

Abstracts

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Atherosclerosis Across 4000 Years of Human History: The Horus Study of Four Ancient Populations

Thompson RC, Allam AH, Lombardi GP, et al. *Lancet* 2013;381:1211-22.

Conclusion: Atherosclerosis was common in four preindustrial populations, including preagricultural hunter-gatherers.

Summary: Human beings residing in very hot, cold, or dry environments have independently discovered how to mummify dead members of their society. These, often preindustrial, cultures have created the opportunity to study ancient human beings with modern computed tomography scanning to assess the extent of vascular calcifications in diffuse environments and cultures. Calcium is a nearly universal component of a mature atherosclerotic plaque and is pathognomonic for atherosclerosis (Stary HC et al, *Circulation* 1995;92:1355-74). The authors recently confirmed atherosclerotic calcifications in 20 of 44 Egyptian mummies of individuals who lived during several dynasties between 1981 BC and 364 CE (Common Era) (Allam AH et al, *J Am Coll Cardiol Imaging* 2011;4:315-27). In this current study the authors examined 137 mummies from populations of four disparate geographic regions. Mummies were studied by whole-body computed tomography scanning and included specimens from Ancient Egypt, the Roman Era, Ancient Peru, and five cultures from Southwest America (ca 1500 BCE to 1500 CE, five evacuation sites). Finally, there were five ancient Unangan specimens from the Aleutian Islands of modern-day Alaska. Mummies were selected for imaging on the basis of a good state of preservation and the likelihood of being adult. Random selection was not used. The population examined spanned >4000 years. Atherosclerosis was regarded as definitive if calcified plaque was seen on the wall of an artery and considered probable if artery calcifications were seen along the expected course of an artery. Of the 137 mummies, 47 (34%) demonstrated probable or definitive atherosclerosis: 29 of 76 Ancient Egyptians (38%), 13 of 51 Ancient Peruvians (25%), two of five ancestral Puebloans (40%), and three of five Unangan hunter-gatherers (60%; $P =$ not significant). Atherosclerosis was present in the aorta in 20% of mummies, the iliac/femoral arteries in 18%, the popliteal/tibial arteries in 18%, carotid arteries in 12%, and the coronary arteries in only 4%. Of the five vascular beds examined, atherosclerosis was present in one to two beds in 25% of mummies, in three to four beds in 8%, and all five vascular beds in only 1%. Age and time of death were positively correlated with atherosclerosis: the mean age at death was 43 years (standard deviation [SD], 10 years) for mummies with atherosclerosis vs 32 years (SD, 15 years) for those without ($P < .0001$). Age also varied with the number of arterial beds involved: the mean age was 32 years (SD, 15 years) for mummies with no atherosclerosis, 42 years (SD, 10 years) for those with atherosclerosis in one or two beds, and 44 years (8 years) for those with atherosclerosis in three to five beds ($P < .0001$).

Comment: Atherosclerosis is assumed by many to be a modern disease related to the modern lifestyle. These data, however, with findings of atherosclerosis in premodern humans, raises the more-than-likely possibility that atherosclerosis is reflective of a more basic predisposition to the disease in humans. It may be that atherosclerosis should, to some degree, be considered an inherent component to the human aging process and not necessarily always specifically reflective of any specific diet or lifestyle.

Intestinal Microbial Metabolism of Phosphatidylcholine and Cardiovascular Risk

Tang WH, Wang Z, Levison BS, et al. *N Engl J Med* 2013;368:1575-84.

Conclusions: The production of the proatherosclerotic metabolite trimethylamine-*N*-oxide (TMAO) from dietary phosphatidylcholine is dependent on metabolism by intestinal flora. Increased TMAO is associated with an increased incidence of major adverse cardiovascular events.

Summary: The authors recently described a potential role of the phosphatidylcholine metabolic pathway involving gut flora in contributing to the pathogenesis of atherosclerotic coronary disease in an animal model (Wang Z et al, *Nature* 2011;472:57-63). TMAO is an intestinal flora-dependent metabolite of the choline group of phosphatidylcholine that is excreted in the urine (Simenhoff ML et al, *Lancet* 1976;2:818-21). The

major dietary source of choline is lecithin, a part of the B-complex vitamin family. Choline and its metabolites, such as betaine, can serve as a source of the methyl groups required for proper metabolism of amino acids such as homocysteine and methionine (Zeisel AQ et al, *Annu Rev Nutr* 2006;26:229-50). Diets rich in phosphatidylcholine (those containing eggs, liver, beef, and pork) can contribute to the formation of the metabolite trimethylamine, with conversion to TMAO. TMAO production may be facilitated by intestinal microflora, thereby, potentially, providing a link between atherogenic diets, intestinal microflora, and atherosclerotic disease. The authors investigated the relationship of intestinal microflora-dependent metabolism of dietary phosphatidylcholine, TMAO levels, and cardiovascular events in humans. Plasma and urinary levels of TMAO and plasma choline and betaine levels were measured with liquid chromatography and gas spectrometry after a phosphatidylcholine challenge (two hard-boiled eggs with deuterium [d9]-labeled phosphatidylcholine) in healthy participants before and after suppression of intestinal microbiota with oral broad-spectrum antibiotics. Fasting plasma levels of TMAO were also examined in conjunction with incident major adverse cardiovascular events (death, myocardial infarction, or stroke) during 3 years of follow-up in 4007 patients undergoing elective coronary angiography. The authors found time-dependent increases in levels of TMAO and its [d9] isotopologue, as well as other choline metabolites, after the phosphatidylcholine challenge. TMAO plasma levels were suppressed after administration of antibiotics and reappeared after withdrawal of antibiotics. Increased plasma levels of TMAO were associated with an increased risk of major adverse cardiovascular events (hazard ratio for highest vs lowest TMAO quartile, 2.54; 95% confidence interval, 1.96-3.28; $P < .001$). After adjustment for traditional cardiovascular risk factors, an elevated TMAO level predicted an increased risk of major cardiovascular events ($P < .001$).

Comment: The authors have demonstrated that intestinal flora participate in phosphatidylcholine metabolism, resulting in circulating and urinary TMAO. They also found increased high plasma levels of TMAO associated with increased major adverse cardiovascular events as an independent risk factor, even in low-risk patients. Because elevated TMAO levels are associated with diets rich in eggs and red meats, the authors have potentially established a link between a so-called atherosclerotic diet, intestinal microflora, and adverse cardiovascular events. Modification of intestinal microflora to decrease TMAO levels may someday be a therapeutic approach to treatment or prevention of atherosclerosis.

Comparison of Arteriovenous Fistulas and Arteriovenous Grafts in Patients With Favorable Vascular Anatomy and Equivalent Access to Health Care: Is a Reappraisal of the Fistula First Initiative Indicated?

Disbrow DE, Cull DL, Carsten CG 3rd, et al. *J Am Coll Surg* 2013;216:679-86.

Conclusion: For patients receiving hemodialysis via a dialysis access catheter at the time of access placement, the maturation time, risk of non-maturation, and interventions required to achieve a functional arterial venous fistula (AVF) can negate benefits of an AVF over an arterial venous graft (AVG).

Summary: For >10 years, the Fistula First Initiative has had a profound influence on surgeons performing hemodialysis access, with a sometimes evangelic dedication to the stated goal of increasing AVF use. In 2014, the Centers for Medicare and Medicaid Services apparently plan a pay-for-performance program that would cut reimbursements to dialysis units not meeting set benchmarks for creating AVFs and for use of AVFs. Data underlying the Fistula First Initiative have been based largely on nonrandomized studies comparing outcomes of AVGs and AVFs. Many argue there are clinical scenarios when an AVG makes sense over an AVF if one considers maturation times, revisions required for maturation, and fistula failures. Indeed, "fistula first" was not likely intended to be "fistula only." The authors of this article have questioned blind adherence to the Fistula First Initiative. They contend patients receiving AVFs typically have more favorable vascular anatomy and are referred earlier for access placement than those who receive AVGs. This combination can result in overestimation of the advantages of AVFs. In this study, the authors