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The Race to Unlock the Mystery of Atherosclerosis

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ABSTRACT

Atherosclerosis at the heart of healthcare. It is the silent killer. Enough is enough. Delays have dangerous ends. The race to unlock the mystery of. Atherosclerosis. Atherosclerosis hardening and narrowing of the arteries silently and slowly blocks arteries, putting blood flow at risk. Atherosclerosis starts when the endothelium becomes damaged, allowing the harmful type of cholesterol to build up in the artery wall. Plaque is a sticky substance made up of fat, cholesterol, calcium, and other substances found in the blood. Over time, plaque hardens and narrows your arteries.

.If the blocked artery supplies the heart or brain, a heart attack or stroke occurs. If an artery supplying oxygen to the extremities (often the legs) is blocked, gangrene can result. Gangrene is tissue death. Atherosclerosis is a slow, progressive disease that may start in childhood. In some people, it progresses rapidly in their 30s. In others, it doesn't become dangerous until they reach their 50s or 60s. Some hardening of the arteries is normal as you age. Physical inactivity, diabetes, and obesity are also risk factors for atherosclerosis. High levels of the amino acid homocysteine and abnormal levels of protein-coated fats called lipoproteins also raise the risk of coronary artery disease.

INTRODUCTION

The significant reduction observed in the LDL/HDL ratio is prominent from the therapeutic point of view in the treatment against hypercholesterolemia in experimental atherosclerosis**.(**1)

Atherosclerosis is a disease of the arterial wall. Accumulation of lipid-laden foam cells in the subendothelial region of the arterial wall is an early event in the development of atherosclerosis. (2,3) Alpha-lipoic acid (LA), or 1,2-dithiolane-3-pentanoic acid, is a naturally occurring dithiol compound synthesized from octanoic acid in the mitochondrion (4). LA serves a critical role in mitochondrial energy metabolism and lipid metabolism (5). Recently, values have been observed in the person with age-related macular degeneration (6), and increased glutathione peroxidase (GSH-Px), as well as SOD activities, were found in diabetic rats(7). In high-income countries, there have been dramatic declines in the incidence and mortality from ischemic heart disease and ischemic stroke since the middle of the 20th century. (9) Individuals with PAD are at increased risk of myocardial infarction (MI), ischemic stroke and death.(10,11,12) IHD and stroke are the world's first and third causes of death, respectively, causing247.9 deaths/100,000 persons in 2013, representing 84.5% of cardiovascular deaths and 28.2% of all-cause mortality(13). Cardiovascular diseases (CVDs) are the number one cause of death globally, responsible for at least one-third of all deaths in individuals over 35 (14-15). The American Heart Association has projected that by 2035up to 45% of the US population will have CVD (16). Diabetic macroangiopathy, atherosclerosis secondary to diabetes mellitus (DM), causes Cerebro-cardiovascular diseases, which are major causes of death in patients with DM and significantly reduce their quality of life. (17)Obesity and insulin resistance are major risk factors for cardiovascular disease, but the underlying mechanisms are poorly understood. (18)

Diabetes mellitus elicits cellular, epigenetic, and post-translational changes that directly or indirectly affect the biology of the vasculature and other metabolic systems resulting in the apparition of cardiovascular disease. (19) The effect of body mass index was minimally affected by blood glucose, and diabetes and may suggest an important role of oxidative stress in the deleterious impact of obesity on cardiovascular disease. (20)

HISTORY

While many cases have been observed and recorded, the term *arteriosclerosis* was not used until Jean Fréderic Martin Lobstein coined it while he was analyzing the composition of calcified arterial lesions. (21)

Atherosclerosis was first described in 1575. (22) There is evidence, however, that the condition occurred in people more than 5,000 years ago. Atherosclerosis across 4000 years of human history: the Horus study of four ancient populations. (23)

SIGNIFICANT GAP IN RESEARCH

As blood flow slows down by 10% our heart workload increases by50%. Yes, that is five times. Until recently, there have been no good sub-primate models, but transgenic mice deficient in apolipoprotein or receptors that play key roles in lipoprotein metabolism have transformed this scene. Nevertheless, most of our current understanding of atherogenesis come from human epidemiology and pathology, and from clinical investigations.

Epidemiological studies have identified numerous risk factors for atheromatous disease. Some of these cannot be altered (e.g. a family history of ischaemic heart disease), but others are modifiable and are potential targets for therapeutic drugs. Clinical trials have shown that improving risk factors can reduce the consequences of atheromatous disease. Many risk factors (e.g. type 2 diabetes, dyslipidemia, cigarette smoking) cause endothelial dysfunction, evidenced by reduced vasodilator responses to acetylcholine or to increased blood flow (so-called ‘flow-mediated dilation’, responses that are inhibited by drugs that block nitric oxide radical ($NO^{\bullet}$) synthesis. Healthy endothelium produces $NO^{\bullet}$and other mediators that protect against atheroma, so it is likely that metabolic cardiovascular risk factors act by causing endothelial dysfunction.(24)

IDEAS WHERE THE RESEARCH GO NET?

Cytokines such as interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), interferon-gamma (IF-ɣ), platelet-derived growth factors, and matrix metalloproteinases are released by activated macrophages. This results in thinning of the protective fibrous cap, making the lesion vulnerable to mechanical stress that ultimately causes erosion, fissuring or rupture of

the plaque surface. This common mechanism underlies many of the acute manifestations of atherosclerotic vascular disease, such as acute lower limb ischemia, MI, and stroke.(25)

The majority of cardiovascular disease results from complications of atherosclerosis. An important initiating event for atherosclerosis may well be the transport of oxidized.(26,27) Oxidative stress and the production of intracellular reactive oxygen species (ROS) have been implicated in the pathogenesis of a variety of diseases.(28)

Most proliferating cells are macrophages, and VSMC mitotic rates are lowering advanced plaques than early lesions, even after plaque rupture,(29)

MAJOR ADVANCES AND DISCOVERIES

Immediate revascularization is required in all cases of symptomatic acute arterial thrombosis. Evidence of neurologic injury, including the loss of light touch sensation, indicates that collateral flow is inadequate to maintain limb visibility and revascularization should be accomplished within 3 hours. Longer delays carry a significant risk of irreversible tissue damage.(30). Miracle drug Asprin fights heart disease. It can prevent more than i00 000 premature deaths every year It prevents clots. Build a stronger heart with B vitamins. Nonalcoholic heart healing drinks that contain flavonoids are dark purple grape juice, sweet cherry juice, and strawberry juice. Red wine contains flavonoids. Garlic gets to the heart of good health. Monday morning is hard on your heart. Your ears could warn you of heart disease.(31,32)

CURRENT DEBATE

Atherosclerosis underlies the pathogenesis of coronary, cerebral and peripheral vascular disease, and causes more morbidity and mortality (roughly half of all deaths) in the Western world than any other disorder. Because coronary artery disease is an important manifestation of the disease, epidemiologic date related to atherosclerosis mortality typically reflect deaths caused by ischemic heart disease; indeed, myocardial infarction is responsible for almost a quarter of all deaths in the United States. Significant morbidity and mortality are also caused by aortic and carotid atherosclerotic disease and stroke.

The likelihood of atherosclerosis is determined by the combination of acquired (e.g. cholesterol levels, smoking, hypertension) and inherited (e.g. LDL receptor gene mutations)

risk factors. Acting in concert they cause initial lesions called *atheromas* (also called atheromatous or *atherosclerotic plaques*) that protrude into vessel lumens. An atheromatous plaque consists of a raised lesion with a soft grumous core of lipid (mainly cholesterol and cholesterol esters) covered by the fibrous cap.

Although atherosclerosis-associated ischemic heart disease is ubiquitous among most developed nations, risk reduction and improved therapies have combined to moderate the associated mortality. At the same time, reduced mortality from infectious diseases and the adaptation of Western lifestyles has led to increased prevalence of ischemic heart disease in developing nations. As a result, the death rate for coronary artery disease in the United States now lags behind the death rates in most of Africa, India, and South Asia.

The prevalence and severity of atherosclerosis and ischemic heart disease among individuals and groups are related to a number of risk factors. Thus, two factors increase risk approximately four-fold, and three (i.e., hyperlipidemia, hypertension, and smoking), increased risk by a factor of seven. (33)

The effect of body mass index was minimally affected by blood glucose, and diabetes and may suggest an important role of oxidative stress in the deleterious impact of obesity on cardiovascular disease. Smoking, diabetes and strong independent predictors of systemic oxidative stress Obesity is associated with a state of excess oxidative stress and suggest yet another contributing mechanism for excess CVD and obesity.(34,35,36,37,38,)

Alterations in the cellular redox status modify DNA binding and transactivation activities of a variety of transcriptional activators. This, in turn, leads to changes in the expression of a variety of target genes with ultimate changes in cell function. In the vasculature, this is no exception. In considering the pathogenesis of atherosclerosis, the a strong body of data supports the notion that ROS generated in response to environmental and physical risk factors modulate the signal transduction processes ultimately leading to vascular inflammatory gene expression.(39)

Growing evidence from investigations of animal models and correlative data from human studies implicate oxidative stress in the development of CVD. The development of a new class of antioxidants that are targeted to specific subcellular compartments such as mitochondria may help in combating CVD. (40)

We examined normal vessels and plaques by histochemistry, Southern blotting, and fluorescence in situ hybridization for telomere signals. In matched samples from the same individual, plaques demonstrated markedly shorter telomeres than normal vessels.(41)

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