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New Approaches in Coronary Atherosclerotic Disease: A Brief Overview

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Abstract: Coronary atherosclerotic disease is a pathology of great prevalence in the Western population and that accompanies the human being from intrauterine stage until the end of life. In young people necropsies from Korea and Vietnam wars it was found a 12 to 20% of coronary arteries narrowing in people under 26 years old otherwise healthy. Many traditional treatments in this illness have been considered but in the last years new approaches have appeared and promise a very interesting point of view in coronary disease such as omega 3 oils or antioxidant compounds that could work resetting ischemic tissue disorders. For instance Diabetes Mellitus is a disease very relationed to coronary disease through the formation of AGES. These are proteins modified and altered by glucose. In a hyperglicemic state there are many glucose particles fusioned to proteins; In the beginning this occurs in a reversible way but later the glucose becomes an integral part of proteins. AGES will be- accompanied by Oxygen free radicals- the originators of diabetic complications such as coronary artery disease. Evidently we need to learn more about this illness in order to get a better comprehension of physiopathologic mechanisms involucrated and try to stop or slow its progress. In this briefly monography we try to go through some of these statements.

Keywords: Cell Adhesion Molecules, Oxidative Stress, Insulin Resistance, Resveratrol

1. Introduction

It is estimated that 10 to 13% of the middle-aged American population suffers from ischemic cardiopathy and that more than 60% of heart attacks or sudden deaths occur without prior warning.

Its presence in humans dates back to intrauterine life as Napoli's studies demonstrated the discovery of macrophages and lymphocytes in the wall of the Aorta in human fetuses [1].

Then the question arises of what is the cause that leads to such high morbidity and mortality in the population.

Obviously the cause - under which many factors are grouped - is the rupture of a plaque in the arteries whose obstruction is not so severe (40 to 60%) and therefore have not shown symptoms or have shown minor symptoms or that even can not be detected in an ergometry.

The tunica intima is constituted by a simple layer of endothelial cells that sit on a base membrane. This healthy endothelium acts contrary to what is observed in an atheromatous plaque, since it has antithrombotic, fibrinolytic and vasodilator activities all favoring a good hemostasis. [1]

This endothelium already in adult life is attacked by multiple factors that are part of people's daily lives, which are the so-called risk factors. The intracoronary ultrasound method has demonstrated the presence of diffuse atherosclerosis in patients with risk factors, even in the absence of coronary stenosis.

In obesity, adiponectin levels are reduced and this is associated with increased triglycerides, low HDL, and the presence of small and dense LDL particles, all of which we find in our ischemic patients. [2].

Therefore the sustained aggression of these risk factors to which we can add arterial hypertension and smoking lead to the growth and complication of plaque. Therefore we will have a vulnerable plaque.

Vulnerable plaque is one that has a large lipid nucleus, soft and eccentric, with a large accumulation of leukocytes in the shoulders of the plaque.

It has been seen that ischemia recorded with 24-hour holter

monitoring is followed by a rise in heart rate and arterial pressure and not the other way around, such as ischemia producing an elevation in frequency and others. Whatever the mechanism, there is no doubt in the participation of the restriction to the flow due to the plaque.

So in most cases angina is the result of restriction to flow in moderate to severely stenosed arteries which makes them unable to meet the increased demand for an exercise performed by the patient, although this is also involved in the dysfunction of the endothelium that makes it less sensitive to respond to vasodilator stimuli and instead becomes more hyperreactive to vasoconstrictor stimuli.

2. Physiopathogenesis

At the beginning of the formation of a plaque it happens that when an injury occurs in the endothelium due to the action of the presence of risk factors, circulating cytokines are mobilized to the site of injury which cause the endothelium to express adhesion molecules that are glycoproteins like molecules that adhere platelets to the endothelium (PECAM-1), or intercellular adhesion molecules (ICAM), or vascular cell adhesion molecules 1 (VCAM-1).

This migration is facilitated by chemoattractive substances released by both the endothelial cells and the leukocytes involved. These substances include interleukin 8 (IL-8), platelet-derived growth factor (PDGF) or monocyte chemotactic protein 1 (MCP-1).

This MCP-1 also attracts CD-4 and CD-8 lymphocytes and stimulates monocytes to release cytokines such as IL-1 and IL-6. Therefore a self-sustaining inflammatory process is activated.

When monocytes reach the middle layer of the artery they are called macrophages and begin to engulf lipids present in the wall and at the same time release more cytokines and growth factors that will attract more monocytes and smooth muscle cells to the site of primary inflammation.

Cytokines also stimulate endothelial cells and macrophages to produce free radicals.

This mechanism participates in the fragmentation and oxidation of LDL particles, making them easier to penetrate into the macrophages, which then become foamy cells.

T lymphocytes in turn will produce Gamma Interferon (INF-g) in response to the release of cytokines by activated macrophages.

This INF-g will then participate in the rupture of the plaque cover by inhibiting collagen synthesis by smooth muscle cells. [3, 4].

3. Action of Various Drugs on Endothelial Dysfunction

Given the growing prevalence of atherosclerotic disease in the population, the protective action on the endothelium of many drugs acting on different substrates of atherosclerosis has been investigated through the years. A proper diet and the correction of habits such as tobacco and sedentary lifestyle also help.

One of these drugs is carvedilol, an a-1 beta-blocker with vasodilator effects used in the treatment of high blood pressure and heart failure. It has the ability to inhibit lipid peroxidation of the basement membrane of the myocyte.

The research focused on the release by polymorphonuclear and mononuclear cells of reactive oxygen species (ROS) which were inhibited by the use of 3.12 mg of carvedilol 2 times a day administered to healthy volunteers.

Knowing that the aggressive action of the reactive oxygen species produced by leukocytes on phenylalanine is measured by the formation of the resulting metabolites, the drug was given for 8 days to healthy volunteers forming 2 groups: one with carvedilol and the other without it.

It was found that the production of phenylalanine metabolites (ortho-tyrosine and meta-tyrosine) decreased with the use of carvedilol by 44% for polymorphonuclear and by 35% for that produced by mononuclears.

The production of the metabolites did not change compared to baseline levels in volunteers who did not receive carvedilol.

The study found that carvedilol inhibits the production of ROS by neutrophils and mononuclear cells, which was proven after the decrease in the production of metabolites from the disintegration of phenylalanine. [5].

This becomes important when we know of the release of free radicals by cytokine-activated macrophages inside the plaque.

In another study on endothelium the Pertinent which was in turn a sub-study of the Europa, the effects of Perindopril on thrombosis, inflammation, endothelial dysfunction and neurohormonal activation were evaluated. The expression and activity of Nitric Oxide Endothelial Synthetase (ecNOS) and the rate of apoptosis in human umbilical vein endothelial cells before and after 1 year of perindopril treatment were evaluated as well.

The levels of angiotensin II, tumor necrosis factor alpha (TNF-a), and von Willebrand factor were also evaluated.

A significant increase in nitric oxide synthetase activity, a reduction in the rate of endothelial apoptosis and angiotensin II levels, and a decrease in TNF-a levels and von willebrand factor concentrations were found.

About this matter, we should remember that endothelial cells stimulated by cytokines such as TNF-a produce procoagulant substances such as von willebrand factor. Coagulation activation occurs when blood comes into contact with sub-endothelial collagen fibers and coagulation factor VIIIa is activated when separated from von willebrand factor. [3], [6].

TNF is synthesized in monocytes and macrophages and is involved in the effects of inflammation such as fever, tachycardia. [3]

It is already known that C-reactive protein (CRP) is an independent marker of cardiovascular events in an apparently healthy population. A lot of prospective cohort studies have confirmed that interleukin-6, tumor necrosis factor-a, CRP, fibrinogen and others inflammatory biomarkers are relationed with vascular risk in healthy individuals.[7]. On the other hand,

cytokines increase blood concentrations of markers such as fibrinogen and CRP. [3].

A study of 3745 patients with acute coronary syndrome evaluated the relationship between LDL-cholesterol levels and CRP after treatment with 80 mg atorvastatin and 40 mg pravastatin with the rate of recurrent myocardial infarction and death from coronary cause.

Patients who had an LDL-C level < 70 mg/dl after statin therapy were found to have fewer cardiovascular events than those who had levels of > 70 mg/dl (2.7 vs 4.0 events x 100 people x year).

Something similar was observed with patients who had a CRP < 2 mg/l compared to those who had a value above 2 mg/l (2.8 vs 3.9).

The study concluded that patients who had LDL-C levels < 70 mg/dl and CRP levels < 1mg/l with statin therapy had the lowest recurrence rates of cardiovascular events. [8].

In another study in which Ciprofibrate was used at a dose of 100 mg daily for 8 weeks, the action of this drug on the levels of CRP and fibrinogen was investigated in 30 patients who were not diabetic or who had not had a cardiovascular event in the previous 3 months.

For the measurement of CPR, the nephelometric method was used with a detection limit of 1 mg/l.

Ultrasensitive CRP levels decreased by 36.8% (1.9 mg/l to 1.2 mg/l). Plasma fibrinogen levels were reduced from 292 mg/dl to 273 mg/dl. There was no correlation between decreased CRP us and fibrinogen with changes in plasma lipids. [9].

Going back to another very important harmful factor acting inside the plaque in the early phase of atherosclerosis, reactive oxygen species, these serve as a messenger for the pathways of redox-sensitive transcription (NF-kB) which are what lead to the expression of adhesion molecules by endothelial cells.

It has been said that antioxidants have the function of sweeping these ROS in the cells thus inhibiting the adhesion of the endothelium to monocytes and decreasing inflammation.

Here again comes into action carvedilol a beta blocker with antioxidant action which decreases the oxidation of LDL particles, and inhibits the migration and proliferation of smooth muscle cells.

A study was conducted trying to prove that carvedilol inhibited the production of intracellular ROS dependent on TNF-a. Monocytes were isolated from the peripheral blood of healthy adults to study their adhesion to endothelial cells.

The study was conducted using human aortic endothelial cell culture (HAEC) in a saline buffered solution containing carvedilol, propranolol, prazosin and probucol.

The viability of aortic endothelial cells was evaluated by analyzing cell morphology with hematoxylin and by measuring lactic dehydrogenase (LDH) concentrations in cultures with or without the presence of TNF-a and carvedilol.

Cultures were pre-treated for 18 hours with probucol, carvedilol, propranolol, prazosin before adding TNF-a as a stimulant of cell adhesion.

It was observed during the research that pre-treatment with probucol (5umol/l) or carvedilol (10 umol/l) inhibited the attachment of monocytes to THE EAEC but that this did not occur with prazosin or propranolol, TNF-a was used in doses of 2ng/ml.

It was also observed that pre-treatment with probucol and carvedilol inhibited the expression of VCAM-1 and only with carvedilol the expression of selectins E was inhibited.

Finally, pre-treatment with 10 umol/l of carvedilol for 18 hours reduced the formation of hydrogen peroxide (H202) induced by TNF-a in aortic endothelial cells. TNF-a (2ng/ml) significantly increased intracellular H202 production. [10].

This H202 is a free radical that must be destroyed by anti-oxidant substances such as glutathione peroxidase and catalase to finally produce water and oxygen and decrease toxicity.

Although this was an **in vitro** study, the importance of it is high since it is known that TNF-a can activate the attachment to the membrane of NADPH oxidase and thus increase the production of ROS. The activation of this is associated with an increase in the uptake and metabolism of oxygen in the neutrophil which generates superoxide radical.

4. Oxidative Stress

In nature there is continuously a balanced interaction between oxidation and reduction reactions. This are the REDOX reactions. Living things get their vital energy from these reactions.

When from oxygen there is an uncontrolled production of oxygen free radicals, a damaging environment is created for lipids, proteins, sugars and DNA and enters a state of oxidative stress.

Oxidative stress is an imbalance between the production of reactive oxygen species and the antioxidant systems of the body, either due this imbalance to inflammatory processes, lack of vitamins and minerals or deficiencies in the immune system. Balance is achieved by the endogenous antioxidant action of enzymes such as superoxide dismutase, peroxisome catalase or glutathione peroxidase.

Natural antioxidants include selenium, zinc, vitamins C and E, and phenolic compounds (resveratrol).

These antioxidant substances oppose the toxic action created by the normal reduction of molecular oxygen within cells. [11].

The most important inorganic RLO are the Superoxide radical (O2), the hydroxyl radical (HO), and the hydrogen peroxide (H2O2).

It has already been mentioned that the components of metabolic syndrome are pro-atherogenic, and that the presence of insulin resistance is included in its diagnosis.

Let's briefly review how this insulin resistance is related to oxidative stress.

The mechanism that associates insulin resistance with oxidative stress is the presence of hyperglycemia and the rise of fatty acids in the plasma. By disturbing the peripheral use of glucose, its increase in plasma rises its binding to proteins (glycocylation) and increases the production of oxygen free radicals.

Fatty acids (GAs) also increase their plasma levels by being moved from fat tissue as an energy source and by converting to a greater proportion from glucose. When entering the mitochondria, an excess of glucose and GAs forces their ability to degrade them and excess superoxide radicals are produced.

This exceeds the ability of the cells to handle them, their accumulation will occur and a state of cellular oxidative stress is entered.

This stress will initially be located in the liver - place of formation of fatty acids - but after that it will become systemic, negatively affecting the endothelium of the vessels.

The body has antioxidant mechanisms that work in this situation like the enzyme superoxide dismutase that acts on the superoxide radical (0*) converting it into hydrogen peroxide (H2O2) which will then be destroyed by glutathione peroxidase (GPH) and catalase ending this action in water and oxygen as final products.

If these antioxidant mechanisms fail, natural antioxidants such as glutathione, vitamin C and coenzyme Q-10 would take action. [12].

Glutathione peroxidase (Gpx) has several isoforms the cellular present in all cells, the plasmatica that is manufactured in the cells proximal to the kidney, the hydroperoxide phospholipid that protects against lipoperoxidation, and the gastrointestinal that protects against lipid hydroperoxides of the diet. These are byproducts of the action of free radicals.

In the action of this enzyme glutathione (reducing agent) is consumed and decreased. In states of oxidative stress this decrease is a cardiovascular risk factor.

This is the basis for the medical recommendation to use glutathione in atherosclerosis or in states of hyperglycemia due to its ability to destroy destabilizing lipid peroxides of the cell membrane and which are by-products of the action of ROS. This is the way they protect the endothelium. [13].

5. Omega Acids

They are polyunsaturated acids that are not formed in the body and therefore have to be acquired by eating. They are therefore called essential fatty acids.

They are classified into Omega-6 and Omega-3 acids. Linoleic acid belongs to Omega-6 and alpha-linoleic acid to Omega 3. We also have omega 9 (oleic acid) present in 75% in olive oil and 70% in avocado. But this is a monounsaturated oil.

We will focus the action on omega 3 that are polyunsaturated.

By successive transformations linoleic acid will be turned into long-chain arachidonic acid, and alpha-linoleic acid into eicosapentanoic acid (EPA) which can then be converted into docosapentanoic acid (DPA). All of them can cause prostaglandins, leukotrienes and thromboxanes.

Prostaglandins participate in inflammation and in the production of pain and fever and their transformation product thromboxane A2 favors vasoconstriction and platelet aggregation.

It has been mentioned that Omega-3s, especially long-chain ones, have anti-inflammatory effects and this would be related to a reduction in the concentration of chemoattractive substances, growth factors and adhesion molecules.

Both omega 6 and 3 acids are found in vegetables and are eaten by animals and are stored (linoleic acid) in fat tissue as a reserve to produce arachidonic acid and docosahexanoic acid from omega 3.

Animal meat is eaten by man but should not constitute more than 10% of the daily caloric intake since both omega acids must be in equal parts in human cell membranes to fulfill a beneficial role.

However, due to the modern industrialization of animal husbandry, there is a harmful predominance of omega 6 in the animals we eat. These excess omega-6 have been linked to inflammation and atherogenesis. [14].

The antithrombotic effect of Omega 3 would take place by reducing the concentrations of arachidonic acid that in its metabolism is transformed into thromboxane A2 and prostacyclin [PGI2].

Thromboxane A2 is a platelet activator and prostacyclin is a platelet inhibitor in the endothelium.

The activation of the endothelium at the beginning of the process and also the activation of platelets releases arachidonic acid into the cell membrane.

EPA and DHA (docosahexanoic acid) have also been shown to act by antagonizing platelet receptors for thromboxane A2. DHA is a transformation of docosapentanoic acid.

In a study (the GISSI) that was conducted in 11324 patients with recent IAM, half of the sample took capsules of 0.85 g daily of omega 3 and the other half did not take anything. The follow-up lasted 3 and a half years and a decrease of 15 to 20% was found in the variables of cardiovascular death, non-fatal myocardial infarction and non-fatal AVC.

The anti-inflammatory effect of omega-3s has been proven in vitro studies.

As mentioned before, the recruitment of monocytes to the endothelium depends on the expression of adhesion molecules.

These studies have shown that DHA reduces the expression of ICAM-1, VCAM-1 and ELAM-1/E selectin on the surface of the endothelium, therefore reducing the infiltration of inflammatory cells into the plaque.

It has also been proven that the administration of fish oil in doses of 1.4 g daily of EPA + DHA would contribute to the stability of the plaque.

Finally, there is evidence that the administration of omega 3 oils stimulates ppAR-g found in monocytes and plaque. This activation would reduce the activity of metalloprotease 9, an enzyme involved in plaque instability. [15].

6. Resveratrol as an Antioxidant

It is a polyphenol that is obtained from plants by biotransformation of the amino acid phenylalanine. It is found in cranberries, peanuts, currants and especially in grapes and

red wine obtained from them.

As an antioxidant it would increase the expression of enzymes such as catalase or superoxide dismutase or could be a direct sweeper of oxidizing agents.

Improves endothelial function by raising nitric oxide production by increasing the activity of Sirtuin 1 (SIRT1) which will stimulate the production of nitric oxide endothelial synthetase (eNOS). It should be mentioned that the activation of the signaling pathways of protein G activates the endothelial nitritic synthetase oxide that will increase the production of vasodilator nitric oxide (NO).

Nitric oxide also prevents platelet aggregation, inhibits the adhesion of monocytes to the endothelium and prevents the oxidation of LDL particles.

Sirtuins are enzymes derived from the yeast gene protein (SIR) but also found in animals and humans. Its function is to deacetylate proteins (AMPK) and transcription factors (NF-kB) to raise or lower its actions.

For example, the activation of the transcription factor FOXO 3ª increases the synthesis of catalase or glutathione reductase.

This would support the action of resveratrol to sweep away free radicals, inhibit lipid oxidation and stimulate enzymes like glutathione peroxidase, glutathione reductase, catalase and superoxide dismutase, some of them with an action already mentioned.

In vitro and in vivo studies show that resveratrol produces thrombin inhibition by binding to calcium channels.

In in vitro studies incubating cells with resveratrol, the decrease in triglycerides by stimulation of triglyceride lipase has been observed, increasing the movement of lipids from adipocytes.

It would also have anti-inflammatory effects by decreasing levels of tumor necrosis factor and cyclooxygenase 2.

We should remember oxidative stress produces lipoperoxidation of the membranes and organelles of the cell. [16].

7. Coenzyme Q-10

Ubiquinol (reduced form of coenzyme Q-10) is synthesized in all mammalian cells and to a lesser degree is acquired from the diet. It has an important role in the synthesis of mitochondrial ATP and in them about 95% of the cellular energy is formed. Prevents lipid oxidation of cell membranes.

Positive effects on cardiovascular health of the reduced form of coenzyme Q-10 [ubiquinol] at doses of 450 mg/day have been found when plasma concentrations > 3.5 mcg/ml have been shown to increase the ejection fraction of subjects located in NYHA Class IV.[17].

In experimental models of chronic renal failure in animals, ubiquinol has been shown to lower the production of superoxide radicals and also decrease microalbuminuria. [18].

A 3-month study was realized in 50 patients with diabetic nephropathy. One group took 100 mg of coenzyme Q-10 supplement and the other used placebo. In the control group it was found significant decreases in plasma insulin level and in the Homa test (2.0 vs 1.8) as well as in glycosylated Hb.

There was also a reduction in malon-dialdehyde levels (0.5-1.0 umol/L) and AGES (advanced glycation end products) levels. There were no effects on fasting glucose levels, lipids or matrix metalloproteinases. [19].

In pathologies that decrease ubiquinol levels like type 2 diabetes, an increase in oxidative stress is found, Ubiquinol is a potent fat-soluble antioxidant agent.

In another study with type 2 diabetic and overweight or obese patients with metabolic syndrome and ischemic cardiopathy, one group was assigned for 8 weeks to take coenzyme Q-10 100 mg daily and the other group did not take the supplement. The age of patients ranged from 40 to 85 years. Significant reductions in plasma insulin levels and the HOMA test were found, there was a rise in the concentration of antioxidant capacity, as well as a significant reduction in plasma levels of malondialdehyde which is a signal of lipid peroxidation. [20]

8. AGES

We must remember that AGES are proteins to which glucose has been linked and these will be together with oxygen free radicals the cause of complications in diabetics. This process is called glycation.

However glucose is not the only carbohydrate that can form the end products of advanced glycation (AGES) but as well can fructose, methylglyoxal, glyoxal both products of glucose metabolism, and malondialdehyde that comes from the destruction of fatty acids by free radicals (peroxidation).

When blood glucose levels are normal, the amount of these derivatives is very low but rises in states of hyperglycemia and mobilization of fatty acids like diabetes.

Therefore in diabetes mellitus which is a pathology in which oxidative stress can be found, free radicals increase the formation of AGES since it facilitates the binding of glucose, methylglyoxal and glyoxal to proteins, deforming them and altering or nullifying their function.

This way the different vascular complications of this disease occur.

9. Summary

Since the late 40s since the Implementation of the Framingham Heart Study, cardiological breakthroughs have not stopped in their intention to discover new risk factors for cardiovascular atherosclerotic disease and this has led to the progressive appearance of new risk factors in addition to the classic ones.

Now new terms such as gamma glutamyl transpeptidase, microalbuminuria or advanced glycation end products are used, which let the cardiologist to have a more intimate assessment of the phenomena involved in atherosclerotic disease.

The discovery of the factors involved in this pathology has been progressive and without pause throughout the years, for instance the role of obesity, small and dense LDL particles, the

role of tobacco, so nowadays there is a great interest in the participation of oxidative stress as a trigger for vascular complications in all organs.

Knowledge of the pathophysiology of the creation and development of atheromatous plaque is now at an enormous distance from what was known in the 40s.

This brief review covers some of the current aspects of the pathophysiology involved and the action of certain agents to prevent or delay the series of events that lead to the complication of vascular atheromatous lesions.

Some trials have been conducted in vitro and others need confirmation from studies with a larger population involved, however the importance of these is that they show that inhibition or blocking of many enzymatic steps achieve evident positive results that translate into better health. At the same time, they provide the cardiologist with greater tools to pinpoint the atherogenic risk in their patients.

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