

# Atherosclerosis

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### ABSTRACT

Atherosclerosis is a multifactorial illness marked by the production of cholesterol-containing plaque in the pronounced intima closest to the heart's elastic-type arteries with high blood flow. Plaques occur when the endothelium in areas of turbulent blood flow is damaged by arterial pressure. It affects the majority of the Western population, including children and teenagers. This refutes the idea that atherogenesis is a single-gene disease. It was revealed in 1988 that atherogenesis requires the presence of atherogenic (modified, including oxidised) LDLs. We developed a new hypothesis describing the fundamental determinants of atherogenesis based on our discovery, which suggested that lipid overloading of enterocytes could contribute to the creation of modified LDLs only 8 articles meet the criteria and the data were collected from the 8 articles.

The findings indicated that patient assessment, exercise, physical counselling, diet/nutritional counselling, tobacco cessation, mental health, return to work, lipids, hypertension, cardio-protective therapies are essential components for the rehabilitation after heart valve surgeries, to support patients and their families to cope with challenges related to surgeries. These in return improve quality of life for the patients concerned. The core components for the cardiac rehabilitation programmes as highlighted by the international guidelines can be adapted to the cardiac rehabilitation programme in Namibia if tailored to the contextualized needs for the cardiac patients in Namibia.

**Key Words:** Atherosclerosis; Endothelial cell; Enterocyte; Golgi apparatus; Chylomicron; Glycosylation

### INTRODUCTION

Atherosclerosis is a non-monogenic, diet-related disease characterised by an accumulation of cholesterol in the intima of human elastic-type arteries and the formation of intimal plaques, namely, bulging intima containing a lot of cholesterol within the foam cells, which originate from macrophages and smooth muscle cells, and the formation of intimal plaques, namely, bulging intima containing a lot of cholesterol within the foam cells, which originate from macrophage. It's important to know the difference between atherosclerosis and arteriosclerosis [1]. Because atherosclerosis was identified in the majority of the population, including young people, the illness became nearly universal. This refutes the idea that atherogenesis is a single-gene disease. Atherosclerotic forms in coronary arteries are detected in 65% of boys and 62% of girls between the ages of 10 and 19. Only 11%-12% of men and women in their third decade of life are free of atherosclerotic alterations. Furthermore, fibrous plaques are identified in 46 percent of men and 33 percent of women, and atherosclerotic forms in the arteries of the brain are found in 35-45 years.

Only 4% of men and 7% of women in their forties do not have atherosclerotic alterations, and 3%-4.5% of them have calcinosis. Atherosclerosis, according to current opinion, is a multicausal disease involving numerous physiological and pathological pathways. Genetic predisposition, hemodynamic circumstances in specific regions of the vascular bed, combinations of numerous risk factors (hypercholesterolemia, arterial hypertension, diabetes mellitus), immunological and autoimmune disorders, viral infection, and other variables have all been identified. The retention and subsequent accumulation of Low-Density Lipoproteins (LDLs) in the arterial wall initiates and propagates a series of processes that lead to the development of a lesion. The percentage of stellate cells in an atherosclerotic lesion in the human aorta far surpasses that of the normal intima. In addition, fatty streaks showed thinning and arborization of contact-forming cellular processes. Smooth Muscle Cell (SMCs) are thought to migrate from the middle sheath to the intima, although this is not necessary in large animals, including

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humans, because SMCs are already present in the human intima. Intimal cells lose contact with one another and become foam cells packed with lipid droplets generated by lysosomes rather than the ER, collecting cholesterol in lysosomes rather than the ER. The transition of lipids from smooth ER into lipid droplets is a frequent mechanism for the creation of lipid granules, especially larger ones, under normal conditions [2].

### PAST

Atherosclerosis proposed in the early 1850s that fibrin accumulation in places of injured vascular wall might damage the vessel. R. Virchow noted at the end of the 19th century that lipid accumulation in the vascular intima stimulates cell growth and plaque formation. F. Marchand coined the name "atherosclerosis" in 1904 after discovering the deposition of lipids in atherosclerotic plaques observed in the walls of elastic-type arteries [3]. Ignatowski started feeding rabbits full-fat milk, eggs, and meat in 1907. Rabbits fed animal proteins developed severe aortic atherosclerosis very quickly. In 1908, he published his groundbreaking research effort. In the United States, this achievement is considered one of the top ten medical breakthroughs. W. Dock linked Anitschkow's famous work to Robert Koch's discovery of the tuberculosis pathogen in an editorial in the *Annals of Internal Medicine*. "We might have saved more than 30 years in the arduous fight to settle the cholesterol dispute if the full significance of his results had been acknowledged at the time," Steinberg wrote in 2004.

Harbitz and Müller first described hypercholesterolemia in humans in 1938–1939. Steiner and Kendall used the Anitschkow Chalataw model in dogs to produce atherosclerosis in 1946. Lipoproteins and their link to the risk of coronary heart disease were discovered by Gofman et al. in 1949. Russ et al. revealed in 1951 that distinct lipoprotein classes have varied biological activities. Kinsell et al. discovered in 1952 that saturated fats in the diet raise blood cholesterol in normal persons. In 1955, an international epidemiologic study (the Framingham Heart Study) found that hypercholesterolemia and dietary fat intake were directly associated to the incidence of coronary heart disease.

The risk of coronary heart disease is highest in groups with the highest blood cholesterol levels, according to research published in 1961. K. Bloch was awarded the Nobel Prize in 1964 for discovering the cholesterol production pathway.

It was suggested and later proven that lowering blood cholesterol levels by eliminating saturated fat in the diet reduced the incidence of coronary heart disease between 1966 and 1969. The LDL receptor and cholesterol and lipoprotein metabolism regulation were discovered in 1974. In 1985, the authors (Brown and Goldstein) were awarded the Nobel Prize. The first effective statin was discovered in 1976 by Endo et al. Ross et al. proposed in 1976 that atherosclerosis is caused by Endothelial Cell (EC) destruction followed by platelet adhesion, activation on the exposed subendothelial surface, and macrophage migration into the intima. Y. Watanabe developed Rabbits With Hereditary Hyperlipidemia (WHHL rabbits) that had non-functional LDL receptors in 1980. He may have been a Nobel Prize contender, but he died on December 13, 2008, at the age of 81. Damage to the endothelium and its synthesis of a multilayer basement membrane in places where it is most often damaged, with

this basement having the property of binding more strongly to LDL; intima, which is multicellular, unlike the intima of small animals commonly used for modelling atherosclerosis; violation of glycosylation of chylomicrons by enterocytes when they are overloaded with lipids; and the excretion of chylomicrons by enterocytes. The involvement of well-known genetic abnormalities as potentiators of atherogenesis is still important. We'd like to look at each of these aspects individually, excluding the genetic ones. The first commercial statin, mevinolin (lovastatin), was developed in 1980 [4].

The function of the autoimmune response in the progression of atherosclerosis was recognised in 1981. The Coronary Primary Prevention Trial of the Lipid Research Clinics demonstrated a substantial reduction in primary coronary heart disease events in men with hypercholesterolemia who received cholestyramine in 1984. The decrease of blood cholesterol was proclaimed a national public health priority. Orekhov et al. (for correspondence, he is the author) uncovered the involvement of modified (desialylated and immune complexed) LDLs in the development of atherosclerosis in 1988. In the same year, a team of Japanese researchers led by Kawai reported data suggesting oxidised LDLs induce atherosclerosis as well. Even though Prof. Kawai was 91 years old, these two scientists deserved to be the front-runners for the Nobel Prize. In the same year, it was discovered that rabbits lacking natural antioxidants developed severe arteriosclerosis (without the lipid component). Breslow and Maeda led two groups to generate lipoprotein E-deficient mice in 1992. Apoproteins (ApoB, ApoE, ApoA), LDL receptors, and so-called scavenger receptors were revealed to have a role in the development of atherosclerosis. These researchers were likewise deserving of the Nobel Prize [5]. The Scandinavian Simvastatin Survival Study (Scandinavian Simvastatin Survival Study) was the first large-scale, randomized (based on randomized patient selection) double-blind study to show that simvastatin treatment not only reduced coronary heart disease mortality, but also reduced all-cause mortality.

Steinberg promoted the hypothesis that oxidized LDL is the primary cause of atherosclerosis in 1995. In the clinic, however, these hypotheses were not confirmed: high dosages of antioxidants did not decrease atherosclerosis, despite the power and safety of antioxidants. Monoclonal antibodies against a proinflammatory cytokine were used to treat atherosclerosis. It was discovered in 2015 that lowering LDL levels reduced the severity of atherosclerosis, while attempts to affect atherosclerosis by increasing HDL levels had no therapeutic effect [6].

In the year 2020, a new hypothesis surfaced. When enterocytes are overloaded with fat, fat droplets (chylomicrons) formed in the secretory pathway of small intestinal cells grow in size and contain fewer proteins, despite being dragged into the lymphatic system. When chylomicrons travel through an overburdened Golgi complex (a cellular organelle where a lengthy chain of polysaccharides, such as starch, is stored), the Golgi complex is overloaded.

Our atherosclerosis research was carried out in the same way as Lakatos described it in his scientific programme theory. We began researching atherogenesis in 1985. Endothelial damage and increased cholesterol intake from meals were thought to be the main causes of atherosclerosis at the time. We wanted to know why LDLs adhere more strongly to subendothelial structures in areas of turbulent blood

flow, where the endothelium is injured and split to heal the defect. Our atherosclerosis research was conducted in the manner specified by Lakatos in his scientific programme theory . In 1985, we began studying atherogenesis [7]. At the time, the main causes of atherosclerosis were assumed to be endothelial damage and increasing cholesterol intake from meals. We sought to determine why LDLs stick to subendothelial structures more strongly in places of turbulent blood flow, where the endothelium has been wounded and split to heal the defect. Basement membrane proteins are synthesised and secreted during the G2 phase. Furthermore, it was discovered that thickening the basement membrane causes the endothelium to move quicker during regeneration, but that following regeneration, the endothelium peels off faster under mechanical stress. Then we looked into why many Aspects of atherosclerotic plaque found in humans can't be recreated in small animals, and discovered that it's because the intima of humans, like that of other large mammals, contains pericyte-like cells and even smooth myocytes. As a result, SMC migration from the media, which was found in the arteries of small animals when mimicking atherosclerosis, is not required. Modified LDL, especially oxidised LDL, was discovered to play a major role in atherogenesis in 1988. The topic of how these mutated LDL are created arose.

#### ROLE OF INTIMA

Rodents (mice, rabbits, rats, hamsters, guinea pigs), avian (pigeons, chicks, quail), swine, carnivora (dogs, cats), and non-human primates have all been presented as animal models. Several concepts have been proposed to explain atherogenesis. All of these concepts, however, ignore the function of human intima's unique characteristics. Indeed, a key aspect of human atherosclerosis is the nearly complete lack of comparable disease in other mammals, particularly small animals, where the intima of most arteries is made up entirely of endothelial cells and their reticular basement membranes. However, unlike small animals, intact intima in large animals has a structure similar to that of humans and does not consist only of endothelium, reticular basement membrane, and separate loci of elastic fibres and collagen fibrils as in small animals, although arteriosclerosis, but not atherosclerosis, has been found in giraffes and elephants reviewed by. Arteriosclerosis was found in aged dogs, but not atherosclerosis. Lesions were of two types in giraffes and elephants: intimal arteriosclerosis and medial calcific sclerosis. Arteriosclerotic plaques in elephants are comparable to those found in humans. Most animals don't ingest a lot of lipids, especially after they've been stored in the presence of oxygen for a long time.

Atherosclerosis does not affect small animals. Rats and mice are especially hardy. Their intima is made up of an endothelial cell monolayer and a reticular basement membrane. Steiner and Kendall shown that giving substantial amounts of cholesterol to dogs following irradiation with X-rays causes atherosclerosis to develop. Atherosclerosis does not affect human muscle arteries. Muscle-type atherosclerosis-resistant arteries had minimal to no intimal hyperplasia. Only elastic arteries in people were impacted, but only if the pressure in their lumen was high enough to cause endothelial damage the case of pulmonary artery [8]. Humans and rabbits have distinct intima structures in major arteries. Pericyte-like stellate cells line the intima of the human aorta. Antigens of SMCs and pericytes are found in the majority of intimal cells (84%-93%). In the inner intima, pericyte-like cells have been discovered.

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