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Omega-3 fatty acid supplementation influences adipokines level and improves dyslipidemia in obese patients with arterial hypertension, osteoarthritis and their coincidence

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Abstract
Arterial hypertension Osteoarthritis and their coincidence, as proven, may have benefit from omega-3-polyunsaturated acids implication. Adipokines (leptin and adiponectin) levels are investigated and compared depending on body mass index in patients with mentioned pathology; dynamics of values investigated under influence of omega-3-polyunsaturated acids implication. Established, that omega-3 fatty acid supplementation has potential of restoring of natural balance of adipokines (leptin, adiponectin) and mild lipid-lowering action in obese patients with arterial hypertension, osteoarthritis and their combination, so, seems to be useful in therapeutic patterns for mentioned diseases. Exact mechanisms, dosage and longer duration of therapy may be promising subject for further investigation.

Keywords: omega-3-polyunsaturated acids, leptin, adiponectin, obesity, arterial hypertension, osteoarthritis.

1. Introduction
Recent studies have clearly shown the importance of polyunsaturated fatty acids (as essential fatty acids) and their nutritional value for human health.

On the basis of the pleiotropic signaling actions of electrophilic fatty acids and the apparent safety of many electrophilic FDA-approved drugs, the potential benefits of the in vivo administration of these reactive lipid mediators have been evaluated in a plethora of murine models of disease. ω-3 PUFA can inhibit the production of these inflammatory cytokines such as IL-1, IL-6, and TNF-α, which provide an important stimulus for osteoclastic bone resorption, and suppression of the production of these cytokines by ω-3 PUFA may inhibit bone resorption and prevent bone loss [1, 2].

Diseases or pathologies that are discussed as those which may have benefit from omega-3-polyunsaturated acids implication include (but are not limited by) diabetes and metabolic syndrome, nephropathy, ischemia-reperfusion injury, cardiovascular diseases and arterial hypertension in partial, pulmonary inflammation, and chronic inflammatory disorders. With the rising epidemic of obesity, more efficacious therapeutic strategies are needed to address the complex pathophysiological events that lead to metabolic syndrome.

2. Materials and Methods
100 patients were examined, 35 – with primary arterial hypertension (AH), 35 – with osteoarthritis (OA) and 30 – with AH + coinciding OA among them> All pateoints underwent stationary treatment in cardiological and/or rheumatological depts. Of State communal Establishment "City Clinical Hospital #3" during 2013-2014 years period. Female: male" ratio was 2, 5:1, average age – 49, 6 ± 8, 9 tears. Average duration of AH was 4-12 years (averagely 7,4±3,8 years), and corresponded 2nd stage (ECG-signs of mild to moderate hypertrophy of left ventricle – in 100% cases, specific changes of eye fundus – in ophthalmoscopy – in 96,6%). Duration of OA was 8, 4 ± 4, 6 years. OA was diagnosed using criteria of American Rheumatological Association. Patients with affliction of big joints of lower extremities were prevalent among examined subjects (35% - hip joints arthritis, 60% - knee joint affliction) and hand joints. According to X-ray data, all patients corresponded 2-3rd stages of OA by Kellgren-Lawrence, and everybody included into investigation had no synyitis symptoms (by clinical data). All procedures were approved by Local Ethic Committee, performed after written concent obtaining and corresponded to GCP requirements.

Control measurements were performed in healthy subjects group (n = 22), who had no signs of exacerbation of any chronic pathology or acute diseases including respiratory during minimally

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3-months period. Control group corresponded to clinical groups by age, gender ratio and body mass index (BMI).

Anthropometry – weight and height – was done on same day with blood collection using metrologically controlled devises. Body mass index (BMI) was calculated using standard formula.

Blood for biochemical measurements and adipokines level detection was collected on 1st or 2nd day of patients in hospital, in same time (around 9-10 a.m.), in fasting state, at least 12 hours after last meals intake. Heavy physical loading, alcohol intake and fatty food vere prohibited during 24 hours before blood testing.

Leptin and adiponectin blood content were measured employing ELISA test which use of Assaypro diagnostic kit over certified analyser. Biochemical tests were performed in Central Diagnostic Center of Chernivtsi Region on biochemical analyser «Accent 200» («Cormay S.A.», Poland).

All patients depending on nosology were prescribed standard basic therapy which included: ACE inhibitors (lisinopril), beta-blockers (bisoprolol) in AH, non-steriodal anti-inflammatory remedies (meloxicam, ibuprofen, diclofenak sodium) + chondroprotectors (chondroitin sulphate) in OA. Patients demonstrating dyslipidemia were distributed randomly to 2 subgroups: those obtaining statins (rosuvastatin) only (comparation group) and principal group who got omega-3-polyunsaturated acids as addition to standard therapy (Epadol-Neo, produced by Kyiv Vitamine Factory, registry number UA/9124/01/01 dated 27.11.2008; order № 684 dated

27.11.2008)/ Epadol-Neo includes eicosapentaenoic acid (300 mg), docosahexaenoic acid (200 mg), other fatty acids - 498 mg, d-α-tocoferol (2 mg) it was taken by patients in QD regimen, 2 caps per intake during 2 months.

Results were mathematically proceeded and statistically approved employing variants statistical analysis over PC Pentium III.

3. Obtained results

Analysis of leptin content in blood serum of healthy people revealed mild statistically not supported trend to dependence from BMI, and values of leptin in both people with optimal and increased BMI remained within average for population, determined as normal by analytical set producers (1,1 - 27,6 ng/ml) (pic. 1).

Leptin level in OA patients demonstrated great differences depending on BMI. Those with increased weight had significantly higher leptin levels comparing optimal BMI group (40,5±4,3 vs 16,38±4,87, ng/ml). Around 30% of patients with optimal BMI and 90% - with increased BMI demonstrated increased total cholesterol concentration. Similar trend was observed in patients with AH: much higher statistically significant leptin levels in obese representatives (17,9 ±4,36 vs 49,3±5,48 ng/ml, (p<0,05)), and in those with coincidence of OA and AH (33,0±4,94 vs 55,4±4,62 ng/ml, (p<0,05)), pic.1. 83% patients with AH and 100% - with OA joined with OA demonstrated biochemical signs of dyslipidemia.
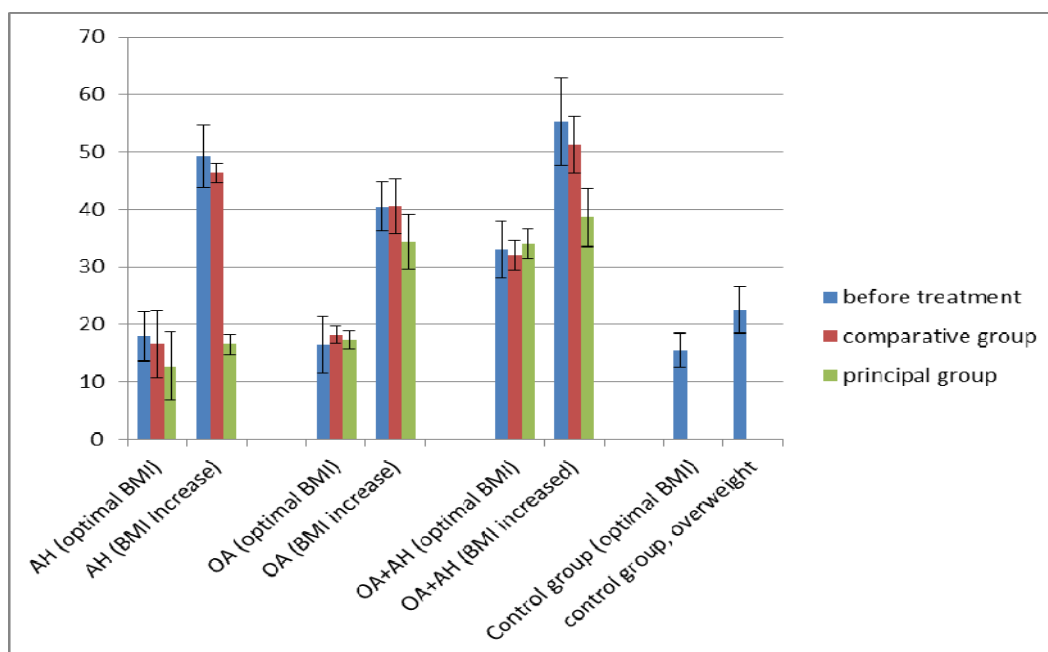
Pic.1: Leptin level in blood of patients before and after treatment (standard therapy and Epadol-Neo).

We observed no significant differences of adiponectin concentration in serum of healthy people with different BMI. Same finding was remarkable for other investigated groups: average concentration remained similar to same in healthy ones in patients with both OA and AH (24,0±2,1 vs 28,1±3,1 ng/ml (p<0,05) for healthy persons with increased and optimal BMI; 33,8±3,42 in subjects with AH and 22,1±3,11 in patients

with OA). Increase of BMI in both subgroups was accompanied with statistically significant decrease of adiponectin concentration - 14, 6±2, 91 ng/ml in obese OA patients and 18, 1±1, 52 ng/ml in obese AH patients. Co-incidence of AH and OA lead to dramatic decrease of adiponectin concentration– 12, 3±2, 02 and 13, 3±2, 21 ng/ml (p<0,05) in subjects with optimal and increased BMI.
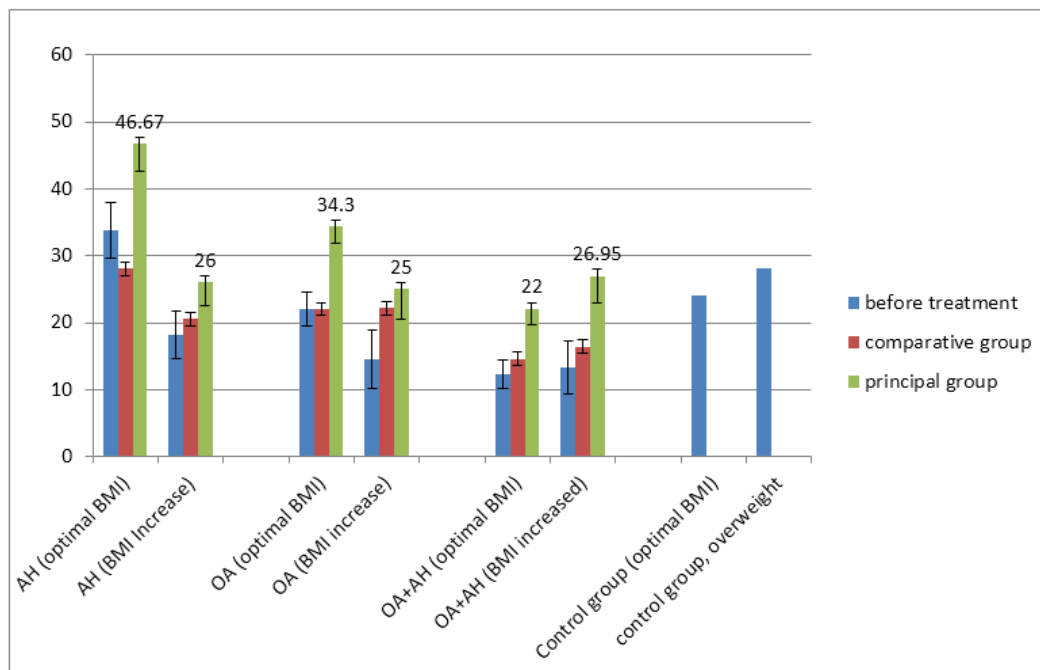
Pic. 2: Adiponectin levels in patients before and after treatment (standard therapy and Epadol-Neo).

Treatment had different influence over adipokines level in blood on patients with AH, OA and their coincidence. So, comparative treatment based on standard medications caused no influence (see pic.1) over both adipokines levels. Additional implication of Epadol–Neo containing omega-3-unsaturated fatty acids markedly significantly decreased leptin content in obese patients with AH: from 49,3±5,48 ng/ml to 16,5±1,73 ng/ml (p<0,05), final value returned to normal range. Less dynamics, but as well proven statistically was observed in OA and combination of OA and AH: decrease of blood concentration of leptin from 40,5±4,3 to 34,3±3,43 ng/ml (p<0,05) and from 55,4±4,62 ng/ml to 38,2±7,61 ng/ml (p<0,05) .

Adiponectin levels were more sensitive to treatment. Ositive statistically approved changes were observed in comparative group patients with all investigated pathologies (isolated OA, AH and their coincidence) after 2 months of administration of standard therapy. Additional prescription of Epadol–Neo containing omega-3-unsaturated fatty acids lead to further improvement of adiponectin level, but difference with comparative group was not proven statistically (pic.2).

Standard treatment of principal disorders improved partially dyslipidemia changes in observed groups (pic.3), so on first glance seemed to be quite effective. So, total cholesterol level decreased from 5,8±0,41 to 4,7±0,32 mmol/l (p<0,05) in comparative group obtaining statins only, difference confirmed statistically. Implication of Epadol-Neo lead to further improvement (4.4±0,22 mmol/l) in principal group. Same positive dynamics was observed for rest indices – HDL level increased after treatment from 1,5±0,12 to 1,6±0,11 mmol/l in comparative group and to 1,73±0,13 (p<0,05) in principal groups; triglycerides content both in comparative and principal groups returned to normal values: 2,2±0,14 mmol/l before treatment; 1,8±0,09 mmol/l (p<0,05) and 1,7±0,07 mmol/l (p<0,05) in comparative and principal groups correspondently.
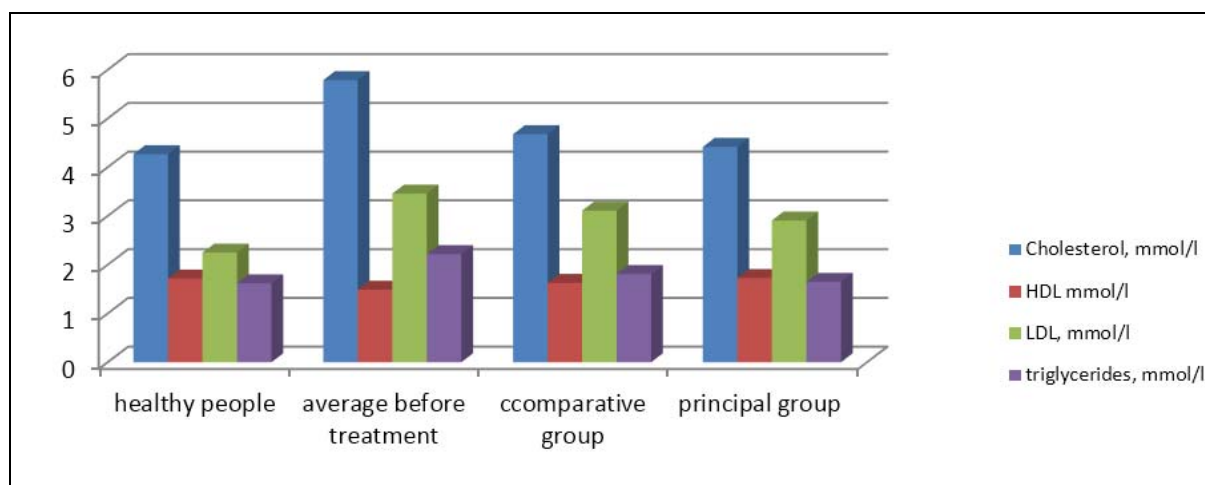
Pic. 3: Lipidogram values dynamics under influence of hypolipidemic treatment – with and without polyunsaturated fatty acids.

4. Discussion
Obesity is increasing in the Western society, and obesity-linked complications are under intense scrutiny. Among these, not only metabolic disorders, such as diabetes mellitus and dyslipidemia, but also cardiovascular disorders, such as hypertension and ischemic heart diseases, have been shown to

be associated with obesity [1, 2]. More recently, also chronic diseases in which inflammation plays a role such as osteoarthritis, rheumatoid arthritis, inflammatory bowel disease, chronic obstructive pulmonary disease, and asthma have been associated with obesity [5-7].

The adipose tissue consists of adipocytes and the stromal vascular fraction, in which a variety of immune cells can be found. Among these, macrophages and T-cells are the most abundant [1, 8]. Expansion of the adipose tissue is accompanied by an increased infiltration of immune cells with a pro-inflammatory phenotype. The cross-talk between the infiltrating cells and the tissue-resident adipocytes leads to secretion of adipokines, cytokines, chemokines, and lipids with a predominant pro-inflammatory character [3, 8]. Moreover, the levels of various adipokines and cytokines are altered in obese individuals compared to lean ones (e.g., leptin, adiponectin, IL-6). So it seems so that one of therapeutic strategies must be directed to normalization of not clinical values only but for correction of mentioned molecular interplay.

This cross-talk has also been shown to affect the function of adipocytes, such as lipolysis, which will most likely result in an altered concentration of circulating free fatty acids. Indeed, obese persons have higher levels of free fatty acids in plasma compared to lean persons [4-6]. Whether and which of these soluble factors (adipokines, cytokines, lipids, etc.) contribute to obesity-mediated inflammatory effects in diseases is still under investigation.

Omega-3-polyunsaturated fatty acids are able to inhibit partly a number of aspects of inflammation including leucocyte chemotaxis, adhesion molecule expression and leucocyte-endothelial adhesive interactions, production of eicosanoids like prostaglandins and leukotrienes from the n-6 fatty acid arachidonic acid, production of inflammatory cytokines and T cell reactivity. Mechanisms underlying the anti-inflammatory actions of n-3 fatty acids include altered cell membrane phospholipid fatty acid composition, disruption of lipid rafts, inhibition of activation of the pro-inflammatory transcription factor nuclear factor kappa B so reducing expression of inflammatory genes, activation of the anti-inflammatory transcription factor NR1C3 (i.e. peroxisome proliferator activated receptor γ) and binding to the G protein coupled receptor GPR120. These mechanisms are interlinked [3, 4].

5. Conclusions
Omega-3 fatty acid supplementation has potential of restoring of natural balance of adipokines (leptin, adiponectin) and mild lipid-lowering action in obese patients with arterial hypertension, osteoarthritis and their combination, so, seems to be useful in therapeutic patterns for mentioned diseases. Exact mechanisms, dosage and longer duration of therapy may be promising subject for further investigation.

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