A Cure for Coronary Artery Disease

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Abstract

To cure coronary artery disease, complete removal of atheroma from coronary arteries is necessary and may be achieved using pharmacological intervention. This hypothesis requires verification by a trial.

The conditions that lead to the formation of atheroma are as follows:

- Insulin resistance and vascular endothelial dysfunction, Atherogenic dyslipidemia, Risk factors for coronary artery disease, Inflammation of coronary arteries, Drugs that increase insulin resistance.

Atheroma formation begins with the formation of fatty streaks on the endothelium, which progress into stable or unstable atheromatous plaques. The unstable plaque has a thin fibrous cap that is prone to rupture. Unstable plaques contain a large lipid pool consisting of oxidized low-density lipoprotein (LDL), apoB and cholesterol that can grow; they are also have heavy inflammatory cell infiltration, including monocytes, macrophages and T cell lymphocytes. Moreover, debris from ruptured macrophages that were overloaded with lipids attracts more macrophages.

The plaque can grow and protrude into the coronary artery lumen. Plaques exhibit overgrowth of vasa vasorum and can they rupture, leading to the formation of a large thrombus that may severely or completely obstruct the coronary artery. Hemorrhage may also occur in the plaque.

Carvedilol and metformin promote plaque stability. The supply of lipids to the lipid pool in the plaque is reduced by statins and evolocumab, and lipids are removed from the lipid pool by apoA-1 and high-density lipoprotein (HDL) as their levels in the blood are increased. Severe inflammation is treated with carvedilol, metformin, statins and apoA.

Growth of vasa vasorum is attributed to insulin resistance and can be reversed by carvedilol and metformin, thereby preventing hemorrhage. The size of the thrombus on a ruptured plaque can also be reduced by carvedilol, metformin and apoA-1, as these three agents prevent platelet aggregation. Thrombi are removed by endothelial thrombolysis. A thrombus may also form in the plaque from intraplaque hemorrhage; if present, the size of this type of thrombus will be small, as vasa vasorum are atrophic. In both cases, thrombi are removed by endothelial thrombolysis. Subsequently, healthy macrophages infiltrate and remove debris, after which the plaque changes to a fibrous nodule that can be removed by endothelial fibrinolysis. The plaque is then completely removed.

Keywords: Atheroma; Insulin resistance; Endothelial dysfunction; Carvedilol; Metformin; Evolocumab; Statin

Introduction

Individuals with coronary arteries disease have multiple atheromas in their coronary arteries that can rupture or become ulcerated, leading to the formation of a thrombus on the ulcerated area of the atheroma or on the ruptured atheromatous plaque [1]. This can lead to a complete or major obstruction of the coronary artery, causing unstable angina, acute myocardial infarction or death [2]. According to the CDC, 610,000 people die of heart disease every year [3].

Coronary artery disease can be cured by the complete removal of atheroma from coronary arteries, potentially via pharmacological intervention with carvedilol, metformin, evolocumab and statins [4-7]. I hypothesize that atheroma can be removed from coronary arteries, thus curing coronary artery disease. However, a trial is required to confirm this hypothesis.

The five conditions underlying atheroma formation are as follows:

- Insulin resistance and vascular endothelial dysfunction [8,9].
- Risk factors of coronary artery disease [7,8].
- Atherogenic dyslipidemia and other lipid disorders [9,10].
- Inflammation of coronary arteries [11,12]. Additionally, insulin resistance works synergistically with inflammation to increase coronary artery disease severity.
- Drugs that increase insulin resistance [4,13].

Treatments that reduce insulin resistance are important for addressing these five conditions.
Vascular Endothelium

The endothelium is a thin monolayer that covers the entire inner surface of the blood vessels, separating the circulating blood from the tissues. Normal or antiatherogenic functions of the endothelium include vasodilation, thrombolysis, platelet disaggregation, antiproliferation, anti-inflammation and antioxidation. Endothelial dysfunction, which is caused by insulin resistance and oxidized low-density lipoprotein (LDL), includes vasoconstriction, thrombosis, adhesion molecule dysregulation, inflammation and oxidant activity [8,9].

Carvedilol promotes the actions of normal endothelium except thrombosis; carvedilol promotes vasodilation, platelet disaggregation, antiproliferation, anti-inflammation and antioxidation. In addition, carvedilol reduces insulin resistance, which is present in patients with coronary artery disease or diabetes mellitus [14,15].

Another agent that promotes the functions of normal endothelium described above is apoA-1. This agent is a very important part of high-density lipoprotein (HDL). ApoA-1 is an antioxidant and anti-inflammatory agent, and it scavenges toxic phospholipids; stimulates reverse cholesterol transport, antithrombotic and profibrinolytic effects and attenuates endothelial dysfunction [8,16]. Therefore, carvedilol and apoA-1 have antiatherogenic effects that promote the functions of normal endothelium. Studies are required to investigate the application of carvedilol and apoA-1 for the treatment of coronary artery disease and for controlling the risk factors for coronary artery disease as well as the extent of improvement they elicit on endothelial function.

The Various Types of Coronary Artery Atheroma

Atheroma development begins with the formation of fatty streaks on the endothelium and progresses via accumulation of material in the tunica intima between the endothelial lining and the smooth muscle layer of the arterial wall. The accumulated material mainly consists of macrophage cells, debris, lipids, calcium and a variable amount of fibrous connective tissue. The accumulated material forms a swelling in the arterial wall, which may intrude into the lumen of the artery, thereby narrowing the artery and restricting blood flow. These lesions are referred to as atheromatous plaques [12,8].

Atherosclerotic lesions are divided into two groups according to the American Heart Association: atherosclerotic intima lesions and progressive atherosclerotic lesions. A third group of lesions is known as healed atherosclerotic lesions, and they are most prevalent.

An alternative approach to characterizing atherosclerotic lesions is based on fibrous cap thickness and the inflammatory infiltrate. Lesions contain monocyte-derived macrophages, T lymphocytes and smooth muscle cells. Interactions between these cell types and the connective tissue determine the extent of plaque progression, including important complications, such as thrombosis and rupture [12].

A thin fibrous cap atheroma is a vulnerable plaque in which the fibrous cap does not contain collagen or smooth muscle cells but is full of inflammatory cells. This plaque has a large lipid-rich necrotic core that comprises 40% of the plaque. There is increased plaque inflammation, positive vascular remodeling, increased vasa vasorum neovascularization and intraplaque hemorrhage [12,17,18]. These characteristics together with the usual hemodynamics, such as pulsating expansion during systole and elastic recoil contraction during diastole, contribute to high mechanical stress on the fibrous cap of the atheroma, thereby increasing its susceptibility to rupture.

Increased hemodynamic stress, especially increased pulse pressure, correlates with major cardiovascular events (such as acute myocardial infarction) during exercise, especially heavy exercise.

Generally, an atheroma becomes vulnerable if it grows rapidly and has a thin cover separating it from the blood flow inside the arterial lumen. Tearing of that cover is called plaque rupture. Repeated atheroma rupture and healing is one of the main mechanisms that lead to arterial stenosis [1,2].

The clot formed by the atheroma contracts over time, leading to narrowing called stenosis. When the vulnerable plaque ruptures and spills its contents into the blood stream, sticky cytokines on the arterial wall capture some of those contents, which are mostly platelets and accumulate at the site of injury, clumping together to form a thrombus of a variable size.

In addition, atheroma rupture may allow blood from the lumen to enter the inner tissue of the atheroma, which increases the atheroma size and leads to its protrusion into the lumen of the artery, causing lumen narrowing or even total obstruction. Hemorrhage in the atheroma can also have similar effects [9].

Imaging modalities for the evaluation of high-risk atherosclerotic plaques include optical coherence tomography (OCT), intravascular ultrasound-derived virtual histology, and infrared spectroscopy.

Risk Factors for Coronary Artery Disease

An important part of treatment is to control all the risk factors for coronary artery disease. The risk factors include hypertension, diabetes mellitus, smoking, hyperlipidemia, obesity, metabolic syndrome, sleep apnea, a diet rich in saturated fats and trans fats, and lack of physical activity. In contrast, smoking cessation, weight loss and exercise increase HDL levels in the blood.

The risk factors that cannot be treated are age, gender and family history of coronary artery disease. High levels of homocysteine are also a risk factor. Obesity and smoking are sometimes very difficult to treat. The risk factors that cannot be controlled increase insulin resistance, thereby causing endothelial dysfunction. This rise in insulin resistance can be reduced by carvedilol and metformin, thereby preserving endothelial function [7].

Drugs Used to Remove Coronary Atheroma

Four drugs can be used to remove coronary atheroma: carvedilol, metformin, evolocumab and statins, and they can be used together.

Carvedilol

Carvedilol is a third-generation beta-blocker that blocks beta 1, beta 2 and alpha adrenergic receptors. Carvedilol is used in the treatment of hypertension, coronary artery disease and congestive heart failure. It reduces insulin resistance and stimulates insulin receptors. Carvedilol promotes the functions of normal endothelium, as described earlier; it reduces platelet aggregation, prevents LDL oxidation and increases the level of HDL. The dose is 25 mg given twice a day. The side-effects are low blood pressure, bradycardia, dizziness, drowsiness, nausea, vomiting, diarrhea, dry eyes, fatigue, joint pain, cough and decreased sex drive [15,19].
Metformin

Metformin belongs to the biguanide group and is used to treat diabetes mellitus as it reduces blood glucose levels; it also reduces insulin resistance. Metformin is also an anti-inflammatory drug and prevents platelet aggregation. It lowers cholesterol and LDL levels but increases the level of HDL. Metformin must not be used in patients with renal failure, serious infections or liver failure. Its side-effects include nausea, vomiting, diarrhea and lactic acidosis [5].

Evolocumb

Evolocumb is a monoclonal antibody and a PCSK9 inhibitor. It can lower LDL levels by 71% over 12 weeks if used at its maximum dose with statins. It is given subcutaneously; therefore, there can be pain, swelling and redness at the site of injection. Evolocumb can cause acute infection of the nose, throat or sinuses. The dose is 140 mg given twice a month or 240 mg given once a month [20-23].

Statins

Statins are HMG-CoA (HMOA) reductase inhibitors and are used to lower cholesterol and LDL levels; simvastatin and rosuvastatin also increase HDL levels. Statins are anti-inflammatory agents. When used as a secondary prevention measure for acute myocardial infarction, statins lower the rate of relapse by 30%. Statins can cause mild or severe muscle pain, jaundice and abdominal pain. Rarely, statins can cause rhabdomyolysis with liver and kidney damage, especially if used at a high dose [6].

The average dose of atorvastatin is 40 mg daily, and the maximum dose is 80 mg daily. The average dose of simvastatin is 40 mg daily, and the maximum dose is 80 mg daily. The average dose of rosuvastatin is 10 mg daily, and the maximum dose is 40 mg daily.

The levels of apoA-1 are low in patients with coronary artery disease due to increased insulin resistance; carvedilol and metformin decrease insulin resistance and increase the level of apoA-1. Moreover, apoA-1 is the major component of HDL, and HDL levels are also increased by carvedilol and metformin. Simvastatin and rosuvastatin also increase HDL levels. Therefore, HDL and apoA-1 levels can be increased by several methods [16]:

- Lowering insulin resistance using carvedilol and metformin increases HDL levels.
- Carvedilol, metformin, simvastatin and rosuvastatin increase HDL levels.

Moreover, the highest level of HDL that can be achieved by reducing insulin resistance via carvedilol, metformin and rosuvastatin therapy will be interesting to study.

Treatment of Stable Atheromatous Plaques

Stable plaques progress into unstable plaques due to insulin resistance [24]. Carvedilol and metformin decrease insulin resistance and improve plaque stability, thereby preventing the progression of a stable plaque into an unstable plaque [17]. The lipid core of the plaque is full of fat. The supply of LDL and apoB to the lipid pool of the atheroma is markedly reduced by evolocumb and statin treatment. Additionally, LDL oxidation is prevented by carvedilol [23]. LDL, apoB and other toxic lipids from the lipid pool are removed by HDL and apoA-1, whose levels are increased by drug treatment as explained earlier. ApoA-1 also removes toxic phospholipids [16].

Statins are prescribed to treat inflammation in the atheroma, but it is only partially effective. The combination of statins with carvedilol, metformin and apoA-1 may reduce inflammation in the plaque, but studies are required to determine the dose and number of drugs required to eliminate inflammation. Smooth muscle cells proliferate under conditions of insulin resistance, and their proliferation can be reversed by decreasing insulin resistance with carvedilol and metformin [24].

Carvedilol also has antiproliferation properties, which can reverse smooth muscle proliferation. The proteases produced by macrophages remove smooth muscle cells and degrade collagen fibers. The extracellular matrix is damaged by MMP-9, which is an enzyme produced by macrophages [16]. As a result, the atheroma can rupture or ulcerate, and a thrombus may form on the ulcerated area. The treatment of these two conditions and intraplaque hemorrhage is similar to the treatment of unstable plaques. With combination drug therapy including carvedilol, metformin, evolocumab and statins, everything contained in the atheroma could be removed. Following the reduction of the lipid pool, inflammatory cells, and smooth muscle wall hypertrophy, healthy macrophages will infiltrate and remove the debris. The atheroma will then be reduced to a fibrous nodule on the intima, which can be removed by endothelial fibrinolysis [8]. Thereafter, the process of coronary artery repair can begin.

Treatment of Unstable or Vulnerable Atheromatous Plaques in the Coronary Artery

To achieve the goal of entirely removing atheroma from the coronary artery, the risk factors for coronary artery disease must first be controlled.

The unstable plaque is smaller and prone to rupture, and their formation is due to insulin resistance [8,9]. Insulin resistance can be treated with carvedilol and metformin, which will increase plaque stability. Treatment of insulin resistance can also repress MMP-9 secretion, which causes the thinning of the fibrous cap; therefore, inhibition of MMP-9 secretion leads to fibrous cap thickening and reduces the risk of rupture. Statins also inhibit MMP-9 secretion by macrophages and damaged endothelial cells. MMP-9 dissolves the extracellular matrix and increases the risk of plaque rupture, and amelioration of insulin resistance represses MMP-9 [16].

The large lipid-rich necrotic core of the plaque, which contains oxidized LDL and apoB, may be ameliorated by decreasing the supply of LDL and apoB with statin therapy combined with evolocumab. Carvedilol can also be administered to prevent LDL oxidation. The removal of LDL and other toxic lipids from the lipid-rich necrotic area can be achieved by apoA-1 and HDL, whose levels in the blood are increased by the combination drug therapy as explained earlier. Therefore, eliminating the lipid supply and removal of the lipids from the atheroma will severely shrink the lipid core of the atheroma.

Macrophages sometimes become overloaded with oxidized lipoprotein particles and become foam cells. Some of these cells die, releasing fat- and cholesterol-laden membranes in the intercellular space, which attracts more macrophages. The macrophage-induced enzymes erode the fibrous membrane beneath the endothelium so that the cover separating the plaque from the blood flow in the lumen becomes thin and fragile [16]. The treatment for this situation is to reduce the supply of LDL and apoB, prevent LDL oxidation and remove LDL, apoB, cholesterol and toxic lipids via the actions of HDL and apoA-1. The macrophages will shrink and be eliminated by anti-
Inflammatory agents and hyperinsulinaemia, as hyperinsulinaemia due to insulin resistance accelerates macrophage death [16].

Anti-inflammatory drugs, such as statins, carvedilol, metformin and apo-A-1, can eliminate inflammation. Changes in apoA-1 are negatively correlated with high-sensitivity C-reactive protein levels, as apoA-1 has anti-inflammatory and antithrombotic effects. Smooth muscle cell proliferation is not present in unstable plaques as smooth muscle cells are removed by macrophages. The plaque can rupture, and an atheroma can form on the ruptured plaque [2]. However, the formation of a thrombus on the plaque can be prevented by carvedilol, metformin and apoA-1, as these drugs prevent platelet aggregation. Even if a thrombus forms, it would not be large and could not cause a major blockage of a coronary artery that can lead to unstable angina or acute myocardial infarction (MI). Instead, the thrombus will be small and able to be dissolved by endothelial thrombolysis as endothelial function is improved by the drug therapy. Carvedilol and apo-A1 supplement the actions of vascular endothelium, and carvedilol reduces insulin resistance, thus preserving endothelial function.

Hemorrhage can occur inside the plaque, and this can be prevented by reversing the growth of vasa vasorum [18,22]. Vasa vasorum grow due to insulin resistance, which is reduced by carvedilol and metformin; therefore, the proposed drug treatment may decrease the number of plaques. If hemorrhage occurs, the resultant thrombus will be small, as carvedilol, metformin and apo-A1 prevent platelet aggregation. The thrombus will then be removed by endothelial thrombolysis.

The unstable plaque may undergo the following changes after treatment: development of a stable fibrous cap, and elimination of the lipid core or inflammatory cells. Neovascularization may be markedly decreased or eliminated due the reduction of insulin resistance by carvedilol and metformin treatment. If there is a thrombus in the plaque, that thrombus will be dissolved by endothelial thrombolysis [8]. Then, healthy macrophages can infiltrate and remove all the debris and other waste. The plaque will then shrink to a small fibrous nodule on the intima of the coronary artery, which will be removed by endothelial fibrinolysis, thereby resulting in the complete removal of atheroma from the coronary artery. A trial is required to verify this hypothesis. Alternatively, if a plaque ruptures and causes major or total occlusion of a coronary artery, resulting in unstable angina or acute myocardial infarction, then those patients should be treated with PCI or coronary artery bypass grafting.

**Conditions that Lead to Atheroma Formation**

**Insulin resistance**

Insulin resistance causes endothelial dysfunction due to its associated complications. Insulin resistance can be associated with hyperglycaemia or normal blood sugar levels. Insulin resistance can also be associated with hyperinsulinemia and normal or low levels of insulin. Carvedilol increases insulin secretion when blood insulin levels are low, thereby decreasing insulin resistance. Metformin also reduces insulin resistance. Whether there is synergy between carvedilol and metformin requires further study [4,8,24].

**Atherogenic dyslipidemia and other lipid disorders**

Insulin resistance decreases lipoprotein lipase activity, which increases apoB-lipoprotein, very-low-density lipoprotein (VLDL), LDL and triglyceride levels. There is increase in hepatic lipase activity that increases the removal of HDL and decreasing HDL levels in the blood. Carvedilol and metformin decrease insulin resistance and increase the activity of lipoprotein lipase, thereby decreasing the levels of apoB-lipoprotein, VLDL, LDL and triglycerides. Therefore, atherogenic dyslipidemia can be treated with carvedilol, metformin, evolocumab and statins. The latter two drugs lower LDL levels, and carvedilol prevents LDL oxidation [9,10].

Heterozygous or homozygous familial hypercholesterolaemia was difficult to treat before evolocumab was approved; evolocumab has since reduced the incidence of acute MI and acute cerebrovascular accident (CVA) among those patients. Beta-blockers are used extensively in the treatment of cardiovascular disease. Vasoconstricting beta-blockers reduce HDL levels. Carvedilol is a vasodilator beta-blocker and decreases LDL, VLDL, total cholesterol and triglyceride levels as well as increase HDL levels [8].

Individuals with very high levels of triglycerides are prone to developing coronary artery disease is debatable. However, very high levels of triglycerides can be ameliorated using ethyl eicosapentanoic acid. This drug reduces LDL and triglyceride levels.

**Drugs that increase insulin resistance**

Drugs that increase insulin resistance must be avoided, including thiazide diuretics, beta-blockers, steroids and antipsychotic drugs. Beta-blockers increase insulin resistance but are used extensively to treat cardiovascular disease. Carvedilol is a better beta-blocker substitute. Statins also increase insulin resistance, but they decrease cardiovascular morbidity and mortality. Statins inhibit platelet function and vascular smooth muscle cell proliferation and reduces the accumulation of inflammatory cells [13].

**Inflammation of coronary arteries**

Oxidized LDL and VLDL may activate inflammatory functions of vascular endothelial cells. Hypertension and diabetes mellitus are associated with inflammation, which need to be treated. Carvedilol, metformin and statins are anti-inflammatory drugs. Carvedilol can be used to treat hypertension in lieu of other beta-blockers. Metformin and statins are used to treat diabetes mellitus. Patients with coronary artery disease and rheumatoid arthritis are treated with methotrexate for inflammation [12].

The endothelium can produce a variety of different molecules, including agonists and antagonists, which contribute to homeostasis. The endothelium produces vasodilators and vasoconstrictors depending on the levels of nitric oxide and endothelin. The endothelium also produces coagulants and anticoagulants; inflammatory and anti-inflammatory agents; fibrinolytic and anti-fibrinolytic agents; and many other molecules. When the inflammatory response is incited, fatty streaks appear, and all markers of inflammation begin to increase in the blood [8].

The effect of recombinant ApoA-1 Milano on coronary atherosclerosis was studied in patients with acute coronary syndrome in a randomized control trial. A recombinant ApoA-1 Milano phospholipid complex (ECT-216) was used in this study. Five weekly infusions of placebo or ETC-216 at 15 mg/kg or 45 mg/kg were administered. Intravascular ultrasound (IVUS) was performed 2 weeks after an acute coronary event and repeated after the 5-week treatment. The absolute reduction in atheroma volume in the combined treatment group was 4.2% compared to baseline [24].
The PCSK-9 inhibitor evolocumab reduced the incidence of the composite end point of cardiovascular death, myocardial infarction, or stroke by 20% in patients with cardiovascular disease who were already on the maximum tolerated statin therapy in the Fourier trial. The main concern is that evolocumab does not reduce the incidence of cardiovascular death [23].

After many years of research, studies report that lowering LDL to 20-30 mg gives the best results. The Glagov trial showed a reduction of 0.95% in atheroma using evolocumab and statins, whereas the reduction was -0.5% using statins alone [23]. These two trials treated only LDL, and there is no information on whether LDL oxidation was prevented. The drugs used in the trial decreased the supply of lipids to the lipid pool of the atheroma. Statin therapy also decreased LDL levels, but it did not lead to atheroma regression.

Therefore, to cure coronary artery disease, a different approach is needed, which is the elimination of atheroma.

Conclusion

To cure coronary artery disease complete removal of atheroma is necessary and this can be done by pharmacological intervention. A trial is needed to verify this hypothesis.

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