Introduction

The Mediterranean diet is characterized by high consumption of olive oil, vegetables and fresh fruits. Depending on the particular geographical area, the traditional Mediterranean diet is not only rich in vegetable oil, but also in n-3 long chain polyunsaturated acids (n-3 PUFA), which are present in fish and seafood (4).

The consumption of food rich in monounsaturated fats (olive oil), n-3 polyunsaturated fats (fish oil), dietary fibres, antioxidants and other non/nutrient substances like squalene, olive oil phenolic substances were found to be associated with a lower risk of cardiovascular diseases, myocardial infarction in particular (9). Mortality rates from ischemic heart disease are in table 1. Studies of single protective nutrients are theoretically interesting, but the effect or a dietary pattern and protective nutrients synergism cannot be overlooked (6).

The effects of this type of diet include:
• Lipid lowering effect
• Blood pressure lowering effect
• Prevention of atherosclerotic plaque rupture (stabilization of unstable plaque)
• Thrombosis prevention
• Protection against malignant arrhythmias
• Protection against low density lipoproteins (LDL) oxidative modification
• Colon cancer and prostatic cancer prevention

Components of the Mediterranean diet

The benefits of the Mediterranean pattern of a diet (low incidence of cardiovascular diseases, protection against cancer) could be explained by the presence of the following nutritional components:
1. Olive oil (monoenic fatty acids - MUFA, squalene and phenolic compounds)
2. Fish oil (n-3 polyunsaturated fatty acids)
3. Fruits and vegetables (natural antioxidants - bioflavonoids, ascorbic acid, soluble and insoluble dietary fibre and phytosterols)

Diet high in oleic acid, n-3 PUFA, lipid soluble antioxidants (alpha tocopherol, squalene) and low in cholesterol and saturated fats (SFA) may provide a plausible explanation for the apparent benefit of the diet (Tab. 2, 3).
Monoenic fatty acids (oleic fatty acid) in the Mediterranean diet

Approximately 90% of monounsaturated fatty acids (MUFA) present in this dietary pattern is cis-form of oleic acid (cis 18:1) and a major part of it comes from olive oil. MUFA enriched diet low in saturated fatty acids (SFA) have a pleiotropic effect in the prevention of cardiovascular diseases:

1. Diets rich in MUFA and blood pressure

A positive relationship has been found between blood pressure and a high intake of SFA, alcohol and salt, whereas dietary intervention trials showed a significant decrease of blood pressure by 9% in individuals consuming the Mediterranean diet – 38% total fat, 22% MUFA (2,11,13).

2. Role of dietary monounsaturated fats (olive oil) in etiopathogenesis of atherosclerosis

Oxidative modification of low density lipoproteins (LDL), endothelial dysfunction and dietary lipids, particularly PUFA may modulate the development of atherosclerosis affecting the structure and function of arterial wall. Dietary fat determines plasma LDL concentration and the susceptibility to oxidative modification (10). The changes caused by the diet in the PUFA and MUFA content in LDL and the availability of antioxidants in plasma can modulate the formation of modified LDL deposited in atheromatous plaques via macrophages scavenger receptors.

Lipoproteins rich in MUFA show less oxidability in comparison to the LDL particles enriched by n-6 PUFA and according to some studies also LDL particles enriched by n-3 PUFA. High levels of alpha tocopherol do not suppress enhanced oxidation of LDL enriched by n-6 PUFA (1,15).

Some findings suggest that LDL rich in monosaturated fatty acids when exposed to oxidative stress caused less monocyte chemotaxis (52% decrease), lower monocyte adhesion (77% decrease) and suppressed significantly pro-inflammatory effect (15).

Consumption of the Mediterranean type diet rich in MUFA and antioxidants could protect arterial endothelium, improve endothelial dysfunction and restore endothelium-dependent vasodilatation to normal (3).

3. Dietary MUFA and carbohydrate metabolism

The development of polymetabolic syndrom and type 2 diabetes mellitus is related to overeating, high intake of mono-, disaccharides and saturated fats. High intake of simple and complex carbohydrates had a negative metabolic effect on obese and diabetic patients. A diet based on high carbohydrate consumption could give rise to triacylglycerol synthesis and very low density lipoprotein plasma level. The accumulation of triacylglycerols in the muscles suppresses muscle insulin sensitivity, deteriorates hyperlipoproteinaemias and lowers plasma levels of high density lipoproteins.

The reduction of SFA and carbohydrates in the diet and replacing SFA by MUFA results in the decrease of both postprandial plasma glucose and insulin concentrations, lowers peak postprandial glucose level and decreases 24-hours glucose urinary excretion (7).

Possible role of squalene in the Mediterranean diet

Squalene, an isoprenoid compound similar to beta carotene is intermediate metabolite in the cholesterol synthesis. In tissues, squalene appears to be a quencher of singlet oxygen and indispensable precursor in dolichol and ubiquinone synthesis (Coenzyme Q 10).

Many polypropenyl compounds similar to squalene, performing critical metabolic functions are found in the nature including vitamin A, vitamin K, tocopherols, dolichols etc.
Squalene received its name because of its occurrence in shark liver oil. Reasonable amounts of squalene in plants are found only in olive oil (1%) and amaranth oil (7%). In humans, 60% of dietary squalene is absorbed and transported by lipoproteins to the tissues. In lipid metabolism squalene reduces cholesterol and triacylglycerol plasma concentrations in hyperlipemic individuals (5).

Rao at al. (12) assessed squalene chemopreventive efficiency on colonic abberant crypt foci. The diet containing 1% of squalene in fat inhibited abberant crypt formation by about 46%, suggesting chemopreventive activity against colon carcinogenesis.

### Phenolic components with antioxidant properties in the Mediterranean diet: protective effect against coronary heart disease and cancer

It has been postulated that the lower incidence of coronary heart disease and prostatic and colon cancer in the Mediterranean region is due to the influence of numerous nutritional factors. Olive oil as a source of 30 phenolic compounds exerts strong antioxidant properties. The major phenolic compounds in olive oil are tyrosol, hydroxytyrosol and oleuropein (16). High consumption of virgin olive oil, particularly rich in these phenolic antioxidants as well as in oleic acid and squalene provides protection against coronary heart disease, against colon cancer and exerts the inhibition of oxidative stress (8).

### Health promoting effect of n-3 PUFA

Epidemiological and clinical trials with fish oils (eicosapentaenoic acid, docosahexaenoic acid) have demonstrated a significant effect in the prevention of cardiovascular diseases (4). Several mechanisms explain the cardioprotective effect of n-3 PUFA's, including hypolipidemic, anti-arrhythmic, anti-inflammatory and anti-thrombotic. Eicosapentaenoic acid inhibits the synthesis of thromboxane A2, an eicosanoid which causes increased platelet aggregation, platelet adhesion and vasoconstriction (table 4).

**Tab. 4: Effect of n-3 and n-6 PUFA (modified from Manner T, Askanazi J. Fish oils and lung. Clin Nutr 1993; 12: 131–146).**

|                      | n-3 PG13, TXA3 | n-6 PGE2, TXA2 |
|----------------------|---------------|---------------|
| Platelet aggregation | ⇑ ⇑             | ⇐            |
| Pulmonary vasoconstriction | ⇑ ⇑      | ⇐            |
| Blood viscosity       | ⇑ ⇑            | ± ⇑          |
| Membrane fluidity     | ⇑ ⇑            | ⇐            |
| Vascular permeability | ± ⇑           | ⇐            |
| Cancer cachexia       | ⇑ ⇑            | ?            |

(PGI - prostaglandin, TXA- tromboxane)

The consumption of at least 1-2 fish meals per week reduced the risk of sudden cardiac death by 52% (p=0.03) compared with the subjects consuming fish only once a month (4).

Endothelial dysfunction is corrected by n-3 PUFA because eicosapentaenoic and docosahexaenoic acids enhance the vasodilatory effect of nitrous oxide (NO) and reduce the endothelial expression of vascular cell adhesion molecules and leukocyte binding to the endothelium (17). The effect of n-3 PUFA is predominantly antiatherogenic and reduces also the complications of atherosclerosis in the secondary prevention (antithrombotic and anti-inflammatory effect in stabilization of atherosclerotic plaque).

Fish oil in the diet has a significant effect in reducing total plasma cholesterol and plasma triacylglycerols in hyperlipidemic patients. Unlike some vegetable oils (sunflower oil) rich in n-6 PUFA's, fish oil containing predominantly n-3 PUFA's does not lower high density lipoproteins (HDL) (Table 4).

### Cholesterol lowering effect of phytosterols

Western population ingests only a small amount of plant sterols like sitosterol, campesterol and stigmasterol (approximately 250 mg per day). Vegetable oils and vegetables are rich sources of plant sterols, which are poorly absorbed from the gastrointestinal tract. The Mediterranean population ingests about 2.5-3 g or even more of plant sterols, but the absorption is only 5-10 mg per day. Phytosterols or phytostanols intake over 2 g per day decreases effectively cholesterol absorption from gut, reduces plasma cholesterol by around 10%, LDL cholesterol by 10–15%, with minimal change in HDL cholesterol and does not cause malabsorption (14).

### Conclusion

The high intake of MUFA in the Mediterranean diet results in multiple health benefits including the improvement of insulin resistance in type 2 diabetics and in patients with polymetabolic syndrome, the decrease of atherogenic lipoproteins in plasma and a reduction in LDL oxidizability.

Substantial evidence suggests that oleic acid enriched LDL is more resistant to oxidative modification, the reduction of oxidized LDL in plasma improves endothelial dysfunction, endothelium dependent vasodilation and lowers the adhesion of monocytes to the endothelial surface.

Squalene and phenolic compounds present in olive oil have shown considerable protection against coronary heart disease and probably chemopreventive effect in prostatic cancer and colon cancer.

The evidence from randomized clinical trials suggests a daily dose of 750–1000 mg of n-3 PUFA's in the primary or secondary prevention of coronary heart disease.

This dose should be consumed in two or more fish meals per week.
The content of phytosterols in vegetable oil and vegetables (sitosterol, stigmasterol, campesterol etc.) suppresses cholesterol absorption from the gastrointestinal tract. A daily intake of 2–3 g of phytosterols in the diet could lower total cholesterol in hypercholesterolemic patients by 8–10%.

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