PHARMATUTOR
PHARMACY INFOPEDIA
ISSN: 2347-7881

Review Article

Atherosclerosis: Research review

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ABSTRACT

Atherosclerosis a disease of the larger arteries is the major cause of heart disease and stroke. Nowadays, serve as leading reason of death not only in senility peoples but in youth also worldwide. Researches in the atherosclerosis disease have led to many persuasive hypotheses about the pathophysiology of atherosclerotic lesion development and of tricky situation such as myocardial infarction and stroke. It is now unambiguous that atherosclerosis is not simply an unavoidable degenerative consequence of ageing, but somewhat a chronic inflammatory situation that can be transformed into an acute clinical occasion by plaque rupture and thrombosis. Evidently, crystallization of information concerning atherosclerosis will approach only by the appropriate free interplay and satisfactory fusion of the three foremost looms to the trouble, epidemiologic, clinical and investigational.

Keywords: Atherosclerosis, Coronary artery disease, Cerebrovascular disease,Peripheral Arterial Disease

INTRODUCTION

Atherosclerosis or arteriosclerosis is a sluggish and progressive building up of fatty substances, plaque, cholesterol, cellular waste products, fibrin and calcium in the inner lining of an artery. The deposition of plaque in arteries, may subsequently leads to partially or fully blockage of artery.

Atherosclerosis can not only affect arteries in the heart but also brain, arms, legs pelvis and intestines leading to disease of those organs.

There are 4 types of atherosclerosis which include as follows:

a. Coronary artery disease (CAD):

When deposition of fat take place, and plaque formation results, in the coronary arteries, supply of oxy-rich blood to heart is reduced or completely prohibited leading to chest pain and ultimately heart attack.

b. Cerebrovascular disease:

If plaque formation takes place in carotid arteries, it will result in partial or complete supply prohibition of oxy-rice blood to brain and thus cause stroke.[1]

c. Peripheral Arterial Disease (PAD):

Plaque formation in the arteries of legs causes narrowing of arteries. And thus inhibition in supply of blood to leg, arms and pelvis leads to numbness, pain and vital infections.[1]

d. Abdominal Angina and a Bowel Infraction:

Atherosclerosis leads to narrowing of arteries supplying blood to the intestines causing abdominal pain and is called abdominal angina. Complete or sudden blockage of blood supply to intestines leads to bowel infection.

Although, the atherosclerotic causing process is not has been completely understood till now.

How to cite this article: S SIngh; Atherosclerosis: Research review; PharmaTutor; 2014; 2(8); 162-169

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ISSN: 2347-7881

Atherosclerosis is intimated by inflammation in the endothelial cells of the arteries walls when it retains low density lipoprotein molecules. Some researches signify that atherosclerosis could be caused by an infection of the vascular smooth muscle cells.

In Chickens, atherosclerosis develops when infected with the Marek's disease herpes virus. Herpes virus infection in arterial smooth muscle cells found as causative agent of cholesterol ester accumulation, that is related atherosclerosis.[1,7,9]

CAUSES OF ATHEROSCLEROSIS

Following is a catalog of causes of atherosclerosis

- High cholesterol
- Atheroma
- Primary-atherosclerosis
- Verners syndrome-atherosclerosis
- Xanthoma-atherosclerosis
- Carbon disulfide induced cardio vascular diseases atherosclerosis
- Progeria-atherosclerosis
- Chemical induced cardiovascular diseases atherosclerosis
- Pseudoxanthoma elasticum, forme frusta-atherosclerosis
- Premature aging-atherosclerosis
- Smoking
- High blood pressure
- Obesity
- Soaring amounts of sugar in the blood because of insulin resistance of diabetes
- Physical inactivity[1,7,8]

SYMPTOMS OF ATHEROSCLEROSIS

Regrettably, atherosclerosis produces no signs until the harm to arteries is severe enough to block blood flow. According to research studies data for the year 2004, about 66% of men and 48% of women, the first symptom of atherosclerosis is heart attack or sudden cardiac death.

Though some individuals have nuisance symptoms with short term flushing reactions, especially to begin with, cautious selections of brand, dosing strategy, etc. are usually serious to success.[6,7,8]

PATHOPHYSIOLOGY OF ATHEROSCLEROSIS

Atherogenesis is the progressive process of athermanous plaque. Accumulation of fatty and cholesterol substances in arteries called plaque. The buildup of plaque is steady process, it may start developing from childhood but mostly its effects are seen in with passes of time. In some recent hypothesis found that, for unidentified reasons, leukocytes, such as monocytes or basophiles, start attacking the endothelium wall of the artery lumen in cardiac muscles. The resulting inflammation results to formation of artheromatous plaque in arterial tunica intima, located in between the endothelium and the tunica media. The expansion of these lesions is due to excess fat collagen and elastin. Thus, stenosis is a late process, which may never take place and is often the outcome of repeated plaque rupture and therapeutic responses, not just the atherosclerotic development by itself.[11]

DIAGNOSIS OF ATHEROSCLEROSIS

Severe plaque formation, stenosis, is easily detectable by angiography in arteries. To a lesser extent stress testing also has been in focus as diagnostic techniques for cardiovascular disease. However, these diagnostic methods can detect only chronic narrowing, not the starting point. As established by clinical studies, most severe incident occurs where, heavy plaque found. Plaque rupture can result to artery lumen occlusion within few seconds or minutes, and likely permanent weakness and sometime unexpected death.

Ruptured plaque is known as complicated plaques. Cracks in extracellular matrix of lesion occur, typically at the shoulder of fibrous cap

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that disparate from arterial lumen, where the bare thrombogenic components of the plaque, primarily collagen always trigger thrombus formation. The thrombus move downstream towards the other blood vessels, and thus blood clotting can partially or completely obstruct blood flow.

Whether, the blood flow is absolutely blocked, due to lack of oxygen cell death take place resulting in necrosis. The blockage of can take place in any artery within the body. Complete blockage of arteries supply to heart muscle leads in a heart attack, while the hindrance of arteries procuring the brain result in a stroke.

Besides, the time-honored diagnostic methods named as angiography and stress-testing. Some other diagnostic techniques have been soaring in the past decades for former detection of atherosclerotic disease. Some of the revealing approaches take in anatomical detection and physiologic measurement.

Unveiled some techniques of anatomical detection consist of:

(a) Coronary calcium scoring by CT,

(b) Carotid IMT measurement by ultrasound, and

(c) Intravascular ultrasound (IVUS).

Examples of physiologic measurement methods comprise of:

(a) Lipoprotein subclass analysis,

(b) HbA1c,

(c) hs-CRP

(d) Homocysteine.

Both techniques consist of anatomical and physiological methods that allow early detection sooner than symptoms confirm disease staging and way of disease progression. Anatomic methods are costly and some are invasive methods, example IVUS. Whereas, physiological methods are found less expensive moreover they are much safer also.[2,12]

Preventions processes

The lifestyle that cure and prevent from atherosclerosis, also prohibit it from soaring up and becoming a chronic disease. Some of them are mentioned below that patient should adopt for being cured from atherosclerosis.

Maintain suitable diet plan ardently comprises of fruits and vegetables. Along with whole grains, seafood, poultry without skin, lean meat and fat-free milk. Healthy diets secure low sodium, sugar, refined grains and solid fats.

In initiation, make sure that patient is not suffering from overweight or obese, make schedule with your doctor supervise fat or get rid of it.

Should be physically active as much patient can, physical activities can improve fitness and health. Try to consult doctor regarding type and amount of exercise.

Quit Smoking, can harm and tighten blood vessels and elevate risk for atherosclerosis. Consult with doctor regarding programs and medicines that can help to get rid of smoking. In addition, avoid secondhand smoke.

Awareness of own family history towards atherosclerosis is essential. In case somebody in patient's family suffers from atherosclerosis, be sure to inform doctor.

If, lifestyle changes do not bring out any sufficient results. Evidently, consult doctor and consume properly prescribed medicine.[13]

TREATEMENT

a. Various medication procedures:

(i.) Cholesterol medication:

Aggravate lowering of low density lipoprotein (LDL) cholesterol, can slow, stop or reverse the makeup of fatty deposition in arteries. Enhancement of high density lipoprotein cholesterol can help out patient to cure atherosclerosis.[4]

(ii.) Beta-blocker medication:

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ISSN: 2347-7881

Beta-blockers are mainly used for coronary artery diseases. These medicines help out to lower heart rate and blood pressure. Relief from chest pain as well as lower the chances of heart attack.[8]

(iii.) Anti-platelet medication:
They reduce the clumping in narrowed arteries from blood clot and any caused further blockage.[8]

(iv.) Angiotensin converting enzyme (ACE) inhibitors:
ACE inhibitors slow down the progression of atherosclerosis by lowering blood pressure and providing amity effects on the heart arteries. ACE inhibitors resist angiotensin converting enzyme, thereby declining the stress of blood vessels and blood volume, consequently lower blood pressure.[1,7]

(v.) Calcium channel blockers:
Input method of calcium channel blockers is lowering of blood pressure.[8]

(vi.) Diuretics
High blood pressure is a foremost risk factor of atherosclerosis.
Diuretic drug lowers blood pressure.[5]

B. Surgical procedures
When, the conditions become chronic, the drugs and precaution fail to cure patient atherosclerosis. In that condition doctors prefer patents to go through surgery. Numerous surgical treatments, make patient feel good for in short term only, take in minimally invasive angioplasty that might include stents to physically expansion of narrowed arteries and foremost invasive surgery, as such bypass surgery, to generate additional blood supply links that go around the more chronic narrowed areas.[6]

(i.) Angioplasty
During this procedure, a long tube introduce (catheter) into the blocked or narrowed portion of artery. Flexible tube along with a balloon at its tip threaded throughout a blood vessel to the exaggerated artery. Just the once, in place balloon is inflated to reduce the plaque alongside the artery wall. Thus, restores blood flow through the artery.[4]

(ii.) Endarteretomy
In some cases, fat deposition ought to be surgically detached from the walls of narrowed artery. The same process is when resumed on arteries in neck known as carotid endarterctomy. [6]

(iii.) Thrombolytic therapy
If artery is found to be blocked by clots, clot dissolving medicines are inserted into artery at the spot of the clot to rupture it up.[3]

c. Herbal treatment:
Herbal treatments are safest & most reliable method of any disease treatment. Here are some best known herbal treatments of atherosclerosis.

(i.) Garlic
Include fresh garlic in diet, a great way to treat atherosclerosis. Garlic has been proved naturally good body cholesterol management. It lowers cholesterol and thus keeps the arteries unclogged and unhardened. Note that fresh garlic is superlative, raw if available. [4,5]

(ii.) Rutin
Engulf along with vitamin C Rutin persuade good cell heath and help out in keeping arties clear, unblocked and unhardened. Best result is seen when consumed 500mg of rutin daily along with 500 mg of vitamin C. [4]

(iii.) Onion
Produce same effect as garlic use to be (unbeatable cholesterol management). Include

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ISSN: 2347-7881

some fresh raw onion to daily diet for good results. Consumption of patenttea-spoon of pure onion juice found supplementary affective.[5]

(iv.) Grape seed extract

Grape seed extract, inhibit enzymes that damage tissues of arteries by removing things like collagens and elastage that are important in keeping arteries, supply to function accurately. Nowadays in market packed grapes seed extracts supplements are easily available.[4]

(v.) Pomegranate juice

Pomegranate juice well known for its anti-oxidant properties and thus it help in curing atherosclerosis. It produces effort by reducing oxidation of lipids as effective atherosclerosis treatment.[5]

Anti-atherosclerosis Drugs are mainly classified into five categories:-

HMG-COA Reductase inhibitors (stains):

*Example:- Fluvastatin, simvastatin, pravastatin, rosuvastatin.

Bile acid sequestrants:

* Example: - colesevelam, colestipol.

Fibrates:

* Example: - clofibrate, gemfibrozil, fenofibrate.

Inhibit triglyceride synthesis and lipolysis:

* Example: - niacin.

Other: Probucol, Gugulipid.

PHARMACOLOGY OF ANTI-ATHEROSCLEROSIS DRUGS

Anti-hyperlipidemic drug

Low-density lipoprotein carries cholesterol to the peripheral cells. When the huge deposition of cholesterol take place to the peripheral cells the excess cholesterol discarded in blood. These depositions of cholesterol can easily penetrate the arteries wall and result in atherosclerosis. Cholesterol deposition results in narrowing lumen of the arteries. When these fatty deposits take place in coronary arteries results in coronary heart disease. Atherosclerosis can be reversed or arrested by lowering the blood cholesterol levels in the vessels and can extensively decrease the occurrence of heart disease. This is done with the help of Anti-hyperlipidemic drug by inhibiting HMG CoA reductase, leading to reduce in cholesterol level in cells. Low intracellular cholesterol arouses the synthesis of LDL receptors. Amplified number of LDL receptors props up uptake of LDL from blood. Low down intracellular cholesterol reduce the secretion of VLD and enhance in LDL receptors. Reduction of intracellular cholesterol reasons the cell to increase the number of definite cell surface LDL receptors that can attach and internalize circulating LDL.

On the whole, about 70-75% of plasma LDL is detached by hepatocytes, through receptor-mediated endocytosis cholesterol esters beginning LDL molecules is hydrolysed in the liver to liberated cholesterol.

Statins inhibits the enzyme hydroxyl methyl glutaryl co-enzyme A reductase, the rate limiting enzyme.

Simvastatin and Atorvastatin, elevate HDL level in several patients and lesser the triglyceride levels.

Lovastatin is partly absorbed and has a tot biological half-life. It works as prodrug, which is rapidly transformed in the liver into active metabolite.

Bile acid binding resins

The bile-acid sequestrants particles are highly positively charged and rapidly bind negatively charged particles of bile acids. For the reason that of large size, the resins are not absorbed even in tot amount, and the bound bile acids are discharged in the stool. Given that over 95% of acids are generally reabsorbed, interruption

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of this process drain the pool of bile acids, furthermore hepatic bile acid syntheses are enhanced.

Hepatic cholesterol content does turn down, stimulating the making of LDL receptors, as useful as similar to that of statins. The amplification in hepatic LDL receptors increases LDL deficit and lesser LDL-C levels, but this effect is partly offset by the better cholesterol synthesis caused by positive regulation of HMG-CoA reducatase.
Reticence of reductase activity by a statin significantly increases the effectiveness of the resins.

Fibrates
They arouse lipoprotein lipase action and hydrolysis of triglycerides in the plasma. They decrease the amalgamation of fatty acids in VLDL within the liver, thus resist the synthesis and secretion of VLDL. Fibrates are almost entirely absorbed from the gut, are exceedingly protein bound, chemically transformed in the liver and are released in urine as glucuronides.

Inhibit triglyceride synthesis
Ezetimibe discriminatory inhibits the intestine assimilation of dietary and biliary cholesterol in the small intestine leading to a decline in the supply of intestinal cholesterol to the liver. This reasons a decrease of hepatic cholesterol storage and a boost in clearance of cholesterol as of the blood. Extimibe use to lesser the LDL of cholesterol by 17%, triacylglceros by 6% and enhanced HDL cholesterol by 13%. Exetimibe is primarily metabolized in the small intestine and liver through glucuronide conjugation, with ensuing biliary and renal secretion. Ezetimibe and ezetimibe glucuronide both of them are slowly eradicate from plasma, through half life of approx 22 hours.

Adverse effects
Lorastain and other statins may source reversible rise in hepatic amino transferase levels. Amalgamation of a stain with fibric acid derivatives & Nicotinic acid or cyclosporine has efficient effect on the increase in plasma CPK level; dose dependent myalgia, muscle weakness and infrequently myopathy have been accounted. Doses used to not seem to provoke deficit of other chief steroids derived from cholesterol.[7,8]

Lovastatin and simvastatin undergo wide-ranging first-pass metabolism and their toxicity can be amplified by the simultaneous use of hepatic microsomal enzyme inhibitors. Fluvastatin, though probably causes lesser drug interactions.[7,8]

Rarely, statins may results impotence, gynaecomastia, peripheral neuropathy and memory failure. During pregnancy, breast-feeding, in children and patients suffering from severe liver disease statin is find as contraindicated drug.[7,8]

Therapeutic uses
Statins are valuable in lesser blood LDL cholesterol particularly in therapy. Statins have been found unbeaten to decrease the succession of atherosclerotic and occurrence of myocardial infarction.
Statins, if used alone can decrease LDL by 40-60% whereas along with cholestyramine resins can more sorely lower the LDL level. Adding up, of nicotinic acid slighter the LDL level nearer to 70%.

The statins produces several non-lipid favorable effects such as reduce in platelets aggregation and in fibrinogen levels, progress in endothelial function, depletion in macrophage infiltration into the vessel wall, depletion in arteries proliferation and depletion in LDL oxidation in the vessel wall.[7,8]

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RESEARCH

In JAMA 2006 research published with confirmation of that human Apo-A1 Milano HDL bacterial synthetized is highly useful in reduction of coronary plaque volume in only 6 weeks. This article represents the function of HDL on atherosclerosis has been through the rare Apo-A1 Milano human genetic types of HDL protein.

Niacin indicates efficient HDL raising effects in clinical trial studies, found beneficial in coronary Drug Project. Whereas, drug niacin is found as more effective, when consumed along with any lipoprotein agents. Some individuals show side effects, nuisance with short term flushing reactions. So, brand selection, dosing strategy should be carefully judged before its consumption. However, enhance HDL by any means is not essentially helpful. Drug named torcetrapib, most effective agent known currently for increasing HDL (up to 60%) found in clinical trial resulting raised in death by 60%. All studies concerning this drug were brought to an end in December 2006.[14]

Another research approaches that the lowering of LDL-c can be seen through lowering of production of VLDL precursor, Microsomal-triglyceride transfer protein (MTP). MTP is essential for the proper formation of the VLDL precursor and it is found that the inactivation of the MTP protein, results in regression atherosclerosis.[15]

Immunomodulation of atherosclerosis is a technique that represents reverse action of macrophage on antherosclerosis plaque formation.[16] Immunomodulation has been practiced with considerable achievement in both mice and rabbits since nearly 2002. In recent follow up studies in 2011 found that the 70% reduction in atherosclerosis by mean to immuno-modulatory mediators (like as cytokines). Immunotherapy is nowadays considered as much effective means of treatment of atherosclerosis, and efforts to repress the pro-atherogenic auto-immune response now days has been possible avenue of research, which may aid in its healing.

Dr. Hyo-Soo Kim and team explained that the progenitor cells in the arteries have potential to work as osteoblast and osteoclasts. Therefore, help in regulating atherosclerosis when treated with PPARy, a protein to facilitate the production of osteoclasts and obstruct osteoblast production. When, team studied on mouse models they administrated cells that could turn into either osteoblasts or osteoclasts, and raised the rigorousness of calcium accumulaton in arteries, as result they found that with PPARy significantly reduced calcium accumulation, reversed calcification.[10]

Some controversial research studied link between atherosclerosis and pathogens present in arteries of heart e.g, nanobacteria Chlamydophila pneumonia, through the outcomes is not as expected. Antibiotics used for this trial are successful in suppressing growth or killing bacteria have not been effective in progressive outcomes. [17]

The immunomodulation approaches mentioned above, because they deal with innate responses of the host to promote atherosclerosis, have far greater prospects for success.

CONCLUSION

Diet control although represent significant role in atherosclerosis cure. Whereas statins along with diet control signify better treatment than simply of diet control, with the minor side effects. Patients should have to go far surgery when the atherosclerosis becomes chronic. The immunomodulation approaches mentioned above, because they deal with innate responses of the host to promote atherosclerosis, have far greater prospects for success.

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ISSN: 2347-7881

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