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# Atherosclerosis as a problem in postmenopausal women

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## Summary

**Introduction:** Atherosclerosis is defined as a disease in which plaque, consisting of fat, cholesterol and other substances found in blood, builds up in arteries. This leads to stiffness and narrowing of the blood vessels resulting in limiting the flow of the blood rich in oxygen to tissues. The negative effect of atherosclerosis among women can be opposed by the female hormones. The aim of the article is to review clinical approach to atherosclerosis in post-menopausal women.

**Material and methods:** Articles in the Google Scholar, Pub Med database have been analysed using keywords: atherosclerosis, plaque, cardiovascular diseases, menopause, postmenopausal women, female hormones, estrogens, older people.

**Results:** Atherosclerosis process in the arterial walls is based on accumulation of lipids accompanied by inflammatory factors. One of the most important risk factors of this disease are quantitative and qualitative changes of the plasma lipoprotein, especially increasement of LDL cholesterol after menopause, which can be evaluated during lab tests. The diagnosis of atherosclerosis and its progress can be performed by using different methods, including

physical examination and medical imaging. Development of atherosclerosis leads to peripheral artery disease connected with cardiovascular diseases, such as stroke or heart attack, which be life-threatening and should be immediately treated.

**Conclusions:** This risk of the negative effects of atherosclerosis can be decreased by both lifestyle change and pharmacological treatment. The usage of estrogen-based hormone replacement therapy combined with statins in postmenopausal women presents benefits by the decreasement of LDL cholesterol and the increasement of HDL cholesterol and reduction of calcification of coronary vessels, which reduces the risk of cardiovascular diseases. However, the time of the start of hormone replacement therapy is crucial – performed too late can result in additional development of atherosclerotic plaque and increasement of the inflammatory processes in the arteries with advanced atherosclerotic changes.

**Keywords:** atherosclerosis, plaque, cardiovascular diseases, menopause, postmenopausal women, female hormones, estrogens, older people.

## Introduction

Cardiovascular diseases (CVD) are among leading causes of deaths, but prevalence is higher in post-menopausal women than in woman before menopause. The explanation for that is protective influence of female sex-hormones [1].

Atherosclerosis and CVD (connected to this disease) are one of leading causes of death in the world. The risk of developing atherosclerotic changes for woman is strictly associated with the moment of menopause – women, who are under 50 years old (before menopause) are rarely developing this disease, because they are protected by hormones. After menopause, when protective function of female sex hormones fades out, risk of developing atherosclerosis in woman rises. In age of 70, risk becomes equal for both man and woman [2].

Because going through menopause is the critical moment associated with significant rise of the risk of atherosclerosis, it is essential to use proper diagnostic methods in post-menopausal women group. For years atherosclerosis has been considered to be a passive process – inevitable part of organism's aging process. Nowadays it is known, that this disease is associated with lipid metabolism, active cellular interactions, inflammation and matrix remodeling. Effective diagnostic and early introduced preventive treatment methods allow to decrease risk of death and atherosclerosis-related diseases [3].

In this publication we focus on clinical approach to atherosclerosis in post-menopausal woman problem. We describe currently used diagnostic methods, commenting their advantages and disadvantages, as well as available treatment methods which are in accordance with actual medical knowledge.

In this article we also show how the development of atherosclerotic changes occurs, especially focusing on the plaque development and hormonal changes after menopause, which may predispose to atherosclerosis. We believe, that profound understanding of foregoing issues is essential for both understanding pathogenesis of this disease and current directions of atherosclerosis-related medical treatment and diagnostic procedures. It also increases a capability of developing new, effective methods for diagnosing and therapy [4].

**Epidemiology**

Atherosclerosis is a very serious problem for today's medicine. Its development is often unnoticed or underestimated by patients. Meanwhile, it can lead to very serious complications such as coronary artery disease, acute myocardial infarction and stroke, since it is observed that women with atherosclerosis symptoms and related complications appear on average 10 years later than men. Most likely, this is due to the fact that premenopausal women have a protective effect of estrogens. CVD disease risk in women increases after the menopause. Therefore, a special group of patients who should be considered in the context of atherosclerosis are postmenopausal women [5].

N. Gerard, T. T. J. Judith, S. Gustave, described a study conducted on 232 Cameroonian women. They were divided into 2 groups - 105 of them were in the postmenopausal period, 127 in the premenopausal period. It has been observed that the percentage of patients with dyslipidemia is larger in the postmenopausal group (64 women, 61%) than premenopausal (58 women, 45.6%). Statistical data of the LDL fraction were very similar in both groups. LDL hypercholesterolemia was observed in 34.3% of postmenopausal women and 33.1% in premenopausal women. Larger differences occurred in triglyceride and HDL cholesterol levels. Hypertriglyceridemia was found in 7.6% of postmenopausal and 2.4% premenopausal patients. HDL hypocholesterolemia occurred in 26.7% of subjects in the postmenopausal period and 18.9% in the premenopausal period [6].

In the study conducted between 1 January and 31 December 2013, took part in 370 postmenopausal women. The patients were examined, among others, for carotid atherosclerosis. In published results it was found in 161 subjects. It was noted that women with carotid atherosclerosis were older and were more likely to develop diabetes. Patients with more

children were also more prone to atherosclerosis. Importantly, the fact that on the SCORE scale the cardiovascular risk of both patients with the presence and absence of atherosclerosis was very similar [7].

In the other examination which involved 120 greek woman it has been observed that changes in total testosterone and free androgens have the greatest impact on carotid artery intima media thickness. Women with one or more atherosclerotic plaques had on average higher levels of lutenizing hormone than women without the presence of atherosclerotic plaques [8].

The equivocal results of the studies do not leave any doubt that the protective effect of estrogens on the atherosclerosis process as well as the epidemiology of this disease in postmenopausal women should be further investigated.

**Mechanism of atherosclerotic plaque formation**

Atherosclerosis mainly attacks sites of arterial tree along inner curvatures and near branch points. Typically it affects coronary arteries, abdominal aorta, carotid bifurcations and iliofemoral arteries [9]. The continuous evolution of changes in the arterial walls causes gradual development of atherosclerosis. These changes are focused on the accumulation of lipids and the accompanying inflammatory response [10].

At the beginning in the case of increased LDL (Low Density Lipoprotein) levels, LDL particles leave the blood, then enter the arterial intima, where they accumulate [10]. Cells located in the arterial wall in multiple pathways secrete oxidation products that can initiate lipid oxidation [11]. It is thought that there are two stages of oxidative modification of LDL [11]. In the first stage, when monocytes are not recruited yet, lipids of LDL are oxidized, while changes of apoB are insignificant [11]. When monocytes are recruited, the second phase begins. Monocytes change into macrophages with strong oxidative properties. LDL lipids are still oxidized, along with the protein portion of LDL. These changes result in shift in receptor recognition, which results in uptake of the LDL and in massive accumulation of cholesterol. Such cells with foamy cytoplasm, which are loaded with cholesterol are called foam cells[11]. Foam cells are characteristic for fatty streak [11].

As chronic stimulators - oxidative modification products affect the adaptive and innate immune response [9]. They induce expression of adhesion molecules, chemoattractants and growth factors, which through interactions with receptors on monocytes, cause their migration, homing and differentiation into dendritic cells and macrophages [9]. LDL-modified atherosclerosis and other autoantigens are recognized by the immune system, resulting in

development of lesions [9]. Together with foam cells in the inner membrane, T helper 1 cells secrete pro-inflammatory cytokines such as INF-γ (interferon-γ) and TNF-α (tumour necrosis factor-α) [9]. Also collagen, elastic fibres and proteoglycans are secreted by intimal smooth muscle cells into the extracellular matrix [10]. Many factors induce apoptosis and secondary necrosis of smooth muscle cells and foam cells, which is an important reason for the formation of necrotic core and further inflammation is provoked by this necrotic debris [9]. These changes cause a gradual distortion of the architecture of the intima, and the dominant necrotic stems in the central part may eventually occupy 30% to 50% of the arterial wall [10].

In places of lesions, the tissue covering the necrotic core is initially the tissue of the inner membrane or its adaptive thickening. As the disease progresses, loose fibromuscular tissue is replaced by fibrous tissue rich in collagen, which forms the fibrous plaque. Elastin proteoglycans and collagen forming the fibrous matrix are mainly produced by smooth muscle cells [9]. Along with progressive atherosclerotic lesions calcifications appear, which with age appear more and more often. Over time, the necrotic core may completely calcify and even the most atherosclerotic plaque may calcify [9].

Atherosclerosis is a common disease, and the ratio of its occurrence in men is significantly higher than in women. The level of HDL and LDL cholesterol is related to the level of sex hormones. Also in postmenopausal women the increase of triglycerides, cholesterol, LDL and decrease of HDL (High Density Lipoprotein) concentration is observed. Estrogen and androgen receptors are present in the visceral and subcutaneous adipocytes, suggesting that endogenous sex hormones may influence lipid metabolism [13]. It was shown that activity of lipoprotein lipase enzyme is positively correlated with testosterone concentration and inversely correlated with estradiol concentration. Some studies showed the association of estrogens with favourable lipid profile and the association between androgens and unfavourable lipid profile [12]. What is more menopause seems to be associated with decrease of HDL2 subfraction levels and increase of cholesterol in the HDL3 levels [12].

**Laboratory tests used in diagnosis and monitoring atherosclerosis**

The onset of atherosclerotic lesions is a long-term process and its mechanism is not fully understood. A lot of evidence indicates that modified LDL and their uptake by macrophages have an important role in the development of atherosclerosis [14]. Increased LDL infiltration is promoted by elevated LDL and endothelial dysfunction, for example as a result of hemodynamic effects in hypertension or under the influence of bacterial toxins [15]. Epidemiological studies indicate that the quantitative and qualitative changes of plasma

lipoproteins are important, so-called lipid risk factors for atherosclerosis. The most important lipid risk factors for atherosclerosis include blood cholesterol [16].

The most commonly performed laboratory test is the measurement of total blood cholesterol, which can be carried out in a sample taken at any time. This is a kind of "screening test" for detecting people with hypercholesterolemia [17]. According to the recommendations, the best procedure is to assess the lipid profile including measurements of CH, HDL-CH and TG concentrations [18]. Based on them, in most cases, LDL-CH concentration can be calculated using the Friedewald formula [19]. For primary prevention, lipid profile assessment should be performed in all adults (> 20 years) once every 5 years [20]. During the 3 weeks preceding the examination, the patient should keep his usual diet and constant weight. More frequent measurements are necessary for people with multiple risk factors and people undergoing lipid-lowering treatment [21]. The tests included in the lipid profile should be performed in blood collected under standard conditions, on an empty stomach [22]. Plasma lipid concentrations are lower than in serum, so a constant choice of material for testing should be kept [23]. The diagnosis should be based on at least two tests performed within 2 to 3 weeks. During pregnancy, there is a physiological hyperlipidemia, during which time women should not be included in screening tests [24].

In practice, the measurements of apo B and apo A-I concentrations are also used [25]. Epidemiological studies have shown that this ratio is the strongest risk factor for atherosclerotic cardiovascular disease [26].

The measurements are carried out using enzymatic methods, allowed to eliminate lipid extraction steps from the plasma, and are also characterized by high specificity and precision [27]. Currently, methods of direct determination of LDL cholesterol are also increasingly used. When using direct methods, it is allowed to measure HDL-CH and LDL-CH in non-fasted blood [28].

**Clinical tests used in diagnosis and monitoring atherosclerosis**

As it comes from the origin of the word atherosclerosis causes the stiffness of arterial wall. There are many ways to examine it – ankle-brachial index (ABI), pulse wave velocity(PMV), brachial-ankle pulse wave velocity (baPMV) and the cardio-ankle vascular index (CAVI) [29].

Atherosclerosis may lead to peripheral artery disease which can result in intermittent claudication. The easiest way to diagnose atherosclerotic changes in the arteries of lower limb is measuring the ankle-brachial index(ABI). This method is easy, inexpensive and non-invasive. It may be also used to assess the cardiovascular risk in the future. To measure the

blood pressure on both arms and the ankle Doppler ultrasound and inflatable cuff is used [32][33]. Those methods are easy and available to detect the ongoing process of atherosclerosis. However, it is in decline in western societies due to the development of more accurate diagnostic tools. Nevertheless, the examination of arterial stiffness is used as an easy tool to screen patients in the office and in developing countries.

PMV is measured by applanation tonometer – it reconstructs the pressure wave in aorta based on the wave in peripheral arteries. It is a very reliable examination and is commonly used and accepted method to assess the risk of cardiovascular diseases [30]. The baPMV is to become a more simple solution in comparison to carotid-femoral pulse wave velocity (cfPMV) which is well-proven marker for increased cardiovascular risk. cfPMV is assessed by Doppler ultrasound or tonometry. The disadvantage of cfPMV is that measuring it requires trained medical staff and access to inguinal region. In comparison, baPMV is measured by an oscillometric method which is way easier in use in clinical practice [34]. There are studies claiming that baPWV correlates with cfPMV and aortic PMV measured in a direct way [35]. baPMV may be used to screen patients who are at risk of developing cardiovascular diseases [34].

Not only physical examination may be used to diagnose atherosclerosis. Nowadays medical imaging is an ultimate tool to diagnose and measure the progress of atherosclerosis. The imaging may be divided into non-invasive and invasive methods. The ultrasonography enables to observe the changes in arteries. Carotid arteries are examined in particular to detect the plaques and stenosis. Intima-media complex index is used as a predictor of cardiovascular diseases. Further non-invasive imaging methods are computed tomography and magnetic resonance imaging which allow the visualisation of the coronary arteries. Angiography may be an example of an invasive imaging method which may be useful in measuring the stenosis of arteries [31].

**Prevention and treatment**

In the menopausal period, women have a high increase in LDL cholesterol in a short time. Usually, it becomes noticeable around the age of 50. Hypercholesterolemia is the main cause of atherosclerosis  Therefore, in women of post-menopausal age, the problem of treating this disorder should be given special attention.

The most important in therapy is a lifestyle change - a healthy diet, weight reduction and physical exercise. Unfortunately, often the effectiveness of these methods is relatively low compared to pharmacological treatment. However, it should be remembered that a healthy

lifestyle should be carried out even during pharmacological treatment. This further increases the chances of therapeutic success [36].

Statins are among the most commonly used drugs in the treatment and prevention of hypercholesterolemia. They reduce the synthesis of cholesterol by inhibiting the 3-hydroxy-3-methylglutaryl coenzyme A reductase. Unfortunately, there are not many studies describing their effect on hypercholesterolemia in post- menopausal women. Michiya Igase, Katsuhiko Kohara, Yasuharu Tabara published a study in which they described the effect of one-year Rosuvastatin therapy on women in the menopausal age. The effects were visible. Changes such as reduction of LDL and non-HDL cholesterol levels and reduction of Carotid intima-media thickness were observed [37].

Mustafa H. Issa, Alvaro Cerda, Fabiana D.V. Genvigir carried out research on Atorvastatin. They described the effect of this drug on the expression of apolipoprotein gene mRNA. It is a protein involved in the metabolism of cholesterol and triglycerides in the body. Atorvastatin reduced the mRNA expression of the apolipoprotein gene in mononuclear peripheral blood cells. The consequence of this was not only the reduction of total cholesterol but also the level of triglycerides and VLDL cholesterol, which high concentration may also lead to atherosclerosis [38].

Studies on the use of hormone replacement therapy (HRT) in post-menopausal women has been conducted for over 30 years. Many works have been devoted to this issue. At the beginning of the twenty-first century, many scientific research began to suggest that the use of HRT brings more harm than benefits. First of all, there was an increase in the risk of breast cancer. Currently, it is claimed that the benefits of HRT in menopausal women outweigh the side effects, especially when therapy is started within the first 10 years of the beginning of menopause. HRT can be used in the prevention of diseases such as coronary artery disease or atherosclerosis. The use of hormone replacement therapy, especially estrogen, has a positive effect on the course of atherosclerosis in postmenopausal women. Its use has a beneficial effect on the lipid metabolism - it lowers LDL cholesterol and causes an increase in HDL cholesterol. In addition, HRT reduces calcification of coronary vessels, which correlates with the advancement of atherosclerosis. Consequently, it reduces the risk of cardiovascular events [39][40].

Statins and hormone replacement therapy are widely used therapies in the prevention and treatment of atherosclerosis in postmenopausal women. However, the question was asked: whether both these therapies can be combined? One of the concerns was whether statins, reducing cholesterol synthesis, would not affect the level of steroid hormones - estrogens and

androgens in the serum. A. Peck, S. Chaikittisilpa, R. Mirzaei published a study in which they ruled out the effect of statins on steroid hormone levels and suggested that combined estrogen and statin therapy could be used [41].

Another method of prevention and treatment of hypercholesterolemia and its effects - atherosclerosis are phytoestrogens. These are natural compounds that are similar in structure to endogenous estrogens. They occur in some fruits and vegetables such as cabbage, figs and sunflower seeds. Research on their use in therapy has been conducted for several years. It is suggested that the use of phytoestrogens may cause lowering of total and LDL cholesterol. However, their effectiveness is low, which means that they should be used only to prevent atherosclerosis and not to treat it. However, phytoestrogens are a big potential for further clinical trials [42].

**Discussion**

Comparing both genders by age, in population of women during the period, when the estrogen hormone is produced, cardiovascular disease rather occurs than in population of men in the same age. It is connected with progressive dysfunction of endothelium. After the menopause period, the weakening of endothelium is comparable in women and 60 years old men [43].

Thus, the naturally lowered estrogen hormone levels resulting from the organism stopping its production in postmenopausal period, leads to loss of ability to produce nitric oxide by the endothelium. Vasoconstriction is a reflection of endothelial dysfunction, which leading to an increase in atherosclerosis [43].

Important, according the Sullivan hypothesis from 1981, is the higher level of iron ions in postmenopausal period than premenopausal, has an impact to development of atherosclerosis. It is connected with formation of modified fraction ox-LDL which are internalized by macrophages, to create foam cells [44].

Furthermore, the accumulation of calcium in the arteries is the additional cause of increasing arterial resistance. There is no study confirming the impact on the destabilization of atherosclerotic plaque. However, the TNF- α factor from infiltrating macrophages and oxidative stress stimulate calcifying vascular cells (CVCs) differentiation to osteoblasts. The CVCs of mid-aortic muscle cells occurs with calcifying atherosclerotic lesions. The presence of indicators, like osteocalcin, alkaline phosphatase have been observed. According to science, this is the evidence of connection between atherosclerosis process and accumulating calcium ions in arteries. Moreover, researches' examination on calcium occurrence in the coronary

arteries was correlates with the LDL fraction level in the blood and others factors like glucose level, blood pressure. The HDL fraction decrease the differentiation of CVCs [45].

The oxidative stress has an impact, not only in stimulating CVCs differentiation [3], but also in the formation of hydroxyl radical, compatible with the mechanism of Fenton's reaction. This redox reaction uses the Fe3+ ions, which react with superoxide. In the second stage, reduces iron ions react with the hydrogen peroxide, forming the hydroxyl radical and hydroxyl anion. The first product, is necessary to oxidative modification of LDL. oxLDL activate endothelium and macrophages with the scavenger receptors leading to create foam cells, endothelial dysfunction and progress of atherosclerosis [45].

The researchers hypothesised that it is possible to have a protective effect that reduces the risk of cardiovascular disease by using hormone replacement therapy. However, the time of the starting therapy has a big impact to its effectiveness. Hormone replacement therapy increases the inflammatory processes in the arteries with advanced atherosclerotic changes, which causes additional development of atherosclerotic plaque [43].

**Conclusions**

Atherosclerosis is a serious problem among women in postmenopausal period. It is related with rapid increase in LDL cholesterol during menopause. Higher androgen levels and lower estrogen levels can lead to higher risk of cardiovascular disease, unfortunately there is no decisive results in studies. The elevated level of testosterone baseline is also not confirmed risk factor of atherosclerosis in this group of women.

Screening test measuring the total cholesterol level in blood with assessment of lipid profile is the best procedure in laboratory diagnosis of atherosclerosis risk.

With the ankle-brachial index (ABI) it is much easier to diagnose atherosclerotic changes in the arteries of lower limb, it is non-expensive, non-invasive and does not require specially trained medical staff.

In the case of postmenopausal atherosclerosis treatment there are positive effect with either use of Rosuvastatin or and Atorvastatin. Which in both cases leads to decreased levels of non-HDL cholesterol. The use of hormone replacement therapy can lower LDL cholesterol, increases HDL cholesterol and effectively reduces calcification of coronary vessels. Thus reducing the risk of cardiovascular diseases. Both estrogen and statin therapy can be combined as one treatment for atherosclerosis in postmenopausal women.

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