NON-PHARMACOLOGICAL CONCEPTS OF ENDOTHELIAL DYSFUNCTION IMPROVEMENT

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Endothelium plays an important role in maintaining normal vascular tonus and blood fluidity reducing thrombocyte activity and adhesion of leukocytes as well as limiting response of vascular inflammation. However, in certain pathological conditions such as hypercholesterolemia, hypertension, and diabetes, endothelium improves vasoconstriction, inflammation and thrombocytic events.

Non-pharmacological concept is based on recognition of genetic factors, environmental factors, or combination of risk factors for the occurrence of endothelial dysfunction, general and individual education of the significance of adequate nutrition, physical activity and regulation of body weight, regular check-ups and the application of antioxidants that can regulate and protect several aspects of endothelial functions. *Acta Medica Medianae 2007;46(2):63-67.*

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Introduction

The term *endothelial dysfunction* (ED) is widely used in relation to several pathological conditions such as altered anticoagulant characteristics of endothelium or disregulation of vascular remodeling. Recently, however, this term has often been related to decreased capacity of endothelium-dependent vasodilatation on acetylcholine of coronary and periphery blood vessels. Since this type of vasorelaxation is connected to endothelial production of NO that affects smooth muscle cells, decreased production and/or increased consumption of endothelial NO are usually associated with ED.

There are several methods that are now being used for the assessment of ED. One of the most frequently used and accepted tests include assessment of plasma markers such as von Wilerbrand's factor, cell molecules of adhesion (E-selectin, intercellular molecules of adhesion-1 (ICAM-1), thrombomobulin and studies about circulation of forearm as a response to hypoxia, induced by stress or intraarterially administered drugs such as acetylcholine. There is great evidence suggesting that oxidative stress is highly responsible for the ED pathogenesis.

The mechanism which is taken as reference in pathogenesis of endothelial dysfunction is associated with increased production of free radicals. This spends bioavailable NO and makes local oxidative stress worse by direct reaction of NO and peroxinitrite, which inevitably keeps oxidative injury of endothelium.

Increased production of free oxidative radicals which has not been effectively destroyed by endogenic antioxidative systems may reduce local production of NO or its bioavailability affecting and cleansing NO in order to produce peroxinitrite. A few potential enzymic sources of free radicals in vascular cells have been described and they all may be responsible for the decrease of NO availability. The greatest atten-tion has been devoted to xantin oxidase, nicotin-amid adenin dinucleotid, nicotinamid adenin dinucleotid phosphate oxidase (NADH/ NADPH oxidase), lipoxigenase and cyclooxigenase. Free radicals may also be included in endothelial dysfunction regulating the level of occurrence of endothelial NO synthase (cNOS), the integrity of which and maintenance of enzymic activity are of great significance for preserving continuous and adequate amount of NO that is available to endothelium. However, data in vitro surprisingly show that free radicals cause the increase of eNOS protein levels. This is generally considered to be secondary reaction to local deficit of NO. (1,2,3).

Concept of endothelial dysfunction improvement may be non-pharmacological in nature consisting of diet, life-style change, body mass regulation, physical activity, increased synthesis of NO/L-arginine), and antioxidants.

Hypercholesterolemia represents one of the most important factors for endothelial dysfunction and consequently for the disorders of cardiovascular system. Therefore, diet is the basic and initial measure in therapy of dyslipidemias. Its application may lead to decrease of LDL-C up to 10%. The response to the diet may be very good and show effects only after few weeks.

Approximately 10% of population is resistant to diet. Besides its positive effects on lipid concentration, the diet has antithrombotic ant antioxidative effects with endothelial dysfunction improvement. Although the effects on LDL-C may be minimal, the suggestion is to be very persistent with the diet.

The adequate diet decreases the risk through various mechanisms including body weight loss, decrease of blood pressure, positive effects on lipid, possibility of thrombosis as well as glucose control.

Coordinating Committee of The National Cholesterol Education Program (NCEP) suggests a therapeutical change of life style including nutrition with reduced intake of saturated fatty acids less than 7% of total calorie intake, the intake of plant stanole/sterole-2 grams per day and the increase of viscose soluble fibers (10-24 grams per day), weight reduction and increased physical activity (Table 1).

Table 1. Therapeutic changes of life style according to NCEP

Component	**Recommendation**
Nutrients elevating LDL-C	
Saturated fatty acids	<7% out of total calories
Diet cholesterol	<200 mg/ per day
Therapeutical options for LDL-C decrease	
Plant stanoles/steroles	2gr/ per day
Viscose fibres	10-25gr/ per day
Total calories (energy)	Reaching and maintaining of wanted body mass
Physical activity	Moderate physical activity for consumption of at least 200 ccal/per day

In the "step by step" model of therapeutical changes of life style, the first doctor encounter implies the beginning of life style change including reduced intake of saturated fatty acids and cholesterol, as well as recommendation of mild physical activity.

The next step includes doctor's evaluation of LDL-C after 6 weeks. If the desirable level is not achieved, the reduction of saturated fatty acids and cholesterol is reactivated together with addition of plant sterols, increased intake of fibers and dietitian's advice.

In the case when the level of LDL-C is not adequate, drug therapy and increased physical activity are included.

The general examinations are continued within the period 4-6 months in order to evaluate the effects of life style change.

There is a great number of the so called "sound heart" diets, such as Atkins, South Beach, Ornish and DASH diet 1 based on the use of:

- great amounts of plant food (wholemeal bread, cereals, fresh or boiled vegetables and fruit),
- non-hydrogenised plant oil as basic fat source, especially oil rich in monosaturated fatty acids (olive and palm oil),
- products without or little fat,
- fish and chicken (skinless)
- light meat and eggs only 4 times a week (the white part of an egg is allowed in larger amounts) (4,5).

Life style change includes not only diet based on reduction of intake of saturated fats and cholesterol, but also increased physical activity, body weight control, smoking cessation, blood pressure regulation and hyperglycemia.

Target levels of LDL cholesterol in primary prevention depend on absolute risks for cardiovascular diseases and these values should be less than 3,4 mmol/1. Due to this risk, it is advisable to limit intake of Na and alcohol to moderate extent. Moderate alcohol intake has cardioprotective effect based on HDL-C elevation. Total mortality is less in people who consume 1-2 drinks a day, and drastically increases in the individuals who consume more than three drinks a day. Great amount of alcohol use is an important risk factor for stroke.

Body weight regulation is important to patients with dyslipidemia and cardiovascular disorders, as well as asymptomatic individuals at high risk. Body weight reduction is recommended to the obese and those with abdominal type of obesity.

In the attempt to prevent obesity, it is necessary to take into account both energetic intake energetic consumption.

Increased intake of cereals, fruit and vegetables, decreased level of high calorie food, regular physical activity and combination of these two habits are modes for obesity prevention.

It has been established that physical activity has protective effect on the development of atherosclerosis and cardiovascular diseases. Therefore, it should be promoted in all age groups (both in children and adults), in all patients and individuals at low risk to the extent that is not harmful to their health. Physical activity effects lipoprotein profile in blood, leads to HDL-C increase on the expense of HDL2 and triglyceride reduction. This kind of effect depends on intensity and length of physical activity. The mechanism of this effect is accomplished by enzymes included in lipid metabolism. The aim of physical activity (aerobic and dynamic) recommended to individuals at high risk for cardiovascular diseases in primary and secondary prevention is to increase minute heart volume, ventilation and oxygen consumption.

Physical activity influences the increase of energetic expenditure (calorie burning,) which is very significant in maintaining ideal body mass, prevention and obesity treatment. It also aids in reduction of stress, risk cholesterol levels and blood pressure; increases myocardial perfusion, fibrinolytic activity, decreases adherence of thrombocytes due to increased prostaglandin synthesis, influences the growth of antiatherogenic lipids, increases glucose tolerance and insulin sensitivity (3,4,6).

American Heart Association (4) recommends physical exercise as a part of primary and secondary prevention including all age groups and pointing to risk in inactive individuals.

In determining the level of physical activity, the overall health state should be taken into account. Recommended physical activity per day is 30-60 minutes, 4-6 times a week or 30 minute every day. Physical activity should be performed gradually, starting with light exercises and tailored individually. The risk of cardiovascular death is the least with moderate physical activity consisting of biking, swimming and everyday fast walking.

EAS recommendations for working-out

1. Maintaining of target heart frequency
2. Warm-up is achieved with 5 to 10-minute stretching and movement exercises.
3. Exercise phase is achieved with walking, bicycle riding, swimming, climbing stairs, light weight lifting, mountain climbing, running, skiing. It is done 4 to 5 times a week, where working out lasts 20 to 30 minutes and if it is done 2 to 3 times a week, it lasts 40 to 60 minutes.
4. 5 to 10-minute rest with gradual reduction of working-out intensely.

Table 2. Heart frequency of healthy individuals

Heart frequency of healthy individuals	
Age	Heart frequency
20-29	115-145
30-39	110-140
40-49	105-130
50-59	100-125
60-69	95-120

Arginine is a non-essential amino acid better known as L-arginine (L representing natural amino acids) and a natural herbal and animal protein component. Natural sources of arginine are kernel fruits, brown rice, raisins, chocolate, sesame as well as ingredients rich in protein. Although a non-essential amino acid (human organisms can synthesize it in substantial quantities for its habitual needs) endogen synthesis can be insufficient in certain catabolic conditions such as fever. In such a case, arginine can be considered conditionally essential an amino acid. Some of the arginine functions are protection from heart disease by reducing the cholesterol level, lowering blood pressure and improving circulation. Arginine is a key component of the path of nitrogen-oxide and an important cascade element in reactions connected with vasodilatation (expansion of blood vessels as a consequence of loosening blood vessel muscle wall) as well as cardiovascular function. Arginine supplements reduce symptoms connected with heart diseases and can slow down the advancement or arteriosclerosis. In the body, arginine serves as the ground for synthesis of nitrogen-oxide enzymes and arginine catalization, citruline and nitrogen-oxide are produced. In the cells which surround blood vessels, endothelium cells, production of nitrogen-oxide causes vasodilatation. Nitrogen-oxide (NO) is included in general regulation of systemic vascular resistance where it blocks cell adhesion and foreign matter to the blood cell walls helping suppress overgrowth of smooth muscle cells that coat blood vessels. In people where cholesterol level is increased, it is quite common to notice reduced endothelial capability to produce NO, the very reason for cholesterol to effectively spread. Accordingly, due to the reduced NO production blood cells will probably attach to outer blood cell walls and bring about/add up to clotting. Arginine supplements (18-21 g daily) have shown to regenerate endothelial vasodilatation in coronary arteries in people with high cholesterol level, thus reducing the possibility of blood cell adhesion to blood vessel walls. Arginine is used today for sports supplementation due to its potential ergogenic effect on the hormone system. It is considered that arginine supplements cause anabolic effects consequently increasing muscle mass. The important effect on the physiology of sports performance is seen in its capacity to increase the overtake of glucose on the part of a muscle tissue. Arginine can be found in retail in the form of tablets, capsules and powder which contain less than 1 gr of an active substance. In heart patients, arginine supplements are used in 20 gr doses per day. For the improvement of blood flow through coronary artery, 9-14 gr per day dose is applied. Before the intake of arginine supplement, consultation with a physician-nutritionist is recommended (8).

Warn a patient about the negative effect of cigarette smoke and consequences it produces. Recommendations for quitting smoking comprise individual counseling within special programs which are performed in groups of 4 to 6 people and therapy for nicotine swap (patches and chewing gum). In May 1996, American FDA allowed the use of bupropion as the first non-nicotine product to serve as a helping hand to quit smoking (as an aid). The efficiency of acupuncture and hypnosis as a non-standard technique has not been proven. (9)

Substantial number of studies that have included humans which as the aim have had to prove the effect of antioxidant on ED, have obtained positive results. These included studies on peripheral vessels, resistant blood vessels and coronary vessels. Vitamin C has improved ED in chronic smokers, insulin in dependent and non-dependent diabetes, hypercholesterolemia, essential and renovascular hypertension in people with chronic heart problems even in healthy people due to the fact that ED is experimentally induced. Apart from that, only a few studies have inquired whether or not Vitamin C has the effects on reduction of any oxidative stress marker.

Treatment with Vitamin E has improved ED in patient with coronary spastic angine. Its long-lasting application has improved ED in smokers with hypercholesterolemia which has been characterized with lower of auto-antibodies on oxidated LDL. Finally, vitamin E has kept intact endothelial vasomotor function after treatment with metonine, well established experimental procedure to produce high quantities of homocisterne which later

produced ED in resistant vessels. However, some confusing results have also been obtained in studies which investigate effects of combination of vitamin E and C. In one study, therapeutic approach to children hypercholesterolemia recovered ED even without significant effect on biomarkers of oxidative stress that is to improve ED in type 1 diabetes and showed in the other that it is efficient for type 2 diabetes. As opposed to them, another study showed that long lasting oral application of these two vitamins does not improve ED in patients with coronary artery disease. Finally, HMGCoA inhibitors of reductasis showed the return of ED increasing NO levels and reducing oxidative stress in the absence of reduced lipid level effect.

Endothelial cells subjected to AGE increase, monocyte adhesion and expression of ICAM-1 both of the effects are inhibited with vitamin C and E. On the other hand, the intensified expression of key adhesive molecules on monocyte-macrophagus and neutrophils occurs soon after exposed to cytokines or products of lipid oxidation can be modulated with antioxidants. Over-exposure to CU, Zn COD and catalysis reduces expression of adhesive molecules, inhibits adherence of leukocytes to endothelial cells far better than in case of sole exposure to SOD and catalysis.

The long applied vitamin C has reduced leukocyte adhesion of central microcirculation in diabetic amice. Probucole has improved the interaction of leukocytes and endothelium in diabetic rats at least in the part where the expression of adhesive molecules is returning in vasculature. Several studies have shown that neutrophils which are enriched with Vitamin E reduce their adhesiveness both in vitro as well as in vivo. This is secondary in the low regulation of expression of adhesive molecules. Smoking is known to increase levels of free oxygen radicals in vivo and it is one of the main risk factors of atherogenesis. Cigarette smoke increases adhesiveness of leukocytes on the endothelium in animal models. Increased monocyte adherence on endothelium cells is considered an initial reaction in ED pathogenesis caused by cigarettes. Leukocytes treated with vitamin C and SOD and not vitamin E have a reduced adhesion. Oral admission of vitamin C for 10 days reduced the level of the increased adherence of monocytes on human endothelium cells ex vivo in smokers in comparison to the non-smokers level. Substitution therapy with vitamin C did normalize monocyte adhesion on endothelial cells only in healthy non-smokers with low levels of vitamin C in the serum. Lastly, short term administration of vitamin C and E reduced the levels of IL-1β, IL-6, VCAM-1 and soluble ICAM-1 and improved vasodilatatory response to reactive hyperemia in healthy young smokers. Compensation of vitamin E reduces levels of circulation of sICAM-1 and metabolizes NO in hypercholesterolemic patients as well as in healthy people. In the latest double-blind prospective studies it has been showed that the supplementation of antioxidants reduces progression of atherosclerosis in patients with heart transplantation (2,12). Antioxidative paradox – as mentioned earlier, many altered endothelium functions are considered precursors of vascular atherosclerosis, while anti-oxidants have had a beneficial impact on them. While most studies performed on animals show that the application of antioxidants has beneficial impact on experimental models of atherogenesis, the outcomes of clinical studies have had disappointing results. The results of major prospective, controlled clinical studies connected to the efficiency of antioxidant therapy (mostly with vitamin E) in prevention of cardiovascular diseases are controversial. Two studies (CHAOS and SPACE) have proved the efficiency of vitamin E while seven other (ATBC, GISSI, PPP, SECURE, HOPE, HPS and VEAPS) did not show their efficiency. Reasons for the discrepancy are not clear, but factors such a choice of patients with different levels of oxidative stress as well as different doses of antioxidants could have has an impact on the final outcome. (1)

Conclusion

Non-pharmacological concept represents multidisciplinary activity with intention to influence lipid and non-lipid risk factors with non-pharmacological measures that justify their long-term application in primary and secondary prevention of endothelium dysfunction.

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NEFARMAKOLOŠKI KONCEPT POPRAVLJANJA ENDOTELNE DISFUNKCIJE

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Endotel igra važnu ulogu u održavanju normalnog vaskularnog tonusa i fluidnosti krvi smanjujući trombocitnu aktivnost i adheziju leukocita kao i ograničavajući reakciju vaskularnog zapaljenja. Međutim, u određenim patološkim stanjima kao što su hiperholesterolemija, hipertenzija, dijabet, endotel olakšava vazokonstrikciju, inflamaciju i trombotske događaje.

Nefarmakološki koncept se bazira na prepoznavanju genetskih, faktora sredine ili kombinacije faktora rizika za nastanak disfunkcije endotela, generalnoj i individualnoj edukaciji o važnosti primene pravilne ishrane, značaju fizičke aktivnosti i regulaciji telesne težine, redovnim kontrolama i primeni antioksidanata koji mogu da regulišu i zaštite nekoliko aspekata endotelnih funkcija. *Acta Medica Medianae 2007;46(2):63-67.*

***Ključne reči**: endotel, disfunkcija endotela, nefarmakološki koncept*