We are IntechOpen, the world's leading publisher of Open Access books
Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

BOOK CITATION INDEX
CLARIVATE ANALYTICS
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Overview of Some Risk Factors in Cardiovascular Disease

Elena Cojocaru, Alexandra Mastaleru,
Bogdan Tamba, Raluca Vasile,
Razvan Cosmin Tudor, Carmen Valerica Ripa,
Roxana Cobzaru and Maria Magdalena Leon

Additional information is available at the end of the chapter

Abstract

Much more specialists are nowadays aligning themselves on the view according to which the prevalence of cardiovascular disease will reach epidemic levels in the near future due to the increase of hypertension, diabetes and obesity. Most epidemiological studies indicate that we are confronted with a multiplication of risk factors, with an emphasis on their genetic conditioning as well as an acceleration of the effects generated by non-genetic factors. According to WHO recommendations, the appropriate methods of reducing the cardiovascular risk are those that combine health policies with efficient education measures. Long-term results of these measures aim to decrease the incidence of complications and associated costs with their treatment at the same time with increasing the quality of life. Approximately 50% of deaths from heart disease could be prevented through sustained action on the main cause—hypertension—and by treating risk factors, primarily hyperlipidemia and elevated body weight. Atherosclerotic disease requires a rigorous approach because identifying predisposing risk factors with proven implications in the initiation and progression of this disease, as well as modulation of those with protective role, can have a significant impact in finding an appropriate treatment in order to improve cardiovascular diseases and their consequences.

Keywords: hypertension, diabetes, obesity, atherosclerosis, metabolic syndrome

1. Introduction

Significant research has suggested that vascular segments that have fingerprints of the atherosclerotic lesions (endothelial dysfunctions, macrophage activation, cellular proliferation

and thrombosis) respond differently on medication, starting from the idea that we can accept as a initial point either inflammation or normal lipid profile perturbation [1, 2]. Therapeutic approach of the atherogenic dyslipidemia imposes the correlation with proatherogenic individual tendencies in order to correct the further risks. Atherosclerosis must be seen as a continuous process that starts from small endothelial dysfunctions and leads to important alterations of the vascular wall [3, 4]. The use of pharmacotherapeutic agents must be done in a tight correlation with the local pathophysiology, evaluating not only the risk factors but also the dynamic knowledge and clinical manifestations of this global disease [5, 6]. Although there are certain atherogenic risk factors considered causal agents for atherosclerosis, this disease can appear and evolve in their absence. Thus, there have been revealed atherosclerotic plaques in patients deceased from ischemic cardiomyopathy and especially from myocardial infarction, regardless of the blood pressure values, or the cholesterol and triglycerides values, and the presence or absence of smoking [7].

2. Main body

Myocardial infarction, stroke and venous thromboembolism represent the most important causes of death among female and men. Coronary heart disease, due to atherosclerosis, is a cause of myocardial infarction and is the first cause of death in women and men worldwide [7]. Strokes by venous or arterial thrombosis are more frequently in menopausal woman, whereas the stroke with cerebral hemorrhage, even if is less frequent, appears in young female and is caused by a cerebral vascular anomaly. Venous thrombosis includes superficial thrombosis that are autolimitated and deep thrombosis, most frequently at the level of pop-liteal and femoral vein. In approximately 10% of cases, a part of the thrombus or the entire thrombus can detach and determine pulmonary embolism [8].

Cardiovascular disease appears in coronary arteries when the atherosclerotic lesions evolve from an initial accumulation of isolated foam cells in the arterial intima to fatty streaks, fol-lowed by the accumulation of cholesterol deposits and atheroma formation. Once the atheroma is formed, the collagen from the fibrous cap stabilizes the plaque and prevents its rupture. But, matrix metalloproteinases, which are produced by the inflammatory cells from the lesion level, may degrade the collagen, and in case of a rupture of the fibrous cap, the resulted thro-mbus can block the affected coronary artery [9].

Cardiovascular disease may have their origin in the intrauterine life, but also a low birth weight and an extremely rich diet increase the risk of obesity and a specific metabolic syn-drome in adults. Cardiovascular disease incidence and mortality are very low in reproductive age women, but it increases with age [8].

Estradiol (E2) reduces the development of the early atherosclerotic lesions, in some measure, by its effects on the lipid metabolism, with a reduction of the lipid deposits from the intima. On the other hand, at the level of the already made atheroma, the estrogens increase the matrix metalloproteinases expression, which can lead to the disruption of the fibrous cap and the rupture of the plaque. In this case, a turbulent blood flow is produced; the estradiol

has thrombogenic properties and leads to clot formation that may obstruct the arterial lumen [10]. Therefore, through various mechanisms, the estrogens inhibit the early development of the atherosclerosis but at the same time increase the risk of complications once the atherosclerosis has been installed. Atherosclerotic lesions from the carotids and cerebral vessels may be affected by similar mechanisms; thus, in comparison with men, women are relatively protected by the thrombotic stroke before menopause, and any hormonal impact leads to changes in the status of the coagulation, anticoagulation and thrombotic factors [11].

World Health Organization conducted numerous studies regarding the mortality due to myocardial infarction, stroke and venous thromboembolism in many countries across the world [12]. Mortality by myocardial infarction in women increases exponentially with age. It is twice as high in American population as in the West Pacific population. The mortality rate of this condition is smaller in reproductive aged people, being 1–7 in 100,000 women aged 35–44 years/year. Reproductive aged women have 3–5 times smaller mortality rates than men, becoming similar over the age of 65 years. Consequently, age has a major influence because the number and the severity of the lesions increase with age; for this reason, the prevention of the atherosclerosis progression is very important, even in the seventh or eighth decade of life [13]. Atherosclerosis is not symptomatic until midlife or later, when the arterial lesions determine organ injury. However, cardiovascular signaling markers were frequently identified in children in the last few years. Anatomopathological examination of coronary arteries sampled from children who died in accidents showed fatty streaks and fibrous caps, in smoking, high blood pressure, obese or dyslipidemic subjects. Therefore, it is mandatory to identify the risk factors at an early age in order to prevent the premature appearance of myocardial infarction [14, 15]. Epidemiological studies revealed an increased incidence of myocardial infarction approximately five times higher in individuals between the ages of 40 and 60 years [16].

Hormonal contraceptives, pregnancy and polycystic ovary syndrome in young women and menopause in older women are directly linked with cardiovascular diseases [17]. The use of combined hormonal contraceptives has minor effects in cardiovascular disease, given the low incidence of myocardial infarction, stroke and venous thromboembolism in young women. However, women who already have risk factors or cardiovascular diseases should take into consideration alternative contraceptive methods. In pregnant women, cardiovascular diseases are rare; even in West countries they determine a significant proportion of maternal mortality compared to the substantial decrease of obstetrical mortality. The frequency of venous thromboembolism is 15 in 10,000 in pregnancy and post-partum period [18]. In older woman, it seems that menopause determines a higher risk of myocardial infarction, even if the results of numerous studies show a significant risk of heterogeneity. It is known that estrogen reduces the risk of developing atherosclerosis in premenopausal women, whereas in post-menopause, in women with atherosclerotic disease, the estrogen increases the risk of myocardial disease by its effects over the plaque stability and clot forming. The recent study results indicate that hormonal treatment in menopause does not always improve the risk of myocardial infarction, stroke or other vascular diseases. Thus, cardiovascular disease prevention should be based on diet and sport, small doses of platelet antiaggregant and treatment of high blood pressure, hyperglycemia and hyperlipidemia [19, 20].

The atherosclerosis complications are unusual in premenopausal women, with the exception of the ones predisposed to diabetes mellitus, hyperlipidemia or high blood pressure. The incidence of diseases related to atherosclerosis increases in menopause, probably being connected to the disappearance of the hormonal protection [16]. Some data demonstrated that estrogen replacement therapy has a favorable effect over the risk, increasing HDL and decreasing LDL levels [21]. The use of steroid hormonal contraceptives increases two to three times coronary atherosclerosis risk, mainly in smoking female over 35 years [22].

In the last few years, the criteria for metabolic syndrome have been reviewed: abdominal obesity, increased serum cholesterol, high blood pressure, insulin resistance with or without impaired glucose tolerance, pro-inflammatory status, a high level of C-reactive protein and a prothrombotic status with a high plasmatic fibrinogen and coagulation factors level [23].

Morphological and experimental studies have demonstrated connections between hyperlipidemia, especially hypercholesterolemia, and atherosclerosis, both in women and in men. The content of the atheroma plaque, which is made of cholesterol and cholesterol esters, the structure of the foam cells and the experimental production of atherosclerosis by a high-fat diet, has been initial arguments for the implication of lipids in atherosclerosis genesis. Cholesterol and triglycerides are the lipids with the highest impact for atherosclerosis and ischemic cardiomyopathy. Prospective studies showed that patients with a plasmatic cholesterol level over 260 mg% have a three or four times higher incidence of atherosclerosis than the patients with a level under 200 mg% [24]. From the total cholesterol, the major component that is associated with a high risk is LDL-cholesterol that has an essential physiological role in supplying the cholesterol to the peripheral tissue [25]. In opposition, HDL-cholesterol has the role of uptaking the cholesterol from the forming atheroma or from those already formed and transport it to the liver. Beside the ability of removing the cholesterol from the cellular level, HDL-cholesterol has anti-inflammatory, antioxidant and antithrombotic properties that contribute to the improvement of the endothelial function and atherosclerosis inhibition. Therefore, as the HDL-cholesterol level is higher, the risk of developing atherosclerosis lowers [26, 27]. In different experimental models, carbohydrate restriction proved to be efficient in the decrease of the plasmatic triglycerides, increase of HDL-cholesterol and modifying the repartition of the LDL-cholesterol [28]. The physical exercises and moderate consume of ethanol increase the HDL-cholesterol level, whereas the obesity and smoking decrease it. High cholesterol diets or saturated fats, like the ones from the butter, animal fats and yolk, increase the level of the plasmatic cholesterol, whereas the diets poor in cholesterol and polyunsaturated fats decrease it. Omega-3 fatty acids, found in fish oil, are probably beneficial, whereas the unsaturated fats produced by the artificial hydrogenation of the vegetable polyunsaturated fats and used in alimentation may influence negatively the cholesterol profiles, conducting to atherosclerosis. Beneficial effects of the omega fatty acids have been observed in the Northern countries, where the consumption of a large quantity of fish determined a decrease of the cardiovascular disease. If the cholesterol value cannot be diminished by diet, we can use drugs named statins that reduce the indirect circulating cholesterol by inhibiting the HMGCoA-reductase, a key enzyme necessary for the biosynthesis of the cholesterol in the liver [16, 29, 30]. From the existing statins on the market, studies showed the efficacy in cardiovascular disease prevention for Atorvastatin and Rosuvastatin [31].

Early coronary artery disease appears usually in patients with medical history of hypercholesterolemia. Numerous laboratory tests showed significantly higher levels of cholesterol and lower levels of HDL-cholesterol (especially of HDL2) in patients under 40 years old with coronary artery disease (men or women) compared to patients over 60 years old to whom the disease could be noticed [32].

The screening involves dosing cholesterol and LDL-cholesterol levels, and it is recommended to all the adults, especially to young people with a familial history of early ischemic cardiomyopathy. The actual dyslipidemia guideline highlights the importance of maintaining the LDL-cholesterol value within normal limits and reporting the cardiovascular disease to this value [33].

Polycystic ovary syndrome should be seen as a metabolic disease, with a high risk in developing diabetes mellitus type 2 and different cardiovascular disease [34]. If the glucose value is between 110 and 120 mg/dl, it is mandatory to perform the oral glucose tolerance test that allows us to precocious discover the diabetes mellitus and remove the complications. According to an international consent about the diagnostic criteria (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004), this syndrome is characterized by oligomenorrhea/amenorrhea, hyperandrogenism and polycystic ovaries. In addition, this syndrome is frequently associated with obesity and insulin resistance. Although women with this syndrome require medical assistance for unregulated menstrual cycles, hirsutism and infertility, it should not neglect the high risk of developing cardiovascular disease; therefore, clinician attention should be directed also to long-term prevention over these diseases [35].

Recent clinical studies regarding this syndrome established the existence of some metabolic risk factors in these women. The intermediary results include endothelial dysfunction, platelet dysfunction, increased number of leukocytes or high levels of C-reactive protein, coronary calcifications and the increase of the intima-media thickness at the carotid level. A study conducted on 161 patients with polycystic ovary syndrome also established frequent alterations in the metabolic syndrome parameters [36]. Regarding intermediate results, 33 women aged between 40 and 59 years, with histological confirmed syndrome, have been followed up to 2–3 decades concluding that they developed obesity, high prevalence of diabetes mellitus and high blood pressure, compared with a same aged group [37].

Concerning the cardiovascular events, limited studies on females with polycystic ovary syndrome provided contradictory results, even if it has been established a certain correlation with a metabolic syndrome. We must highlight the fact that most studies are retrospective, on a small number of patients, on a short follow-up and a lot of questions regarding the control groups [38, 39]. Large prospective cohort studies, like Framingham or Nurses Health Study, focused over results about cardiovascular disease or cancers, could not identify hyperandrogenism and anovulation as a separate risk phenotype. If we talk about American population, they can calculate their death risk by cardiovascular disease using Framingham score. In Europe, we should take into consideration SCORE risk charts (Systematic Coronary Risk Evaluation Project). This allows each person to simply calculate his death risk by cardiovascular disease in the next 10 years. It has the advantage that is very easy to use and all we need to know is gender, age, smoking status, blood pressure and cholesterol level. It can be used by

anybody and brings precious individualized information based on which it can be prescribed a treatment. A retrospective study from Great Britain, which included 786 women diagnosed with polycystic ovary syndrome between 1930 and 1979, could not establish the increase of the cardiovascular disease [40] or the morbidity [41] in these patients.

Cardiovascular disease is less frequent in women in reproductive age. First report regarding the cardiovascular disease as a secondary effect of the contraception took place in 1961, short after the discovery of the combined oral contraceptives [42]. Starting from 1960, estrogen and progesterone doses from contraceptive pills have been dramatically reduced and were created new progestatives that are theoretically safer. Substantial data regarding the effects of the combined oral contraceptives over the cardiovascular disease exist, but there are less evidence for the contraceptive pills that contain only progesterone [43].

High blood pressure is a condition characterized by an increase of the systolic value over 140 mmHg and of the diastolic value over 90 mmHg, being a major risk factor for atherosclerosis at all ages, females being less affected [16]. Prothrombotic condition and Lp(a) are two risk factors correlated with the development and the progression of the organic damage in high blood pressure and also in the evolution of the atherosclerotic process [44]. Antihypertensive drugs reduce the incidence of atherosclerosis-associated diseases, such as strokes and ischemic heart disease [45]. High blood pressure is a risk factor common in old people compared to young people with a myocardial infarction, frequently found in females [46]. Mechanisms by which the high blood pressure accelerates the atherogenesis include: the direct lesion of the endothelial cells from the susceptible zones from the mechanic stress exercised over the vascular lumen, the alteration of the endothelial permeability with the increase of the lysosomal enzymes activity, the gradual thickening of the arterial intima caused by the proliferation of the smooth muscle fiber and connective tissue components [16].

Another extremely important risk factor involved in women atherosclerosis is heredity. Variable damage of the genes together with the environmental factors determines a different atherogenic predisposition among the population. It has not been identified yet a genetic marker for atherosclerosis, but it seems that the genetic predisposed subjects for this degenerative disease are more vulnerable if associated with risk factors. Familial predisposition to atherosclerosis and ischemic heart disease is most probably polygenic [16] and normally is associated with other risk factors, like high blood pressure and diabetes mellitus. Familial risk for ischemic cardiomyopathy is extremely high in some dyslipidemia: familial hypercholesterolemia, polygenic hypercholesterolemia and polygenic hypoalphalipoproteinemia [47].

Numerous proatherogenic factors have been discovered in various studies. Apolipoprotein E, with its three principal variants (E2, E3, E4), is a good example of genetic polymorphism involved in the atherosclerotic process [48]. In different populations, it was demonstrated that Apo E polymorphism is a major determinant for coronary disease. The risk of myocardial infarction is smaller in patients with epsilon 2–E2 allele than the patients with epsilon 4–E4 allele [49]. A decreased frequency of epsilon 4 allele has been found in the Northern countries of Europe, whereas this increases in the Southern Europe, like the cardiovascular disease mortality rate. In addition, a strong relationship between the medical history and the epsilon 4 Apo E distribution was established. Despite normal LDL, HDL and total cholesterol

values, Apo E polymorphism has been associated with negative prognostic, which raised the hypothesis that epsilon 4 allele represents a determinant factor for accelerated atherosclerosis in young people with myocardial infarction, by the modulation of other risk factors [50].

Decreased arterial compliance has a high predictive value for cardiovascular events, so its evaluation becomes an important objective in investigating the arterial function [51]. Various epidemiological and clinical studies brought arguments for a genetic component that is involved in the modulation of the arterial wall properties, unrelated with other risk factors [52]. An important number of genes that might affect the structure and role of the arterial wall exist (genes implied in different signaling paths and in modulating the extracellular matrix), and their identification is extremely important, offering on the one hand new biomarkers that are useful in evaluating the arterial compliance, and on the other hand new therapeutic targets in order to decrease the vascular rigidity [53, 54]. Currently, the arteriography allows the noninvasive quantification of vascular rigidity and long-term monitoring in cardiovascular rehabilitation programs.

Recent studies have shown that smoking is the most important adjustable risk factor in women and men under 40 years old with acute coronary syndrome, being observed in mostly equal parts in those with normal coronary arteries and in those with lesions on one or more coronary arteries [55]. Smoking is involved in endothelial dysfunction by reducing the production of the nitric oxide, causing the coronary spasm [37]. Smoking one pack a day or more than one pack for years increases the ischemic cardiac disease mortality rate up to 200%. Smoking cessation considerably reduces the risk of developing the disease [16, 56].

Diabetes mellitus induces hypercholesterolemia and in consequence an increase in predisposition for atherosclerosis in both male and female. The incidence of the myocardial infarction is two times higher at patients with diabetes mellitus compared to patients without diabetes. Also they have a higher risk for strokes and it increases almost 100 times the risk of the gangrene on the inferior limb, induced by atherosclerosis, being most often discovered at smoker patients with diabetes [16]. This disease affects the elastic properties of the arterial wall, no matter the presence of other risk factors or intimal damage in patients with peripheral vascular disease [57]. Acute hypoglycemia causes important physiological changes, affecting cardiovascular system and some hematological parameters, mainly as a consequence of the sympatho-adrenergic activation. In healthy adults, cardiovascular effects are transitory and do not have severe consequences, but can become pathological in patients with diabetes that already have endothelial dysfunction. The risk of localized tissue ischemia may be increased by acute hemodynamic and hematologic alterations; also, major vascular events like myocardial or cerebral ischemia may be precipitated by acute hypoglycemia [58]. Clinical and experimental studies sustain the idea that insulin resistance syndrome and increased levels of circulating insulin are involved in cardiac ischemic disease [59].

High blood pressure and diabetes mellitus are risk factors associated most of the time in patients with cardiovascular diseases. Impaired glucose tolerance is accompanied by an increase in the thickness and the rigidity of great vessels, which determines high blood pressure, macrovascular complications and decreased renal function [60]. Chronic hypertension and diabetes produce physiopathological changes both in great vessels and in microvascularization.

The increase of the arterial rigidity leads to increased systolic pressure and pulse pressure that conducts to a fall in the coronary perfusion. The remodeling of the resistance arteries and the capillary rarefaction causes the growth of the peripheral resistance, with high blood pressure and the amplification of the negative hemodynamic effects of the reduced arterial compliance; therefore, therapeutic interventions that must stop these vascular changes should have the aim to increase the central systolic pressure and the increase of the vascular bed perfusion [61, 62].

Patients with homocystinuria, which is a congenital metabolic disorder, characterized by elevated levels of circulating homocysteine (> 100 μmol/L) and urinary homocysteine, presents an early vascular injury [63]. Clinical and epidemiological studies revealed a connection between the serum levels of homocysteine and peripheral vascular disease, coronary artery disease, stroke, venous thrombosis, meaning that a high concentration of homocysteine is associated with the progression of the atherosclerosis [64]. Also, high concentrations of homocysteine imperil the endothelial function, increase the oxidative stress, affect the methylation reactions and alter the protein structures [63]. Hyperhomocysteinemia can be caused by the reduced absorption of the folic acid and B type vitamins and, in consequence, recent data suggest that folic acid and B6 vitamin ingestion, together with a proper diet, could reduce the incidence of cardiovascular disease, but this remains to be established in further studies [16]. An increase of homocysteine concentration is correlated with a 10% risk of coronary disease. The increase of homocysteine up to 5 micromol/L carries a 41% higher risk, similar to a cholesterol increase with 0.52 micromol/L (20 mg/L). Smoking and high blood pressure amplify the atherogenic action of high homocysteine levels. The association between hyperhomocysteine and factor V Leiden increases three to six times the thrombosis risk [65, 66].

A particular interest is conferred to the infectious etiology of atherosclerosis. Viral infections (herpes viruses, HIV-1), *Mycoplasma* or *Chlamydia* can affect the endothelial cell function and thus an increased adherence of the leukocytes and thrombocytes at the injured vascular section [67, 68]. Numerous studies showed that atherosclerosis can be the consequence of the adaptive immunity due to microbial HSP-60 (Heat Shock Protein-60). Stress factors induce the growth of the HSP expression on the endothelial cells and the cross-reactivity between the antibodies and the microbial HSP that lead to autoimmune reaction and accelerated atherosclerosis. The association between the infectious syndrome and coronary disease has been reported in many studies [69].

It has been issued the hypothesis that the infection of the vascular wall with pathogen agents like *Chlamydia pneumoniae* or cytomegalovirus (CMV) contributes to the appearance of atherosclerosis by insertion of new antigens in the vessel wall [70, 71]. *C. pneumoniae* was evidenced by direct immunofluorescence on endarterectomy pieces or by antibodies anti-*C. pneumoniae* in plasma. *Chlamydia pneumonia* and CMV were absent in non-atherosclerotic vessels. The use of antibiotics in certain infections limits the atherosclerotic process [72].

At vascular wall level where atherosclerosis appears, there is a particular accumulation of mononuclear cells, CD4+ and CD8+ lymphocytes [73]. Endothelial cells, macrophages and dendritic cells have a role of antigen-presenting cells [72]. Infectious agents can infect macrophages and persist for a long time at their level, producing proinflammatory cytokine (INF-γ,

TNF-α, IL-1, IL-6, IL-8), metalloproteinase and integrins [74, 75]. It is important to mention the antigenic mimetism between oxidized LDL and *Streptococcus pneumoniae*; subsequently, the vaccination with pneumococcal antigen induces an immune response against oxidized LDL that might immunomodulate the atherosclerosis process [76].

Other factors that are hard to evaluate include the physical effort, type A of personality (characterized by a stressed lifestyle), obesity; they determine high blood pressure, diabetes mellitus, hypertriglyceridemia and increase of LDL-cholesterol [16]. Regularly physical activity induces the increase of HDL-cholesterol, slowing the atherogenesis process and preventing ischemic cardiomyopathy. Physical and emotional stress and anxiety seem to be precipitating factors for ischemic heart disease and sudden death [77]. In Framingham study, cardiovascular disease incidence was two times higher in obese men and 2.5 times in obese women under 50 years old [78]. Adipose tissue considered for a long time just a fat source, seems to be a proinflammatory endocrine and paracrine secretion organ. It is recognized as being an important source of proinflammatory mediators that can contribute in vascular injury, insulin resistance and atherogenesis. So the inflammation of the adipose tissue can be an important step in developing numerous manifestations in connection with pathological characteristics of metabolic syndrome and may lead to diabetes and atherosclerosis [79, 80]. Defining a relevant obesity phenotype for cardiovascular risk can be done by adipocytokine identification, biomarkers that quantify the metabolic activity of the adipose tissue [81]. According to their effect, adipocytokines can be classified into proinflammatory adipocytokines, mediators of endothelial dysfunction and atherosclerosis that include TNF-α (tumor necrosis factor), IL-6 (interleukin 6), leptin, plasminogen activator inhibitor (PAI-1), angiotensinogen, resistin and C-reactive protein (CRP), and adipocytokines with antiatherosclerotic role represented by nitric oxide (NO) and adiponectin [82].

Multiple risk factors cumulate their effects. The presence of two risk factors increases the risk almost four times; if there are three risk factors, the rate of myocardial infarction increases seven times. Also, the level of exposure at risk factors determines considerable variations in the evolution of the atherosclerotic process and this is the reason why and early determination through different methods would be extremely useful in the evaluation of the cardiovascular risk [83]. Atherosclerosis and its consequences may develop in the absence of any risk factor, even in people who have a healthy life and without an apparent genetic predisposition [16].

In accordance with European Society of Cardiology Guidelines on Cardiovascular Disease Prevention (2007), the population should follow the next formula: 0 3 140 5 3 0, which suggest crucial measurements in keeping the cardiovascular health: without smoking (0), walking 3 km per day or 30 min of moderate activity (3), systolic pressure less than 140 mmHg (140), total cholesterol under 5 mmol/L (5), LDL-cholesterol under 3 mmol/L (3), eviction of obesity and diabetes (0) [84]. Actual guides recommend performing moderate physical activity minimum 30 min per day five times a week [85].

Epidemiologic data show that there are some hemostatic, thrombolytic and inflammation markers that are potential predictors of the risk for major atherosclerotic events, including myocardial infarction and stroke. These markers are related to fibrinolysis (e.g.: PAI 1—plasminogen activator inhibitor 1) or inflammation (CRP—C-reactive protein). PAI-1 plays an important role

in cardiovascular diseases, mostly by inhibiting t-PAC (tissue plasminogen activator) [16, 86]. Inflammation biomarkers, especially CRP and lipoprotein-associated A2 phospholipase, are considered not only as potential risk predictors for stroke but also as prognostic factors [87]. CRP is considered to be a new proatherogenic inflammatory adipocytokine. CRP is an acute phase reactant, being synthesized mostly by the liver and regulated by circulating levels of IL6, IL1 and TNF-α. Recent studies demonstrated that high sensitive CRP is not only an atherosclerotic inflammatory marker but also a disease progression mediator, contributing to the formation and progression of the atheromatous plaque by promoting inflammation, thrombogenesis and modulatory endothelial function [88]. CRP induces the expression of adhesion molecule, selectins and MCP1 in endothelial cellular cultures, by increasing secretion of ET1 and IL6, and also stimulating angiotensin II action over receptors. By inhibiting NO endothelial secretions, CRP diminishes basal production and stimulated production of endothelial NO. CRP effect is potentiated by hyperglycemia and diminished by thiazolidinedione, an insulin sensitizer agent. CRP may also amplify proinflammatory activity of other adipokines, for example, PAI-1 intervention in the suppression of fibrinolysis and thrombogenesis by the inhibition of the activated plasminogen [89]. Increased plasmatic levels of PAI-1 are directly correlated with the cardiovascular risk and type 2 diabetes development. Even if platelets and endothelial cells represent a major source of PAI-1, in men, adipose tissue produces, also, PAI-1. Increased plasmatic levels of PAI-1 are found in obese patients and decrease with lowering weight [90].

Latest advances confirmed the role of Lp-PLA2 in advanced coronary disease evolution, being an important linking factor between lipid homeostasis and vascular inflammatory response. Selective inhibition of Lp-PLA2 reduces the development of the inner core atheroma and leads to plaque stabilization [91]. A lipoprotein is a lipid fraction that looks like an independent risk factor for atherosclerosis. It represents a modified LDL-cholesterol that has a characteristic protein fragment covalent linked to apo B and named apo(a), with an polymorphism and a structural analogy with the plasmatic plasminogen. Also, it has a complex prothrombotic action. Thus, Lp(a) seems to make the connection between atherosclerosis and thrombosis, the two processes being tightly related in atherosclerosis evolution [16, 92].

Serum amyloid A is an acute phase reactant, like CRP, that has been associated with systemic inflammation, related to the atherosclerosis process and used as a predictor for coronary disease and for cardiovascular prognosis. Levels of serum amyloid A are significantly correlated to insulin resistance and obesity in type 2 diabetes patients. Adipose tissue maintains amyloid at low levels in normal conditions, but an excess of it seems to stimulate this reactant. Serum amyloid A replaces apolipoprotein 1 from HDL-cholesterol, increasing the macrophage bond HDL and decreasing the cardioprotective HDL [81].

TNF-α is an inflammatory cytokine, which is released in high levels by obese patients and those with an increased insulin resistance, and contributes to the initiation and development of the atherosclerotic lesions. TNF-α activates the NF-κB nuclear factor transcription that accelerates the experimental atherosclerosis, partly by inducing the adhesion molecular expression, MCP-1 and E-selectin, in vascular smooth muscle cells and aortic endothelium. TNF-α reduces the bioavailability of nitric oxide in endothelial cells and modifies the endothelial-dependent vasodilatation, promoting its dysfunction; in addition of these effects, it might also induce apoptosis in endothelial cells [81].

Epidemiological research showed an obviously different frequency of atherosclerosis between geographic regions. The explanations are related to physicochemical properties of the drinking water and the meteorological factors. Oligoelements as calcium, magnesium, manganese, lithium, zinc, chrome and fluorine have proven antiatherogenic properties. It is known that the chronic absence of some oligoelements from the drinking water, with a consecutive decrease of its hardness is accompanied by an increase of the cardiovascular disease frequency. The opposite is the plumb excess and mostly the cadmium excess, which characterizes the soft water. Meteorological factors do not seem to be implied in the mechanism of the disease development. However, they represent important indicators of a major coronary accident occurrence, on an atherosclerotic fond [93].

Socioeconomical factors also increase the atherogen risk among the population: overstrain in the work place, physical and intellectual overexertion, sudden and frequent changes in the way of life and work, commuting, increased professional and familial responsibilities, conflictual states (familial, professional), social unintegration, irrational use of food, sedentary state, alcohol and excessive smoking. These situations are usually accompanied by an increased level of catecholamines, plasmatic lipids and blood pressure, which involves an intensified aggression over heart vessels [94].

An efficient therapeutic strategy presumes not only obtaining regression or retreat of existing atheroma but also modulating vascular impact in the beginning. It is important to mention the fact that atherosclerosis is one of the most frequent vascular disease in developed countries.

It is well known that the negative effect of high blood pressure over atherosclerosis needs a critical level of circulating lipoproteins [95]. However, antihypertensive treatment effects on atherosclerotic fond are not sufficiently known. Decoding the complex cellular and molecular mechanisms of atherogenesis process might certainly influence the therapeutic choice. Even if it has been tried on numerous ways to reduce LDL-cholesterol, there are a whole series of cardiovascular disease that cannot be efficiently treated. Starting from some medication that is centered over HDL, this promotes some certain antiatherogenic effects: antioxidative, antiinflammatory, antithrombosis and endothelial stabilization [96].

Considering atherosclerosis as a disease with inflammatory substrate, in the acute phase HDL (that normally is anti-inflammatory) may become proinflammatory. Reactive species of oxygen generate an enzymatic system that can modify phospholipids and sterols by oxidation, reducing the HDL-cholesterol protection capacity against the unwanted oxidative changes at the molecular level [97].

Some experimental studies suggest that the use of mimetic peptides, such as apolipoprotein A-1, is capable of removing the oxidative products from lipoproteins and cellular membranes, giving back the normal structure and function of HDL-cholesterol [98]. In order to correct the HDL value, we currently use two classes of compounds: fibric acid derivatives and niacin derivatives. Dyslipidemia is considered as one of the main atherosclerotic risk factors and represents one of the atherogenic therapeutic targets [99].

Modern studies posit the therapy with cardiovascular cells (by exogenous ingestion or by an endogenous cellular mobilization) as effective in preventing and treating atherosclerotic

lesions. Using bone marrow cells or autolog skeletal myoblasts in the beginning, it could be observed the fact that cardiac regeneration is produced through a variable repopulation accompanied by adjacent revascularization. Nowadays, the mesenchymal stem cells have large-scale utilization because of the immunosuppressant capacity and the ability to locate in the damaged tissue areas. The ability of stem cells to form myocardial cells has been studied both in vivo and in vitro research [100, 101]. Cardiomyoplasty is already used as a regeneration method of the damaged myocardium, using different cellular types [102]. This myocardial reconstructive technique, which is under a clinical evaluation and a rigorous immunological monitorization, could change the approach of cardiovascular disease therapy in the near future.

Author details

Elena Cojocaru[1], Alexandra Mastaleru[2]*, Bogdan Tamba[3], Raluca Vasile[4], Razvan Cosmin Tudor[5], Carmen Valerica Ripa[6], Roxana Cobzaru[6] and Maria Magdalena Leon[2]

*Address all correspondence to: alexandra.mastaleru@gmail.com

1 "Gr.T.Popa" University of Medicine and Pharmacy, Discipline of Morphopathology, Iasi, Romania

2 "Gr.T.Popa" University of Medicine and Pharmacy, Discipline of Medical Semiology, Iasi, Romania

3 "Gr.T.Popa" University of Medicine and Pharmacy, Discipline of Pharmacology, Iasi, Romania

4 Psychiatrist in Sf. Nicolae Psychiatric Hospital, Roman, Romania

5 Orthopedic Surgeon in Regional Hospital of Vaslui, Romania

6 "Gr. T. Popa" University of Medicine and Pharmacy, Discipline of Parasitology, Iasi, Romania

References

[1] Poredos P, Jezovnik MK. Does the preventive effect of different drugs depend on location of the atherosclerotic process? International Angiology. 2008;**27**(4):274-280

[2] Fuster V. Chronic multivessel disease: Past, present and future. Rev Esp Cardiol. 2008;**61**(Suppl 2):2-9

[3] Rizzo M, Rizvi AA, Rini GB, Berneis K. The therapeutic modulation of atherogenic dyslipidemia and inflammatory markers in the metabolic syndrome: What is the clinical relevance? Acta Diabetologica. 2009;**46**(1):1-11. DOI: 10.1007/s00592-008-0057-4

[4] Segers D, Weinberg P, Krams R. Atherosclerosis: Cell biology and lipoproteins--shear stress and inflammation in plaque formation: New evidence. Current Opinion in Lipidology. 2008;**19**(6):627-628. DOI: 10.1097/MOL.0b013e328318db32

[5] Moreno PR, Sanz J, Fuster V. Promoting mechanisms of vascular health: Circulating progenitor cells, angiogenesis, and reverse cholesterol transport. Journal of the American College of Cardiology. 2009;**53**(25):2315-2323. DOI: 10.1016/j.jacc.2009.02.057

[6] Lamon BD, Hajjar DP. Inflammation at the molecular interface of atherogenesis: An anthropological journey. American Journal of Pathology. 2008;**173**(5):1253-1264. DOI: 10.2353/ajpath.2008.080442

[7] Rafieian-Kopaei M, Setorki M, Doudi M, Baradaran A, Nasri H. Atherosclerosis: Process, indicators, risk factors and new hopes. International Journal of Preventive Medicine. 2014;**5**(8):927-946

[8] ESHRE Capri Workshop Group. Hormones and cardiovascular health in women. Human Reproduction Update. 2006;**12**(5):483-497. DOI: 10.1093/humupd/dml028

[9] Butcovan D, Mocanu V, Baran D, Ciurescu D, Tinica G. Assessment of vulnerable and unstable carotid atherosclerotic plaques on endarterectomy specimens. Experimental and Therapeutic Medicine. 2016;**11**(5):2028-2032. DOI: 10.3892/etm.2016.3096

[10] Phillips LS, Langer RD. Postmenopausal hormone therapy: Critical reappraisal and a unified hypothesis. Fertility and Sterility. 2005;**83**(3):558-566. DOI: 10.1016/j.fertnstert.2004.11.012

[11] Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J. Long-term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database of Systematic Reviews. 2017;**1**:CD004143. DOI: 10.1002/14651858.CD004143.pub5

[12] World Health Organization. Global Health Observatory (GHO) data [Internet]. Available from: http://www.who.int/gho/mortality_burden_disease/en/

[13] Sawabe M, Arai T, Kasahara I, Hamamatsu A, Esaki Y, Nakahara K et al. Sustained progression and loss of the gender-related difference in atherosclerosis in the very old: A pathological study of 1074 consecutive autopsy cases. Atherosclerosis. 2006;**186**(2):374-379. DOI: 10.1016/j.atherosclerosis.2005.07.023

[14] Chan MY, Woo KS, Wong HB, Chia BL, Sutandar A, Tan HC. Antecedent risk factors and their control in young patients with a first myocardial infarction. Singapore Medical Journal. 2006;**47**(1):27-30

[15] Anderson RE, Pfeffer MA, Thune JJ, McMurray JJ, Califf RM, Velazquez E et al. High-risk myocardial infarction in the young: The VALsartan In Acute myocardial iNfarcTion (VALIANT) trial. American Heart Journal. 2008;**155**(4):706-711. DOI: 10.1016/j.ahj.2007.11.016

[16] Kumar V, Abbas A, Aster J. Robbins & Cotran Pathologic Basis of Disease. 9th ed. Elsevier Philadelphia; 2015. 1408 p

[17] ESHRE Capri Workshop Group. Venous thromboembolism in women: A specific reproductive health risk. Human Reproduction Update. 2013;**19**(5):471-482. DOI: 10.1093/humupd/dmt028

[18] Liu S, Rouleau J, Joseph KS, Sauve R, Liston RM, Young D et al. Epidemiology of pregnancy-associated venous thromboembolism: A population-based study in Canada. Journal of Obstetrics and Gynaecology Canada. 2009;**31**(7):611-620

[19] Atsma F, Bartelink ML, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: A meta-analysis. Menopause. 2006;**13**(2):265-279. DOI: 10.1097/01.gme.0000218683.97338.ea

[20] Archer DF. Premature menopause increases cardiovascular risk. Climacteric. 2009;**12** (Suppl 1):26-31

[21] Lobo RA. Menopause and stroke and the effects of hormonal therapy. Climacteric. 2007;**10**(Suppl 2):27-31. DOI: 10.1080/13697130701550903

[22] Shufelt CL, Bairey Merz CN. Contraceptive hormone use and cardiovascular disease. Journal of the American College of Cardiology. 2009;**53**(3):221-231. DOI: 10.1016/j.jacc. 2008.09.042

[23] Grundy SM, Hansen B, Smith SC Jr, Cleeman JI, Kahn RA, American Heart Association, et al. Clinical management of metabolic syndrome: Report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. Arteriosclerosis, Thrombosis, and Vascular Biology. 2004;**24**(2):e19–e24. DOI: 10.1161/01.ATV.0000112379.88385.67

[24] Talayero BG, Sacks FM. The role of triglycerides in atherosclerosis. Current Cardiology Reports. 2011;**13**(6):544-552. DOI: 10.1007/s11886-011-0220-3

[25] Daniels TF, Killinger KM, Michal JJ, Wright RW Jr, Jiang Z. Lipoproteins, cholesterol homeostasis and cardiac health. International Journal of Biological Sciences. 2009;**5** (5):474-488

[26] Hausenloy DJ, Yellon DM. Targeting residual cardiovascular risk: Raising high-density lipoprotein cholesterol levels. Heart. 2008;**94**(6):706-714. DOI: 10.1136/hrt.2007.125401

[27] Cardenas GA, Lavie CJ, Cardenas V, Milani RV, McCullough PA. The importance of recognizing and treating low levels of high-density lipoprotein cholesterol: A new era in atherosclerosis management. Reviews in Cardiovascular Medicine. 2008;**9**(4):239-258

[28] Fernandez ML, Volek JS. Guinea pigs: A suitable animal model to study lipoprotein metabolism, atherosclerosis and inflammation. Nutrition & Metabolism (London). 2006;**27**(3):17. DOI: 10.1186/1743-7075-3-17

[29] Kapur NK, Musunuru K. Clinical efficacy and safety of statins in managing cardiovascular risk. Vascular Health and Risk Management. 2008;**4**(2):341-353

[30] Nesto RW. Beyond low-density lipoprotein: Addressing the atherogenic lipid triad in type 2 diabetes mellitus and the metabolic syndrome. American Journal of Cardiovascular Drugs. 2005;**5**(6):379-387

[31] Kim HS, Lee H, Park B, Park S, Kim H, Lee SH et al. Comparative analysis of the efficacy of low- and moderate-intensity statins in Korea. International Journal of Clinical Pharmacology & Therapeutics. 2016;**54**(11):864-871. DOI: 10.5414/CP202332

[32] Li Z, Tao Y, Huang J, Wang Q, Zhang DH, Wu XY. The characteristics of high density lipoprotein cholesterol and the relationship between high density lipoprotein cholesterol and the severity of coronary artery lesions in young men with acute myocardial infarction. Zhonghua Yi Xue Za Zhi. 2013;**93**(19):1458-1462

[33] Stone NJ, Robinson J, Lichtenstein AH, Merz CNB, Blum CB, Eckel RH et al. ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults. Circulation. 2013. DOI: 10.1161/01.cir.0000437738.63853.7a

[34] Velija-Asimi Z, Burekovic A, Dujic T, Dizdarevic-Bostandzic A, Semiz S. Incidence of prediabetes and risk of developing cardiovascular disease in women with polycystic ovary syndrome. Bosnian Journal of Basic Medical Sciences. 2016;**16**(4):298-306. DOI: 10.17305/bjbms.2016.1428

[35] Sim SY, Chin SL, Tan JL, Brown SJ, Cussons AJ, Stuckey BG. Polycystic ovary syndrome in type 2 diabetes: Does it predict a more severe phenotype? Fertility and Sterility. 2016;**106**(5):1258-1263. DOI: 10.1016/j.fertnstert.2016.06.040

[36] Apridonidze T, Essah PA, Iuorno MJ, Nestler JE. Prevalence and characteristics of the metabolic syndrome in women with polycystic ovary syndrome. Journal of Clinical Endocrinology and Metabolism. 2005;**90**(4):1929-1935. DOI: 10.1210/jc.2004-1045

[37] Dahlgren E, Johansson S, Lindstedt G, Knutsson F, Odén A, Janson PO et al. Women with polycystic ovary syndrome wedge resected in 1956 to 1965: A long-term follow-up focusing on natural history and circulating hormones. Fertility and Sterility. 1992;**57**(3):505-513

[38] Hudecova M, Jan H, Christian B, Poromaa Inger S. Long-term reproductive and metabolic consequences of PCOS. Current Diabetes Reviews. 2012;**8**(6):444-451

[39] Zhao L, Zhu Z, Lou H, Zhu G, Huang W, Zhang S et al. Polycystic ovary syndrome (PCOS) and the risk of coronary heart disease (CHD): A meta-analysis. Oncotarget. 2016;**7**(23):33715-33721. DOI: 10.18632/oncotarget.9553

[40] Pierpoint T, McKeigue PM, Isaacs AJ, Wild SH, Jacobs HS. Mortality of women with polycystic ovary syndrome at long-term follow-up. Journal of Clinical Epidemiology. 1998;**51**(7):581-586

[41] Wild S, Pierpoint T, McKeigue P, Jacobs H. Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: A retrospective cohort study. Clinical Endocrinology. 2000;**52**(5):595-600

[42] Jordan WM, Anand JK. Pulmonary embolism. Lancet. 1961;**278**(7212):1146-1147. DOI: 10.1016/S0140-6736(61)91061-3

[43] Samson ME, Adams SA, Merchant AT, Maxwell WD, Zhang J, Bennett CL et al. Cardiovascular disease incidence among females in South Carolina by type of oral contraceptives, 2000-2013: A retrospective cohort study. Archives of Gynecology and Obstetrics. 2016;**294**(5):991-997. DOI: 10.1007/s00404-016-4143-5

[44] Catena C, Novello M, Lapenna R, Baroselli S, Colussi G, Nadalini E et al. New risk factors for atherosclerosis in hypertension: Focus on the prothrombotic state and lipoprotein (a). Journal of Hypertension. 2005;**23**(9):1617-1631

[45] Bönner G, Gysan DB, Sauer G. Prevention of arteriosclerosis. Importance of the treatment of arterial hypertension. Zeitschrift für Kardiologie. 2005;**94**(Suppl 3):56-65. DOI: 10.1007/s00392-005-1308-9

[46] Shklovskii BL, Prokhorchik AA, Koltunov AN, Lishchuk AN, Ryzhman NN, Ivanov AV et al. Myocardial infarction in young population. Voenno-Meditsinskiĭ Zhurnal. 2015;**336**(3):38-46

[47] Pérez de Isla L, Alonso R, Mata N, Saltijeral A, Muñiz O, Rubio-Marin P et al. Coronary heart disease, peripheral arterial disease, and stroke in familial hypercholesterolaemia: Insights from the SAFEHEART registry (Spanish Familial Hypercholesterolaemia Cohort Study). Arteriosclerosis, Thrombosis, and Vascular Biology. 2016;**36**(9):2004-2010. DOI: 10.1161/ATVBAHA.116.307514

[48] Davignon J. Apolipoprotein E and atherosclerosis. Beyond lipid effect. Arteriosclerosis, Thrombosis, and Vascular Biology. 2005;**25**(2):267-269. DOI: 10.1161/01.ATV.0000154570.50696.2c

[49] Bennet AM, Di Angelantonio E, Ye Z, Wensley F, Dahlin A, Ahlbom A et al. Association of apolipoprotein E genotypes with lipid levels and coronary risk. JAMA. 2007;**298**(11):1300-1311. DOI: 10.1001/jama.298.11.1300

[50] Heide S, Manfred K, Gläser C, Schulz S. Apolipoprotein E (apoE) polymorphism: A risk factor for fatal coronary sclerosis? Forensic Science International. 2009;**192**(1-3):62-66. DOI: 10.1016/j.forsciint.2009.07.020

[51] Nürnberger J, Kribben A, Philipp T, Erbel R. Arterial compliance (stiffness) as a marker of subclinical atherosclerosis. Herz. 2007;**32**(5):379-386. DOI: 10.1007/s00059-007-3030-z

[52] Lacolley P, Challande P, Osborne-Pellegrin M, Regnault V. Genetics and pathophysiology of arterial stiffness. Cardiovascular Research. 2009;**81**(4):637-648. DOI: 10.1093/cvr/cvn353

[53] Yasmin, O'Shaughnessy KM. Genetics of arterial structure and function: Towards new biomarkers for aortic stiffness? Clinical Science (London). 2008;**114**(11):661-677. DOI: 10.1042/CS20070369

[54] Kingwell B, Boutouyrie P. Genetic influences on the arterial wall. Clinical and Experimental Pharmacology & Physiology. 2007;**34**(7):652-657. DOI: 10.1111/j.1440-1681.2007.04655.x

[55] Trzos E, Uznańska B, Rechciński T, Krzemińska-Pakuła M, Bugała M, Kurpesa M. Myocardial infarction in young people. Cardiology Journal. 2009;**16**(4):307-311

[56] Teo KK, Ounpuu S, Hawken S, Pandey MR, Valentin V, Hunt D,. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: A case-control study. Lancet. 2006;**368**(9536):647-658. DOI: 10.1016/S0140-6736(06)69249-0

[57] Makita S, Matsui H, Naganuma Y, Abiko A, Tamada M, Nakamura M. Diabetic state as a crucial factor for impaired arterial elastic properties in patients with peripheral arterial disease. Atherosclerosis. 2010;**208**(1):167-170. DOI: 10.1016/j.atherosclerosis.2009.06.033

[58] Wright RJ, Frier BM. Vascular disease and diabetes: Is hypoglycaemia an aggravating factor? Diabetes/Metabolism Research and Reviews. 2008;**24**(5):353-363. DOI: 10.1002/dmrr.865

[59] Jia G, DeMarco VG, Sowers JR. Insulin resistance and hyperinsulinaemia in diabetic cardiomyopathy. Nature Reviews Endrocrinology. 2016;**12**(3):144-153. DOI: 10.1038/nrendo.2015.216

[60] Pessina AC. Target organs of individuals with diabetes caught between arterial stiffness and damage to the microcirculation. Journal of Hypertension – Supplement. 2007;**25**(1):S13–S18. DOI: 10.1097/01.hjh.0000271504.62325.a4

[61] Safar ME, Rizzoni D, Blacher J, Muiesan ML, Agabiti-Rosei E. Macro and micro-vasculature in hypertension: Therapeutic aspects. Journal of Human Hypertension. 2008;**22**(9):590-595. DOI: 10.1038/jhh.2008.43

[62] Agabiti-Rosei E. From macro- to microcirculation: Benefits in hypertension and diabetes. Journal of Hypertension – Supplement. 2008;**26**(3):S15–S19

[63] van Guldener C, Stehouwer CD. Homocysteine and large arteries. Advances in Cardiology. 2007;**44**:278-301. DOI: 10.1159/000096748

[64] Fernández-Miranda C, Paz M, Aranda JL, Núñez V, Gómez P, Díaz-Rubio P et al. Homocysteine and progression of carotid atherosclerosis in patients with coronary disease. Medicina Clínica (Barcelona). 2003;**121**(15):561-564

[65] Page JH, Ma J, Chiuve SE, Stampfer MJ, Selhub J, Manson JE et al. Plasma total cysteine and total homocysteine and risk of myocardial infarction in women: A prospective study. American Heart Journal. 2010;**159**(4):599-604. DOI: 10.1016/j.ahj.2009.12.037

[66] Park CS, Ihm SH, Yoo KD, Kim DB, Lee JM, Kim HY et al. Relation between C-reactive protein, homocysteine levels, fibrinogen, and lipoprotein levels and leukocyte and platelet counts, and 10-year risk for cardiovascular disease among healthy adults in the USA. American Journal of Cardiology. 2010;**105**(9):1284-1288. DOI: 10.1016/j.amjcard.2009.12.045

[67] Handzha IM. Viral infection, atherosclerosis, and ischemic heart disease. Likars'ka Sprava. 2001;(1):65-67

[68] Vorob'ev AA, Abakumova IuV. Role of viral-herpetic infections in the etiology of atherosclerosis: Clinical, virological and immunological evidence. Vestnik Rossiĭskoĭ Akademii Meditsinskikh Nauk. 2003;(4):3-10

[69] Grundtman C, Kreutmayer SB, Almanzar G, Wick MC, Wick G. Heat shock protein 60 and immune inflammatory responses in atherosclerosis. Arteriosclerosis, Thrombosis, and Vascular Biology. 2011;**31**(5):960-968. DOI: 10.1161/ATVBAHA.110.217877

[70] Ayada K, Yokota K, Kobayashi K, Shoenfeld Y, Matsuura E, Oguma K. Chronic infections and atherosclerosis. Clinical Reviews in Allergy & Immunology. 2009;**37**(1):44-48. DOI: 10.1007/s12016-008-8097-7

[71] Lunardi C, Dolcino M, Peterlana D, Bason C, Navone R, Tamassia N et al. Endothelial cells' activation and apoptosis induced by a subset of antibodies against human cytomegalovirus: Relevance to the pathogenesis of atherosclerosis. PLoS One. 2007;**2**(5):e473. DOI: 10.1371/journal.pone.0000473

[72] Mehta JL. Inflammatory and Infectious Basis of Atherosclerosis. Basel, Boston, Berlin: Birkhauser; 2001. 267 p

[73] Pasqui AL, Bova G, Maffei S, Auteri A. Immune factors in atherosclerosis. Annali Italiani di Medicina Interna. 2005;**20**(2):81-89

[74] Wang YN, Che SM, Ma AQ. Clinical significance of serum cytokines IL-1beta, sIL-2R, IL-6, TNF-alpha, and IFN-v in acute coronary syndrome. Chinese Medical Sciences Journal. 2004;**19**(2):120-124

[75] Ozeren A, Aydin M, Tokac M, Demircan N, Unalacak M, Gurel A et al. Levels of serum IL-1beta, IL-2, IL-8 and tumor necrosis factor-alpha in patients with unstable angina pectoris. Mediators of Inflammation. 2003;**12**(6):361-365. DOI: 10.1080/09629350310001633360

[76] Nguyen JT, Myers N, Palaia J, Georgopoulos A, Rubins JB, Janoff EN. Humoral responses to oxidized low-density lipoprotein and related bacterial antigens after pneumococcal vaccine. Translational Research. 2007;**150**(3):172-179. DOI: 10.1016/j.trsl.2007.04.001

[77] Longo, Fauci, Kasper, Hauser, Jameson, Loscalzo. Harrison's Principles of Internal Medicine. 18th ed. The McGraw Hill Companies Inc. USA; 2012. 3611 p

[78] Ghandehari H, Le V, Kamal-Bahl S, Bassin SL, Wong ND. Abdominal obesity and the spectrum of global cardiometabolic risks in US adults. International Journal of Obesity. 2009;**33**(2):239-248. DOI: 10.1038/ijo.2008.252

[79] Wisse BE. The inflammatory syndrome: The role of adipose tissue cytokines in metabolic disorders linked to obesity. Journal of the American Society of Nephrology. 2004;**15**(11):2792-2800. DOI: 10.1097/01.ASN.0000141966.69934.21

[80] Berg AH, Scherer PE. Adipose tisue, inflammation, and cardiovascular disease. Circulation Research. 2005;**96**(9):939-949. DOI: 10.1161/01.RES.0000163635.62927.34

[81] Pischon T, Rimm EB. Adiponectine and risk of acute coronary syndrome: Defining the obesity phenotype. European Heart Journal. 2007;**28**(3):274-275. DOI: 10.1093/eurheartj/ehl454

[82] Cao H. Adipocytokines in obesity and metabolic disease. Journal of Endocrinology. 2014;**220**(2):T47–T59. DOI: 10.1530/JOE-13-0339

[83] Depairon M, Hayoz D, Darioli R. Early detection of atherosclerosis. Revue Médicale Suisse. 2006;**2**(51):330-332, 335-336

[84] Katić T, Sakić I, Bergovec M. Primary prevention of cardiovascular disease. Acta Medica Croatica. 2009;**63**(1):71-74

[85] Arias-Palencia NM, Solera-Martínez M, Gracia-Marco L, Silva P, Martínez-Vizcaíno V, Cañete-García-Prieto J et al. Levels and Patterns of Objectively Assessed Physical Activity and Compliance with Different Public Health Guidelines in University Students. PLoS One. 2015;**10**(11):e0141977. DOI: 10.1371/journal.pone.0141977

[86] Gils A. The pathophysiological relevance of PAI-1 in cardiovascular diseases and the development of monoclonal antibodies as PAI-1 inhibitors. Verhandelingen - Koninklijke Academie voor Geneeskunde van België. 2006;**68**(3):179-198

[87] Elkind MS. Inflammatory markers and stroke. Current Cardiology Reports. 2009;**11**(1):12-20

[88] Ridker PM, Silvertown JD. Inflammation, C-reactive protein, and atherothrombosis. Journal of Periodontology. 2008;**79**(8 Suppl):1544-1551. DOI: 10.1902/jop.2008.080249

[89] Khreiss T, József L, Potempa LA, Filep JG. Conformational rearrangement in C-reactive protein is required for proinflammatory actions on human endothelial cells. Circulation. 2004;**109**(16):2016-2022. DOI: 10.1161/01.CIR.0000125527.41598.68

[90] Martín-Timón I, Sevillano-Collantes C, Segura-Galindo A, Del Cañizo-Gómez FJ. Type 2 diabetes and cardiovascular disease: Have all risk factors the same strength? World Journal of Diabetes. 2014;**5**(4):444-470. DOI: 10.4239/wjd.v5.i4.444

[91] Wilensky RL, Macphee CH. Lipoprotein-associated phospholipase A2 and atherosclerosis. Current Opinion in Lipidology. 2009;**20**(5):415-420. DOI: 10.1097/MOL.0b013e3283307c16

[92] Gudnason V. Lipoprotein (a): A causal independent risk factor for coronary heart disease? Current Opinion in Cardiology. 2009;**24**(5):490-495. DOI: 10.1097/HCO.0b013e32832f0a5b

[93] Ong CN, World Health Organization. Water Sanitation Health [Internet]. Available from: http://www.who.int/water_sanitation_health/dwq/nutrientschap5.pdf

[94] Duvigneaud N, Wijndaele K, Matton L, Deriemaeker P, Philippaerts R, Lefevre J et al. Socio-economic and lifestyle factors associated with overweight in Flemish adult men and women. BMC Public Health. 2007;**7**:23. DOI: 10.1186/1471-2458-7-23

[95] Remaley AT, Amar M, Sviridov D. HDL-replacement therapy: Mechanism of action, types of agents and potential clinical indications. Expert Review of Cardiovascular Therapy. 2008;**6**(9):1203-1215. DOI: 10.1586/14779072.6.9.1203

[96] Meyers CD, Kashyap ML. Pharmacologic elevation of high-density lipoproteins: Recent insights on mechanism of action and atherosclerosis protection. Current Opinion in Cardiology. 2004;**19**(4):366-373

[97]   Shah PK. Focus on HDL: A new treatment paradigm for athero-thrombotic vascular disease. Expert Opinion on Investigational Drugs. 2000;**9**(9):2139-2146. DOI: 10.1517/13543784.9.9.2139

[98]   Van Lenten BJ, Navab M, Anantharamaiah GM, Buga GM, Reddy ST, Fogelman AM. Multiple indications for anti-inflammatory apolipoprotein mimetic peptides. Current Opinion in Investigational Drugs. 2008;**9**(11):1157-1162

[99]   Navab M, Reddy ST, Van Lenten BJ, Anantharamaiah GM, Fogelman AM. The role of dysfunctional HDL in atherosclerosis. Journal of Lipid Research. 2009;**50**(Suppl):S145–S149. DOI: 10.1194/jlr.R800036-JLR200

[100] Christoforou N, Gearhart JD. Stem cells and their potential in cell-based cardiac therapies. Progress in Cardiovascular Diseases. 2007;**49**(6):396-413. DOI: 10.1016/j.pcad.2007.02.006

[101] Grosser N, Schröder H. Therapy with NO donors-antiatherogenic and antioxidant actions. Herz. 2004;**29**(1):116-122. DOI: 10.1007/s00059-004-2530-3

[102] Lamb EK, Kao GW, Kao RL. Cellular cardiomyoplasty: Its past, present, and future. Methods in Molecular Biology. 2013;**1036**:1-17. DOI: 10.1007/978-1-62703-511-8_1