the risks. In the modern era, these genetic predispositions we inherited from our ancestors, combined with the unprecedented increase in life expectancy and societal industrialization with its consequent dramatic increase in traditional risk factors, may have played an important role in the epidemic of atherosclerosis today.

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Disclosures

None.

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