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New Vistas of Pharmaconutrition

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Abstract

Pharmaconutrition is a treatment modality where nutrients with specific pharmacological action are administered. Omega-3 fatty acids as well as glutamine were the favorite pharmaconutrients in the past but more and more new nutrients are discovered with significant therapeutic properties. Here we review some of the new members of this group of nutrients, like less known and used fatty acids docosapentaenic acid, conjugated linolenic acid and oleanolic acid or the metabolic byproducts of probiotics (short chain fatty acids). With some examples we point out the avoidable risks of future of these probiotics. Finally, we briefly discuss the popular coenzyme Q10 and creatine supplementation.

Keywords: Pharmaconutrition; Fatty acids; Probiotics; Postbiotics; Coenzym Q10; Creatine

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Introduction

Clinical nutrition means either substitute a deficiency of macro/micronutrients or administer nutrients having pharmacological action to control malnutrition. The latter is referred to as pharmaconutrition. This is a discipline that was invented some 4 decades ago and deals with pharmacological actions exerted by use of supraphysiological doses of various components of food or nutrient. In case of pharmaconutrients dose-response relation is expected therefore, these type of nutrients must be administered according to the strict rules.

The Concise History of Pharmaconutrition

First real pharmaconutrient introduction into the therapy happened in 1962 when the Intralipid was launched. This was the first safe parenteral nutritive emulsion that served not only nutrition purposes but also treated the essential fatty acid deficiency. The emulsion was latter introduced in hospitals as an artificial nutrition source also containing amino acids and carbohydrates [1]. Second milestone was the pharmacological intervention with amino acid solution rich in branched chain amino acids that theoretically could block endogenous production of false neurotransmitter under conditions of hepatic encephalopathy [2]. The third milestone was introduction of new treatment modalities in the field of immunology (immunonutrition). Glutamine as component of parenteral nutrition not just increased protein synthesis and improved nitrogen balance but prevented gut mucosa atrophy and improved immunity, too [3]. In line with this other amino acids (arginine, citrullin, glycine, taurine, etc.) and nucleic acids have also been used with various success for therapeutic purposes. And the series continued by the successful introduction of fish oil in parenteral nutrition that influence – via modification of omega 6 / omega 3 ratio – the inflammatory processes.

Despite the huge amount of positive results and meta-analyses, already some 10 years ago researchers urged reuppraisal of the data to clarify whether immunonutrition (and in wider sense the pharmaconutrition) really brought positive changes in the nutritional therapy [4]. This uncertainty has been confirmed by the warnings of Heylands'publication [5], who based on the REDOXS study pointed out the serious risks of use of this pharmaconutrient (glutamine). This publication undermined the trustfullness in the circle of clinicians [6,7]. But critical evaluation made it soon clear: after careful pondering of the patients' clinical parameter, the product characteristics (indication, contraindication, dosage, route of administration, etc.) and the expenses, the proper use of glutamine, in general, results in positive outcome [8-10]. This was confirmed by ESPEN treatment guidelines as well [11,12].

The progress of pharmaconutrients did not stop. Research for new nutrients with pharmacological property is going on. Here we review some of the promising compounds having already clinical background.

The fatty acids

For a long time medical nutrition used long chain fatty acids only as parenteral nutrient. Later on, during the eighties of last century medium chain fatty acids were introduced because by use of this group of fatty acids (C8-C14) one could facilitate fatty acid entry of high energy dense fatty acids into cells without the carrier carnitine which was fully bound by the huge load of long chain fatty acids in order to support anabolism. From the milenium fish oil and its main components (eicosapentaenoic cid and docosahexaenoic acid) came into the spotlight. To date, an other omega-3 long chain fatty acid, the docosapentaenoic acid and the short chain fatty acids are under extensive research.

Docosapentaenoic acid (DPA)

This is an intermediary product between polyunsaturated fatty acids eicosapentaenoic and docosahexaenoic acids in the omega-3 synthesis pathway that has individual health activitiy as well [13]. Recent meta-analysis with 20,460 individuals confirmed that DPA has better risk reducing effect to stroke than DHA and similar beneficial effect to coronary risk, sudden cardiac death and peripheral arterial disease was demonstrated, too [14]. DPA also superior in beneficial effect DHA and EPA in case of COPD [15]. The DPA-derived protectin D1 substantially inproved neuroinflammation and epileptic seizure duration and frequency [16]. Protectins originate from DHA and DPA display anti-inflammatory and pro-resolving agents, moreover effects in treatment of obesity and diabetes are also studied [17]. Furthermore by administration of DPA the ratio of omega 3 : omega 6 fatty acids can be improved which ratio has a definitive role in inflammatory/anti-inflammatory metabolite (prostaglandins, leukotriens) production.

Conjugated fatty acids

This type of fatty acids are positional and geometric isomers of polyunsaturated fatty acids. Experimental use of animal-source conjugated linoleic acids (CLA; cis-9,trans 11 and trans10,cis12 CLAs) were very promising after the positive animal studies, however, human trials could hardly confirm these benefitial results. In contrast, conjugated linolenic acid (CLNA; C18 fatty acids with 3 double bonds, starting after C5), that occurs mainly in plant seeds, displays positive effects not only in animal studies but also in human trials [18]. The positive results were seen in a randomized, placebo controlled study with 51 hyperlipidemic patients [19]. Also positive experience was seen in CLNA-containing topical dermatological formulations or effectivity against Mycobacterium tuberculosis [20,21]. These results open new ways for further research in various fields such as hypertension, cancer therapy, immunomodulation, etc.

Oleanolic acid

Oleanolic acid is a pentacyclic triterpenoid compound that can be found in the virgin olive oil. From pharmacological point of view anti-oxidant, anti-tumor, anti-inflammatory and antimicrobial effects have been attributed to the compound [22]. Due to the positive pharmacological effect several semisynthetic derivatives were produces, too. In clinical trials it seems to be effective in cancer prevention and therapy as well as in treatment of inflammatory chronic diseases [23,24].

Probiotics and probiotic metabolic byproducts

Recently myriad of publications appeared in the theme of probiotics. As probiotic food (curd, yoghurt, cheese, etc.) is part of our meal, all componenst are out of question nutrients with health impact. More and more clinical studies refere to the modulatory effect of probiotic supplementation on human diseases. Now we arrived to the era when we are able to cure or improve certain illnesses via artificially administered selected bacteria. (Even if the treatments are just in some cases with evidences underpinned [25,26]. Noteworthy, cancer is on the list of diseases where probiotics have impact in treatment modalities and the interventions. Both modulation of carcinogenesis (promotion, prevention) and influencing therapeutic outcomes are effects that are caused or can be reached by microbiota.

Example for negative situation is the microbial dysbiosis in stomach made by Helicobacter pylori. This has been reported as severe risk factor for gastric cancer in a susceptible group of patients [27]. Or colibactin and cytolethal distending toxin (CDT) produced by Escherichia coli, which – among others – may be responsible for DNA-double-strand breaks in the epithelial cells promoting tumor formation [28]. According to animal studies Helicobacter hepaticus and certain enterotoxigenic Bacteroides fragilis can also play a pivotal role in initiating other tumors [29]. But we lack for evidences to direct tumorigenic effect of microbiota [30]. However, probiotics and prebiotics with or without aid of specific antibiotics are able to restore healthy microbiome environment.

In contrast, there are positive examples as follows. By administration of probiotics and their metabolites gut microflora as well as tumor characteristics can be modified. We don't go into details regarding probiotic therapy but display effects of the metabolites. The main probiotic products are short chain fatty acids (SCFA; acetate, propionate, butyrate) originate from bacterial fermentation of intraluminar undigested carbohydrates. After processing of fibres SCFAs are rapidly absorbed by the colonocytes covering ca. 70% of their energy demand. Considerable amounts of SCFAs go to circulation however approximately 2-20% of SCFAs remain intraluminary. In case of colorectal cancer anti-tumor effect of bacterially produced butyrate has been theoretically deducted and in vitro verified [31,32]. Exogenous butyrate as pharmaconutrient in form of monobutyrin of tributyrin resulted in modification of bile acid turnover and microbiome [33]. Propionic acid also belongs to the natural fermentation endproducts that preserve intestinal mucosal barrier via enhancing expression of claudins and occludins [34]. Propionate and butyrate but not acetate are significantly taken up by the liver, too. Cancer-related experiences with propionate are not known yet although trials with succinic acid (C4 dicarboxylic acid), precursor of propionic acid, show

positive results in this respect [35]. In a recent experiment Iplik studied its effect in vitro and found apoptosis of endometrium cancer cells [36]. The majority of acetate adsorbed into the circulation and in contract to other SCFAs, it passes the brain-blood barrier. Acetate is an ubiquiter metabolic intermediate and its pathways are multiple. Noteworthy, after uptake into the brain, acetate influence regulatory neuropeptides as well thus participate in the appetite-suppression, too [37].

Postbiotics (microbial metabolic byproducts) are not only SCFAs but many other compounds, eg. hydrogen peroxide by Lactobacillus johnsonii NCC 533 strain [38]. But bioactive products like bacteriocins, lipoteichoic acid, surface layer and secreted proteins and many others playing a role in preserving intestinal barrier function, too. Active research activity is running in this direction [39].

Cancer therapy may consist of surgical, radiological, immunological and/or chemotherapeutic interventions. While today we have only sporadic information about drug-microbiota interactions it is well-known that some of the gut microbes impair or improve efficiency of the pharmacological treatment [40]. Both actions can be bidirectional: can influence the efficacy as well as the toxicity (incl. advers effects) of the intervention. The initiative of using postbiotics as pharmaconutrients represent an unexplored therapeutic option for preventing, suppressing and/or treating cancer.

Finally it should be mentioned that also use of probiotics and postbiotics needs a certain discretion, because – as with other medicines – even probiotics can cause adverse effects or interactions. First, animal experiments suggest that tumorigenesis may be transmissible among genetically predisposed individuals [41]. It means transmission of carcinogen factors by fecal transfer which is already an usual solution of serious diarrhoea due to Clostridium difficile infection seems to be possible. Second, even probiotics can interact with medication. Matuskova and co-workers published the fact that probiotics significantly (by 43%) modified the pharmacokinetics of antiarrhythmic drug amiodarone [42]. Lehouritis reported that Escherichia coli impaired the efficacy of gemcitabine [43]. And opposite actions are also reported.

Coenzyme Q10

This compound is a bestseller in Europe. There are a lot of myths and beliefs around coenzyme Q10 (CoQ10), named also as ubiquinone. As a matter of fact, it is an endogenous antioxidant and essential component in mitochondrial energy harvesting. Besides it is basic constituent of the food; meat, fish, vegetable oils, nuts and whole grains contain it in different proportion (20-160 mg/kg). Under certain conditions – advanced age, heart disease, neurological disorders and as adverse reaction to statin-treatment – the CoQ10 content decreases, supplementation may be indicated. As CoQ10 is the only endogenously synthesized lipid with redox function, its supplementation can significantly reduce morbidity and mortality of heart failure patients [44]. Several clinical studies have been initiated to clear the impact of CoQ10 supplementation or supraphysiological (>100 mg/day orally) doses. Majority of previous trials conclude positively but to date effectiveness of CoQ10 treatment based on exact endpoints is not well established [45-47]. The research in this field is not closed yet as new formulations are again and again tested. For example efficacy in orthostatic hypotension, immunological reactions, various locations of inflammation and diabetes mellitus was recently suggested by clinical studies [48-51]. It can be taken into account as adjuvant in migrain prophylaxis and in cancer treatment [52,53]. Preclinical (animal) studies were made in order to improve outcome of stroke, the radiation-induced nephropathy or paraquat-induced Parkinson's disease [54-56]. Due to the relative atoxic properties and wrong oral bioavailability of the coenzyme Q10 there are a lot of studies in various direction with this compound. Maybe studies with higher (pharmacological) doses and/or improved formulation will bring new treatment modalities.

Creatine

Creatine is also an endogenous compound that can be found in the food as well. Wild game meat, fish contain it in higher amounts. It is popular among young people as ergogenic aid (exercise performance) for several decades [57]. The use in medicine is also accepted due to its role in ATP-generating processes via phosphocreatine buffer. Because of the intermetabolic involvement of methionine and homocysteine, methyl donor balance is also affected. Morover creatine action through the increase rate of testosterone to the biologically active metabolite dihydrotestosterone is also arised [58]. Normal human doses are around 3 g/day, supraphysiological doses start from 5g/d, therapeutic dose in order to maintain muscle levels is 0.029 g/kgBW [59]. In short term use daily dose of 20 g can be considered as safe [60]. In the frame of medical treatment it is used mainly in neuromuscular disorders, inflammatory myopathies, heart failure and sarcopenia of various origin but beneficial in muscular injuries, too [61-64]. For the future there are stil unexploited fields in medical nutrition as well [65]. Preclinical studies víz. refere to – among others – immunological, cognitive, antidepressive etc. activity of creatine that should be tested and confirmed/rejected in human beings in the future [66-69]. Further trials are needed to affirm its efficacy in the fields of sleep disorders, microvascular reactivity or fatty liver disease and applicability as neuroprotective agent in the central nervous system as well [70-72].

Conclusion

Introduction of immunonutrition and pharmaconutrition represented a smooth paradigm shift in clinical nutrition. In this way some superior health outcome mostly in intensive care and postoperative patients could be obtained. Today new nutrients are in spotlight. In the group of fatty acids use of docosapentaenic acid, conjugated linolenic acid, olenolic acid seems to be interesting. Probiotics are well explored but even so there are problems with their use. Nowadays postbiotics are in limelight, for the first time SCFAs. Due to the generally high expenses of the products in question well-founded decision based on cost/benefit and risk/benefit assessment should be made about use of these treatment modalities.

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