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Metabolic Syndrome (Does It Have a Common Denominator?)

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Abstract: The insufficient or inappropriate supply of PUFA OMEGA-3 (esp. docosahexaenoic and eicosa pentaenoic acid DHA and EPA) can be suggested to be a common factor of the four metabolic syndrome's clinical manifestations. DHA can be considered as one of the most important element of the membrane. The protective and beneficial effects of DHA (and EPA) result from the dynamic qualities of its molecular structure as well as from its recently detected effects on the genetic expression of several cytokines, enzymes etc. Dietary supplementation of DHA improves all clinical symptoms and laboratory biochemical markers of the metabolic syndrome. Together with that, depletion of DHA was found in diabetes and in several cardiovascular diseases. Also the developmental aspect and approach supports our view. With high probability DHA represents one of the connecting components of the development of metabolic syndrome's clinical manifestations. Metabolic syndrome could be therefore interpreted as an insufficient function of the cellular membrane.

Introduction

Reaven syndrome, as it was defined and redefined [1, 2], represents a conjunction of several clinical manifestations into a specific, mutually connected system, with a high incidence. Though the metabolic syndrome was with some difficulties clinically accepted, critical comments appeared, asking whether we really speak about one consistent syndrome with a shared nosology when each of defined clinical manifestations is treated separately and differently.

We can cite from existing publications for example Svačina [3], who asked in his incidence what the connecting factor is. Similar questions were presented by Šamánek and Urbanová [4]. A bit different arguments were used [3] when metabolic syndrome was applied to the description of psychic disorders (schizophrenia), though these disorders are known to be also linked (with a weaker significance) to e.g. insulin resistance [5].

We could cite many of such and similar critical reviews including those based on the possible variations of genetic role with respect to specific clinical components of metabolic syndrome etc.

We studied several specific aspects of lipid metabolism in the long term range and we therefore suggest a new interpretation of the metabolic syndrome (its specific clinical manifestations). One potential common principle could be an absolute or relative deficit of PUFA OMEGA-3, mainly DHA (evt. EPA), which can fundamentally influence the quality and function of plasma membrane and more over, it can modulate gene expression.

Insulin resistance – Diabetes

Several studies proved the decrease of PUFA OMEGA-3, DHA (22:6) in particular, eventually EPA (20:5) in diabetic condition. Or vice versa: significant and documented improvement of clinical condition including laboratory tests

after supplementation of organism with PUFA OMEGA-3. We found out e.g. [6, 7, 8], that a significant deficit of PUFA OMEGA-3 (again DHA in particular) exists in blood serum of mothers and also newborns with diagnosed gestational diabetes. These findings are reproducible also in experiment with alloxan-diabetes [7].

Other studies reveal very similar results: highlighting the fact, that supplementation with fish oil significantly improves impaired glucose tolerance and insulin sensitivity [9, 10, 11]. Remarkable laboratory changes [12] towards normalization of physiological conditions were described in rats with experimental alloxan-diabetes after supplementation with PUFA OMEGA-3.

Also other studies point at the developmental aspect of this problem: breast-fed children, in the long term range, have lower incidence of diabetes compared to non-breast-fed children [13]. Another, very similar work with analogous results was published [14]. Breast-milk (incl. colostrum!) contains standard amount and proportion of PUFA OMEGA-3 [recapitulation 15]. It was confirmed [16], that insufficient intake of PUFA OMEGA-3 in perinatal period increases risk of developing of diabetes (this can apply also for other disorders) [17].

Considering the previous findings, then the fact, that hyperglycaemia decreases the desaturase activity in fatty acids chain (OMEGA-3), seems to be of a major interest. This applies also to accentuated homeostasis affection (e.g. excess of triglycerides, deficiency of plasmatic Mg^{++} [recapitulation 15]. Also high production of free oxygen radicals and therefore a high risk for lipoperoxidative processes represents strong negative factor for the existence and production of unsaturated fatty acids [18, 19] (as result of various stressors – hypoxia, infection, malnutrition, hypo/hyperthermia etc. and following homeostatic changes [20]). The process of unsaturated fatty acids degradation is accentuated specially under long time exposure to stressors.

Cardiovascular System – Hypertension

In this area, many clinical and experimental studies have been published, showing general benefit and protective effects of PUFA OMEGA-3 (DHA, evt. EPA) on the cardiovascular system [21, 22, 23, 24]. Devon [25] wrote a survey on such subject in 1993. Relation and importance of PUFA OMEGA-3 were studied in a wide context – from positive effect on blood rheology [26] to the effect on anticoagulation processes [27]. Large number of studies is given to DHA influence on endothelial functioning [28, 29, 30, 31, 32, 33]. It has been described, that PUFA OMEGA-3 stimulates endothelial renewal, monocyte adhesion to the activated endothelial cells is lowered; and increased production of NO (by activating NO-synthase). DHA turned also to be protective agent against effect of proinflammatory cytokines on endothelium [34]. Series of works describe beneficial effect of fish oil intake on ischemic heart disease morbidity and mortality [35, 36]. DHA decreases the risk of fibrillation significantly.

These and some other findings were repeatedly confirmed [23, 37, 38]. Supplementation with DHA influences the composition of fatty acids in cardiocyte-membrane [39] and brings significant hypotensive effect. Mechanism of this effect is vasodilatation – increased NO production and/or function of some unsaturated fatty acids metabolites. As concerns blood pressure, DHA, as well as EPA, were revealed to have hypotensive effect [40, 41]. DHA normalises vasomotor reactions in favour of vasodilatation [31].

Also in this field, information about the developmental aspect exists: sufficient intake of PUFA-OMEGA-3 in early period of ontogenesis (perinatal period) decreases the risk of hypertensive disease in adults [42].

Dislipidemia

It was found in 1988 already, that EPA (later also DHA) inhibits liver lipogenesis and decreases serum levels of triglycerides and cholesterol [24]. Lowering triglycerides levels in patients with hypertriglyceremia after several months of supplementation with PUFA OMEGA-3 was as high as 31%. Also inhibitory effect of DHA on LDL production was shown [36, 43]. Authors agree that effect of mentioned acids is remarkable particularly in patients with dyslipidemia in risk groups. Experiments also support those findings: significantly lower cholesterol, triglycerides and LDL levels were found in hypertensive rats after being supplied with PUFA OMEGA-3.

These findings on the PUFA OMEGA-3 effect on the parameters of lipid metabolism are respected and widely clinically used.

Obesity

If there are, up to date, several hundreds of papers about the above discussed three "elements" of the metabolic syndrome in relation to PUFA OMEGA-3, then the obesity is probably the weakest link in spite of the fact that abdominal visceral obesity is concerned by many clinicians to be the primary – starting phase of metabolic syndrome. But relevant data about the beneficial or prophylactic effects of the mentioned fatty acids exist also in this area. Hainer [44] indicates in his monograph, that supplementation with OMEGA-3 can reduce visceral obesity [45].

Obesity can result from both genetic and/or epigenetic (alimentary habits etc.) factors inducing sensitivity-changes of some receptors [46] (especially leptin and insulin receptor). We can imagine these changes as a consequence of disproportional representation of specific fatty acids groups in plasma membranes [47, 48]. It was established, that PUFA OMEGA-3 can reduce the degree of obesity in experimental animals on high-fat diet [49]. DHA and EPA are concerned to be factors decreasing (or inhibiting) lipogenesis (limiting hypertrophy and hyperplasia of adipocytes).

Another interpretation was also suggested [50]. In animal model, DHA significantly increased the production of adiponectin (irrespective to the diet type).

Same authors [51] published data about DHA and EPA's influence on mitogenesis succeeded by following enhanced Beta-oxidation of fatty acids in fat tissue. Reduction of body weight by fish oil fatty acid – with reducing the fat reserves – was also confirmed [52, 53].

For a better understanding, interpretation possibilities in the final part of paper are divided into several subchapters.

A. If all the data about DHA's influence on organism (particularly in the relation to metabolic syndrome) are summarized, then after supplementation with fish oil or directly with PUFA OMEGA-3, each specific clinical unit of this syndrome is improved with the clinical status, clinical and laboratory results getting better. This applies also for experiments. At the same time, we can state, that it is the deficit of PUFA OMEGA-3 (mainly DHA) among others, which is related to the manifestations of this syndrome. This deficit can be absolute, but probably more frequently it is only relative, originating from the intake disproportion of particular groups of fatty acids. Often it is the disproportion between OMEGA-6 and OMEGA-3. Many studies were published supporting this fact including the findings that among the population of majority of developed countries (USA) such disproportion (in favour of OMEGA-6) is especially significant [54].

B. Interpretation of positive and protective effect of DHA (EPA) might be linked to the structure/architecture of the cell membrane. DHA is present in mammalian cell membranes in high proportion (around 20% in tissues like cerebral cortex, retina, cardiocytes etc.). The presence of DHA (unsaturated fatty acids and their proportion related to saturated or monoenic fatty acids in general) influences and co-determinate pivotal attributes of plasma membranes such as fluidity, viscosity and ability to accept and maintain functional proteins (receptors, ion channels etc.) in correct orientation and position as well as to maintain continuity of particular elements of informational cascades etc. We tried to elucidate this fact based on physical, structural characteristic of DHA molecule [15, 55, 56]. DHA molecule is characterized by high stereometric variability. This is of an utmost importance for membrane architecture functioning: it allows contouring and fixing (by non-covalent links) the above mentioned functional proteins in adequate positions, in time-space continuities and orientations. Optimal membrane status and its structure is a necessary condition for the implantation and full functioning of the membrane functional proteins. Ion channels, receptors, enzymes, informational cascades can function adequately (optimally) only in such membrane structure, which constitutes a functional complex.

Recently, the number of data about DHA's effects on gene expression is growing [57, 58, 59, 60] – some of the first data about this problem were published in 1990's [61]. This might be related to documented effect of DHA on proinflammatory cytokines expression [38]. Very promising are in this way also the clinical studies.

C. We are dealing with a valid set of results indicating possible link between specific clinical units of metabolic syndrome and PUFA OMEGA-3 (mainly DHA, evt. EPA). These findings can be interpreted as a form of membrane insufficiency caused by a reduction of essential structural-functional elements (DHA-EPA) in comparison to the pre-programmed physiological optimum.

D. Above stated facts (sub A and B) and the hypothesis (sub C) can be supported by several results and data. Important role have findings concerning the developmental aspect. Among the fatty acids, DHA itself represents a developmentally younger, complex, and very sophisticated molecule. If in experimental animals or in risk human neonates (preterm delivery, hypotrophy, low weight – immaturity, gestational diabetes) the fatty acids spectrum in blood serum is studied, the decrease of PUFA OMEGA-3 is always observed including the decrease or even absence of DHA. At the same time significant increase of saturated fatty acids with short chain (C:6, C:8) occurs. We have demonstrated the high statistically significant correlation between birth weight and presence of OMEGA-3 in blood serum [8, 15, 62, 63, 64]. The presence of PUFA OMEGA-3 becomes an important parameter indicating maturation status of the organism.

E. Another supporting fact, which should not be omitted, is the extent of positive – beneficial and prophylactic effects of the mentioned fatty acids. This effect was documented in other clinical fields as immunology, psychiatry, recently in oncology. Such findings in nosologically highly variable scale of pathological conditions suggests that DHA (EPA) effect can not be closely specific but is related to general element of its functioning. Plasmatic membrane could be such element.

F. Other fact supporting above stated concept is, that long lasting or inadequate stress, increased sympathoadrenal tonus [65] are assumed to be a risk factors for the genesis of metabolic syndrome. Production of oxygen radicals is under these conditions always increased and mainly unsaturated fatty acids are destructed by lipoperoxidative process. It is interesting, that PUFA OMEGA-3 are always affected in the highest degree. These facts were documented in animal models as well as in clinical studies [15, 18]. It is also accepted that a disbalance or direct perturbance of homeostasis (pH, glycaemia changes, ion derangement etc.) can be the stressing factor. This will definitely influence the activity of desaturases [66]. Changes caused by impropriate alimentary habits (alcoholism, overload of saturated fatty acids, overload of OMEGA-6 etc.) can take effect in the same matter. Deficit of DHA and EPA can occur also by these mechanisms despite the sufficient (even redundant) intake of basic acid of this group – linolenic acid (18:3 n-3).

Acknowledgments: The author would like to underline, that citation index listed here represents only about 10% of publications dealing with PUFA OMEGA-3 influence on human organism. The author of this article is fully aware of some pitfalls and eventual questions but submits here this hypothesis for discussion (hypothesis is mainly based on authors own findings and was first presented at the 10th Congress on Atherosclerosis in Špindlerův Mlýn – 2006) [56].

Medicine – experimental and clinical – must not be engaged only in the cellular functional proteins (receptors, ion channels and so on), but also in the supporting medium of the basic facility of life – plasma membrane. Moreover: this medium existed at our planet probably long time before the functional proteins occurred.

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