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Synergistic effects of omega-3 polyunsaturated fatty acids and aspirin in the clinical practice – a narrative review

Anna Zajac-Grabiec[1]*, Katarzyna Sroczynska[2], Justyna Miszczyk[1]

[1] Department of Medical Physics, Krakow, Institute of Nuclear Physics Polish Academy of Sciences, Poland
[2] Department of Radioligands, Faculty of Pharmacy, Medical College, Jagiellonian University, Krakow, Poland

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ABSTRACT

The review aimed to illustrate the structure, role and effects of omega-3 polyunsaturated fatty acids (omega-3 PUFAs) in combination with acetylsalicylic acid (aspirin, ASA) in various clinical cases. This verification of earlier single studies may be a guide in the further treatment of civilization diseases. The results of the presented narrative review suggest that aspirin supplementation with omega-3 fatty acids reduces pro-inflammatory biomarkers in sepsis and acute respiratory distress syndrome. Including adequate amounts of omega 3-PUFAs in therapy, rather than increasing the dose of acetylsalicylic acid, may contribute to beneficial effects in treating thrombosis and preventing myocardial infarction or other cardiovascular diseases, which is particularly important in aspirin-resistant patients. As suggested in the literature, a low daily dose of omega-3 fatty acids was effective in slowing the progression of kidney disease with IgA nephropathy. Aspirin supplementation with omega-3 fatty acids has improved clinical and immunological outcomes in the treatment of periodontitis or the therapy of colorectal cancer tumor lesions. The synergistic effect of both compounds is proposed as a new therapeutic option in the treatment of Parkinson's disease. Further research into the synergistic effects of omega-3 fatty acids in combination with acetylsalicylic acid may provide a breakthrough in drug dose reduction, ultimately enabling more effective and safer pharmacotherapy for the patient. Therefore, studies on polyunsaturated fatty acids in combination with nonsteroidal anti-inflammatory drugs *in vivo* are needed.

STRUCTURE, ROLE, SIDE EFFECTS OF POLYUNSATURATED FATTY ACIDS OMEGA-3 AND ASPIRIN

Omega-3 fatty acids belong to the group of essential fatty acids, and are built from an unbranched hydrocarbon chain with an even number of carbon atoms [1,2]. The double bond is located at the third carbon atom, counting from the methyl group located at the other end of the chain terminated by a carboxyl group [1-3]. Acetylsalicylic acid belongs to the group of non-steroidal anti-inflammatory drugs [4] that act on the cell through acetylation [5]. ASA is an irreversible cyclooxygenase (COX) inhibitor, and is 170 times more potent a COX-1 inhibitor than COX-2 [4,5]. Thus, much higher doses of ASA are needed to achieve anti-inflammatory, analgesic and antipyretic effects than those with anti-aggregant effects [4,5]. Cyclooxygenase-1 is responsible for the synthesis of prostanoids associated with the body's homeostatic balance, i.e. by protecting the gastric mucosa, aggregating platelets and ensuring efficient blood flow in the kidneys [4,5]. The COX-2 isoform is involved in the synthesis of prostanoids responsible for the further development of the inflammatory response [5]. The substrates for cyclooxygenase are unsaturated fatty acids: dihomo-gamma-linolenic, alpha-linolenic, eicosapentaenoic (EPA), docosahexaenoic (DHA), and, especially, arachidonic acid (AA) [4,5]. COX-2, as well as COX-1, can use polyunsaturated fatty acids (DHA, EPA) in addition to arachidonic acid as substrates. Subsequently, with the participation of 5-LOX (lipoxygenase), the polyunsaturated fatty acids are formed of resolvins E, D and leukotrienes 5 series are formed [4,6]. These metabolites are responsible for catalysis, for the process of extinguishing inflammation by inhibiting the migration of neutrophils to the site of inflammation, and for reducing the expression of pro-inflammatory cytokines (as shown in simplified Figure 1) [4-6].

* **Corresponding author**
e-mail: anna.zajac-grabiec@ifj.edu.pl

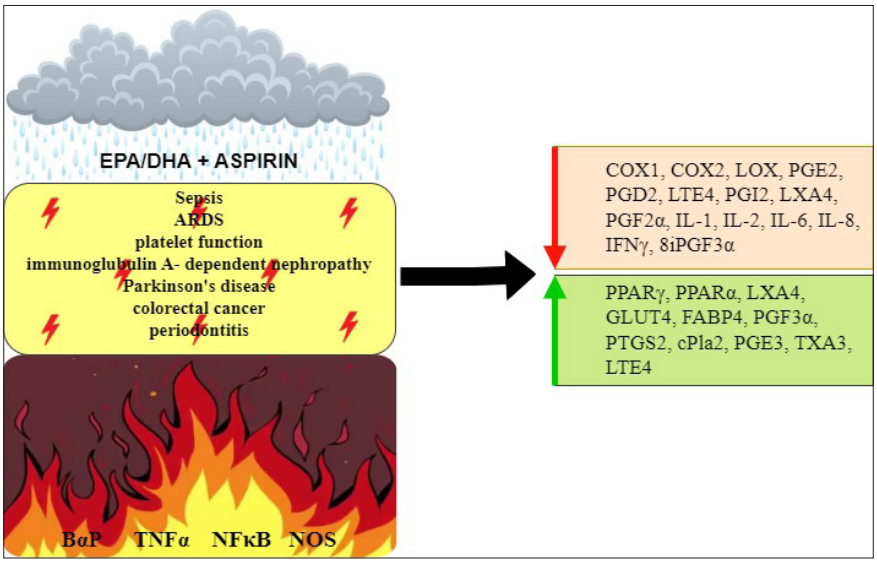

Figure 1. Summary of synergism effect of combination therapy with aspirin and EPA/DHA acids. Decreasing the inflammatory mediators i.e. COX1, COX2, LOX, PGE2, PGD2, LTE4, PGI2, LXA4, PGF2α, IL-1, IL-2, IL-6, IL-8, IFNϒ, 8iPGF3α along with increasing the levels of anti-inflammatory mediators i.e. PPARϒ, PPARα, LXA4, GLUT4, FABP4, PGF3α, PTGS2, cPla2, PGE3, TXA3, LTE4 may cause lowering of the inflammatory factors such as BαP, TNFα, NFκB, NOS and diseases of various origination like SEPSA, ARDS, platelet function, immunoglobulin A-dependent nephropathy, Parkinson's disease, colon cancer, periodontitis

The discovery of anti-inflammatory lipid mediators is of particular importance for the health benefits attributed to the omega-3s: EPA and DHA [7,8]. Three derivatives of omega-3 polyunsaturated fatty acids are known: resolvins, protectins and maresins. Resolvins are lipid mediators with anti-inflammatory potential, depending on the type of omega-3 PUFAs from which they are metabolized. There are two known groups of resolvins: E and D [8,9]. E series are synthesized from EPA acid for inhibiting the migration of neutrophils to sites of inflammation, reducing the release of pro-inflammatory cytokines, stimulating macrophages to phagocytose already dead neutrophils, and preventing osteoclast-dependent bone damage [9]. D series are derivatives of docosahexaenoic acid formed by the same biochemical transformation as the above-described resolvins of the E series. They also show similar anti-inflammatory effects [7,8]. Protectins and maresins are both derivatives of DHA formed under the influence of lipooxygenase [7,8]. They limit the accumulation of multinucleated leukocytes in the area of inflammation under the influence of phagocytic macrophage activity, reducing the migration of neutrophils, together with increasing the relocation of monocytes [7,10,11].

Studies on inflammatory mediators have identified the anti-inflammatory potential of polyunsaturated fatty acids and their derivatives [7,11]. Omega 3-PUFAs regulate the activity of transcription factors, activate peroxisome proliferator-activated receptor gamma PPARγ, inhibit nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) translocation to the cell nucleus, as well as the expression of nitric oxide synthase (NOS), the synthesis of interleukin IL-1, IL-2, IL-6 and the protein kinase C signaling pathway, serve as ligands for G protein-coupled membrane receptors (GPR120), and block the inflammatory response of cells [11,12]. Through activation of GPR120, macrophages reduce toll-like receptor 4 (TLR4) expression, and tumor necrosis factor α (TNF α) synthesis [12,13]. Omega 3-PUFAs, by activating phospholipase A2 (cPLA2) and COX-2, can modify the arachidonic acid metabolic pathway [14,15]. Conversion of eicosapentaenoic acid by the enzyme cyclooxygenase (COX) leads to the formation of anti-inflammatory cytokines: prostaglandin E3 (PGE3) [3], thromboxane A3 (TXA 3) [3], and leukotriene 5 series (LTE 5) [3,7].

It is known that a common feature of most diseases is inflammation. This involves various signaling pathways, transcription factors, pro-inflammatory cytokines and products of arachidonic acid metabolism. All these factors are essential for the development of new therapeutic agents targeting inflammatory diseases [16-18]. As Filipczyk L *et al*., have already shown, the inflammatory process is quite complex [15]. Chronic inflammation within visceral adipose tissue can lead to insulin resistance, lipotoxicity, atherosclerosis, type II diabetes, hyperlipidemia, hypertension and heart disease [18,19].

One of the goals of this review is to illustrate the effect of polyunsaturated fatty acids in combination with ASA on the expression of genes and proteins activated by pro-inflammatory factors in various clinical cases, which has not been demonstrated so far. Currently, few scientific articles discuss the side effects of omega 3-PUFAs supplementation in excessive amounts, such as nausea, abdominal pain, vomiting, reflux, gastroenteritis, liver dysfunction and rashes [16]. Moreover, there are only a few *in vivo* studies that report the synergism between NSAIDs and omega-3s, which would reduce the side effects caused by these compounds and increase the effect of therapy.

Most studies, especially those based on humans, do not report a target dose of omega-3 unsaturated fatty acid derivatives in combination with non-steroidal anti-inflammatory drugs (NSAIDs). For this reason, this review aimed to illustrate the importance of studies presenting synergism between omega-3 PUFAs with specialized drugs and their derivatives as valuable active substances that may be important in the development of new drug combinations and therapeutic regimens.

Acetylsalicylic acid has found wide application in cardiology, acute coronary syndromes, venous thromboembolism and CVD prevention, as it has an anti-aggregative effect on platelets [20]. The application of atherosclerosis as an antioxidant by inhibiting the oxidation of LDL fraction cholesterol particles to oxLDL components involved in atherosclerotic plaque formation [21] has also been presented. Aspirin, a non-steroidal anti-inflammatory drug (NSAID),

is known for its anticancer properties [21,22]. The mechanism of cancerogenesis inhibition by aspirin is not well understood, but in many cancers, an elevated level of COX-2 was found [21,22]. Inhibition of COX-2 activity can induce apoptosis and inhibit the formation of blood vessel processes involved in the pathophysiology of CVD (angiogenesis). Studies performed by Sankaranarayanan R *et al*. suggest that there is a correlation between a diet rich in vegetables and a reduction in colon cancer risk through the presence of salicylic acid in food [22]. Many studies provide information that similar reactions are observed for unsaturated fatty acids. They have a beneficial effect in the prevention of various diseases, including inflammation, autoimmune diseases, rheumatoid arthritis, cardiovascular diseases, neurodegenerative diseases, type II diabetes and colon cancer (Figure 1) [3,18].

In contrast, aspirin, being a COX inhibitor, reduces the synthesis of prostaglandins and platelet aggregation [22]. Aspirin can cause damage to the gastric mucosa, induce toxic effects on the kidneys, and prolong bleeding time [22]. One of the most serious side effects of aspirin use is gastrointestinal complications, which contribute significantly to increased morbidity and mortality [6,22]. ASA, even in small doses, inhibits the excretion of uric acid through the renal tubules, which may result in gout attacks [24]. Moreover, aspirin is contraindicated in children and adolescents up to 16 years of age due to the risk of Reye's syndrome [24]. In order to present data, it should be indicated that more research is needed to assess the exact dose of aspirin in combination with omega-3 fatty acids that is necessary to reach a therapeutic effect or to minimize the side effects of both compounds.

USE OF ASPIRIN IN CLINICAL PRACTICE IN COMBINATION WITH POLYUNSATURATED FATTY ACIDS

Based on the different actions of omega-3 polyunsaturated fatty acids and aspirin together with their role in clinical practice, 7 subsections were identified in this review. Additionally, a summary with data about the number of patients; ASA, omega-3, and omega-6 doses; and duration of treatments, along with main results are presented in Table 1.

1. Polyunsaturated fatty acids together with aspirin as innovative treatments for sepsis and acute respiratory distress syndrome (ARDS)

The main mechanism of sepsis, as well as ARDS, is based on the activation of nuclear factor NF-κB [25]. This component enters the cell nucleus and begins the induction of gene expression for inflammatory mediators [25]. The process is followed by the production of pro-inflammatory cytokines like chemokines [25]. Endothelial degeneration is caused by the adhesion of leukocytes on its surface, which then leads to apoptosis with the participation of pro-inflammatory cytokines, activation of neutrophils, and the release of oxygen free radicals (NO) [25]. Sepsis is a generalized immunodeficiency state with a tendency to exacerbations that involve leukotrienes, thromboxanes, prostaglandin E2 and acute phase proteins [25]. Disruption of the coagulation cascade results in excessive fibrin production and clot formation (activation of factor X or IX) [25].

Aspirin is not only an inhibitor of COX, but also nuclear factor NF-Kβ, thromboxane A2, and nitric oxide. Moreover, ASA is recognized as an activator of lipoxin A4 (LXA4), prostaglandin I2 (PGI2) and has found widespread use in the treatment of sepsis by reducing the rate of disease progression or mortality [25]. However, it still does not eliminate the deficiency of the factor's precursor that extinguishes the inflammatory process, which is a major problem of the disease substrate [22]. Supplementation with polyunsaturated fatty acids and ASA increases the number of anti-inflammatory mediators (resolvins, protectins, marezins, LXA4), inhibits the COX enzyme, thereby properly and effectively extinguishing the inflammatory process in the body [22,25].

A study presented by Schneider TR *et al*., showed that patients with aspirin-induced exacerbation of respiratory disease (AERD) overproduce pro-inflammatory lipids LTE4 and PGD2, which are derived from the metabolism of omega-6 fatty acids [26]. In this study, a two-week analysis was conducted, showing that a diet rich in omega-3 fatty acids and deficient in omega-6 fatty acids improved AERD-related symptoms and reduced levels of pro-inflammatory biomarkers [26]. The dietary intervention altered fatty acid composition by reducing levels of pro-inflammatory biomarkers LTE4 and PGD2 (two inflammatory lipids derived from arachidonic acid), while maintaining unchanged levels of the metabolite PGE2 [26]. A modified diet has also been shown to increase the production of lipid mediators such as resolvin D1 that are derived from omega-3 fatty acids, which can reduce chronic airway inflammation [27,28]. This signifies that for patients with AERD, dietary modification to increase omega-3 fatty acids and decrease omega-6 fatty acids can reduce systemic production of leukotriene series 4 (LTE4) and prostaglandin series 2 (PGD2), which may lead to better control of respiratory symptoms [27,28]. To the best of our knowledge, this is the only study suggesting that a diet rich in omega-3 fatty acids and low in omega-6 fatty acids may be an effective non-pharmacological adjunct in patients with AERD [26]. It should be emphasized that concerning other studies (Table 1), Schneider *et al*. presented a comparison of results after supplementation of omega-3 along with omega-6 fatty acids. Based on these observations, clinical trials with different PUFA combinations using different doses of fatty acids and periods, are needed to determine the efficacy of PUFA/ARDS, not only in sepsis, but also in other diseases identified below in subsections 2-7. However, it should be emphasized that this is a study in which we have a comparison of omega-3 to omega-6 fatty acids, which is a very important aspect in our daily diet.

2. Effects of aspirin in combination with omega-3 fatty acids on platelet function and cardiovascular disease

Cardiovascular disease (CVD) is the leading cause of death worldwide [29,30]. Blood vessel formation through angiogenesis is associated with the instability and breaking of atherosclerotic plaques [30,31]. Cytokines such as TNF α, interleukin IL-6, IL-8, IL 1ß, platelet-derived growth factor

Table 1. Data about the number of patients; doses of ASA, omega-3, omega-6; and duration of treatment along with the main outcomes divided according with subsections 1-7

Research	Number of patients	ASA dose	Omega-3 dose	Omega-6 dose	Duration of treatment	Results
1. Polyunsaturated fatty acids together with aspirin as innovative treatments for sepsis and acute respiratory distress syndrome (ARDS)						
Schneider TR *et al*. [26]	10	Low dose	>3000 mg/day	<4000 mg/day	2 weeks	A high omega-3/low omega-6 diet may be an appropriate adjunct treatment option for patients with AERD
2. Effects of aspirin in combination with omega-3 fatty acids on platelet function and cardiovascular disease						
Block RC *et al*. 2012a [30]	15	650 mg/day	3400 mg/day	-	30 days	These data suggest that EPA+DHA has more pronounced down-regulatory effects on inflammation and angiogenesis than aspirin
Block RC *et al*. 2012b [31]	25	81 mg/day	3400 mg/day	-	4 hours	The combination of aspirin with omega-3 fatty acids shows synergism in attenuating platelet function compared to aspirin alone in healthy adults
Thorngren M *et al*. [32]	10	Two doses: 3.5 and 10 mg/kg/day	2000-3000 mg/day	-	11 weeks	ASA prolonged bleeding time by more than the sum of the increases in bleeding time caused by ASA and by the EPA diet separately, but the synergism was not significantly more than additive
3. Effect of aspirin combined with omega-3 fatty acids in patients with type 2 diabetes, on ApoA1 and HDL cholesterol levels associated with CVD						
Block RC *et al*. 2017 [34]	30	81 mg/day	2600 mg/day	-	53 days	The combination of acetylsalicylic acid with omega-3 fatty acids, especially DHA, has the most beneficial effect on levels of lipid mediators that increase the risk of CVD events
Bowman L *et al*. [35]	15480	100 mg/day	1000 mg/day	-	7 years	Aspirin with omega-3 fatty acids affects the cyclooxygenase pathway, which may reduce platelet function
4. Aspirin combined with eicosapentaenoic acid can stop progressive immunoglobulin A-dependent nephropathy, a potential alternative in immunosuppressive diseases						
Hirahashi J *et al*. [37]	Case 1: 1 patient	100-200 mg/day	1800-2700 mg/day	-	60 months	3 patients with progressive IgA nephropathy were cured with a combination of low-dose aspirin and highly purified EPA as a substitute for steroid therapy
	Case 2: 1 patient	100-200 mg/day	1800-2700 mg/day	-	39 months	
	Case 3: 1 patient	100 mg/day	1800-2700 mg/day	-	42 months	
Alexopoulos E *et al*. [39]	14	-	850 mg EPA and 580 mg DHA/day	-	4 years	Low-dose PUFA is also effective in slowing the progression of kidney disease in high-risk patients with IgAN, especially those with advanced kidney disease
5. EPA in conjunction with aspirin, alone and in combination to prevent colorectal adenoma						
Hull MA. *et al*. [40]	176 179 177 177	- - 300 mg/day 300 mg/day	- 2000 mg EPA/day - 2000 mg EPA/day	- - - -	1 year	The fewest colorectal adenomas were detected in those taking EPA in combination with ASA
6. Combination of DHA with ASA as a new therapeutic option in Parkinson's disease						
Fu Y *et al*. [42]	Patients with Parkinson's disease	ASA (no information about dose)	DHA	-	24 h	The combination of docosahexaenoic acid and aspirin at appropriate concentrations can protect neurons by inhibiting miR-21 and activating PPARα, RXRα in patients with Parkinson's disease
7. Supplementation with omega-3 polyunsaturated fatty acids combined with low-dose aspirin in periodontitis						
Castro Dos Santos NC *et al*. [44]	75	100 mg	3000 mg/day	-	2 months	Supplementation with ω-3 PUFA and low doses of ASA for 2 months as an adjunct to periodontal cleansing promotes clinical and immunological benefits in patients with type 2 diabetes
Keskiner I *et al*. [45]	30	-	6.25 mg EPA and 19.19 mg DHA	-	6 months	Salivary TNF-α levels showed a statistically significant decrease in the test group at 6 months compared to the control group

(PDGF), basic fibroblast growth factor (b-FGF) and vascular endothelial growth factor (VEGF) are associated with the progression of cardiovascular disease [29-31].

The Block RC *et al*. experiment involved a 4-week study [30]. On the first day, patients with atherosclerosis were given a single dose of 650 mg of aspirin [30]. On the second day, patients were given only 3400 mg of EPA + DHA, and on the 30th day, the diet was supplemented with 650 mg of ASA. Using the BioPlex suspension matrix system, the effect of aspirin with EPA + DHA, alone or in combination, on plasma levels of cytokines and angiogenesis factors was determined [30]. In conclusion, 4-week supplementation of omega-3 PUFAs alone and with ASA led to a significant reduction in the levels of cytokines and angiogenesis factors associated with atherosclerosis, such as TNF-α, interleukins IL-6, IL-8, IL-1ß, platelet-derived growth factors (PDGF), basic fibroblast growth factor (b-FGF) and vascular endothelial growth factor (VEGF) [30].

The next analysis of recent clinical trials on EPA+DHA with aspirin intake in healthy adults was also conducted by Block RC *et al*. [31]. Fasting blood samples were taken at the beginning of the study and 4 hours after supplementation with omega-3fatty acids, aspirin, or both, t function was measured using a platelet function analyzer [31]. Plasma levels of lysophosphatidylcholine (LPC), lysophosphatidic acid (LPA), autotaxin, angiogenesis activators and cytokines were measured. Platelet function was determined by measuring plasma levels of lysophosphatidylcholine (LPC), lysophosphatidic acid (LPA), autotaxin, angiogenesis activators and cytokines [31]. As an outcome, platelet function

was shown to decrease in the combination of aspirin with EPA+DHA (p=0.03), while it remained unchanged with ASA and EPA+DHA alone (p>0.05) [31].

Thorngren M *et al*. examined the effects of an EPA-rich diet on platelet phospholipid fatty acid composition, platelet aggregation and bleeding time [32]. The study was conducted on 10 healthy men, the diets of whom were enriched with 2000-3000 mg of EPA daily for 11 weeks. Both before and during the diet, two doses of ASA (3.5 or 10 mg/kg body weight) were administered. Accordingly, the EPA-rich diet prolonged bleeding time by 42% and reduced platelet aggregation [32]. Importantly, the authors found that ASA taken before the diet prolonged bleeding time by the same amount as the EPA-enriched diet alone. Moreover, ASA supplementation during a diet rich in EPA prolonged bleeding time compared with the sum of bleeding time prolongations induced separately by ASA and the EPA-rich diet [32].

The above results suggest a synergistic effect of aspirin with EPA+DHA on platelet function and the anti-inflammatory and anti-angiogenic effects of omega-3 fatty acids *in vivo* [29-33]. The inclusion of adequate amounts of EPA/DHA fatty acids in therapy, rather than frequent increases in the dose of acetylsalicylic acid, may also contribute to beneficial effects in aspirin-resistant patients with atherosclerosis. The question is, would the same effects observed in adults with cardiovascular disease occur in children, or in aspirin-resistant patients? In the studies done by Block RC *et al*. [30], Block RC *et al*. [31], and Thorngren M *et al*. [32], different durations of treatment were applied (from 4 hours to 11 weeks) and a limited number of donors were included (Table 1). These studies should be repeated on bigger groups, along with equal (ASA, omega-3, and omega-6) dosage to confirm/deny the synergism of ASA and omega-3 fatty acids in attenuating platelet function compared to aspirin alone in healthy adults. Additionally, further studies are needed to ascertain the exact dose of omega-3 fatty acids in combination with aspirin for the treatment of thrombosis, for prevention of myocardial infarction, or for remedying other CVD-related diseases.

Finally, it must be pointed out that in the studies by Block RC *et al*. [30], Block RC *et al*. [31] and Thorngren M *et al* [32], there is a very large scatter in the duration of treatment and too few patients to obtain a definitive result of the synergism of ASA and omega-3 fatty acids in attenuating platelet function compared to aspirin alone in healthy adults.

3. Effect of aspirin combined with omega-3 fatty acids in patients with type 2 diabetes, on ApoA1 and HDL cholesterol levels associated with CVD

The pathophysiological basis of cardiovascular disease in patients with diabetes is difficult to explain. Low-dose aspirin is the drug of choice for CVD prevention, while people with diabetes may be resistant to ASA [34,35]. Higher levels of omega-3 PUFAs have a beneficial effect in reducing CVD events. Aspirin with omega-3 fatty acids affects the cyclooxygenase pathway, which may reduce platelet function [34,35]. HDL cholesterol (HDL-C) is associated with CVD risk, where ApoA1 is the major protein component of HDL-C and is essential for HDL-C biogenesis, and function. A key protective role of apoA1 is the ability to turn on/off HDL-C molecules [34]. The study by Block RC *et al*. 2017 involved only adults with type 2 diabetes, in which patients were given aspirin, EPA, and DHA. As an outcome of this work, aspirin was found to haven a statistically significant effect on HDL-C levels, replacing apoA1 when DHA or EPA levels were moderate, on plasma levels in patients with type 2 diabetes [34].

The presented results suggest that the combination of acetylsalicylic acid with omega-3 fatty acids, especially DHA, has the most beneficial effect on levels of lipid mediators that increase the risk of CVD events, and in patients with type 2 diabetes treated with ASA, a personalized dose of omega-3 PUFAs may be a beneficial option in aspirin resistance [34].

In a study by Wang IE *et al*., the authors demonstrated a specific role for ASA at a low dose of 75-100 mg/day in combination with omega-3 fatty acids in reducing CVD risk also in aspirin-deficient and diabetic patients [36]. Other studies describe personalized DHA/EPA dosing in patients with aspirin-resistant diabetes or patients with CVD in combination with aspirin. In the context of study limitations, unlike the study by Block RC *et al*. [30,31,34], the work of Bowman L *et al*. [35] would be relevant for clinical practice because of the large number of patients included in this study (Table 1). On the other hand, an advantage for the next research study design is the similar applied doses of ASA and omega-3 fatty acids in both studies [34,35].

4. Aspirin combined with eicosapentaenoic acid can stop progressive immunoglobulin A-dependent nephropathy, a potential alternative in immunosuppressive diseases

Immunoglobulin A-dependent nephropathy is a disease of the kidney and the immune system [37]. The pathomechanism of IgA-dependent nephropathy involves the deposition of IgA antibodies in the glomeruli, which leads to an inflammatory reaction within them, neutralizing the negative charge of the filtration membrane, thereby promoting protein adhesion and limiting resorption [37]. In addition, the NFκB signal transduction pathway is activated, as well as the expression of NOS and TNF-a, leading to kidney damage [38].

The study done by Hirahashi J *et al*. aimed to halt progressive immunoglobulin A-dependent nephropathy in three patients treated with acetylsalicylic acid in combination with EPA/DHA [37]. They were initially given 100 mg of aspirin with 1800 mg of EPA daily, instead of the steroid drugs they had previously been treated with. The doses of acetylsalicylic acid were increased to 200 mg/day and EPA to 2700 mg/day to improve the patient's condition [37]. In the first patient, minimal hematuria was observed, proteinuria decreased from 2.55 g/g to 0.21 g/g, renal function appeared stable (whereas previously it had not), as well as a remission of the disease was seen. A similar situation was observed in the second and third patients, whose urinary protein levels decreased from 0.81 to 0.08 g/g, and in the third from 2.64 g/g to 0.37 g/g [37].

In the next study, Alexopoulos E *et al*. showed that a very low daily dose of omega-3 fatty acids was effective in slowing the progression of kidney disease in high-risk patients with IgA nephropathy, especially those with advanced kidney disease [39]. In this study, patients were

supplemented with 850 mg of EPA and 580 mg of DHA daily. Fourteen patients received very low doses of omega-3 fatty acids (PFA), while the control group consisted of 14 asymptomatic patients [39]. The two groups were similar in terms of serum creatinine concentration (Scr) as well as glomerular filtration rate (GFR). Patients were treated for four years with the same pattern. The primary endpoints were an increase in Scr of 50% or more or a decrease in GFR of 50% or more at the end of the study. It was shown that during treatment in the PFA group, the mean annual change in Scr was 0.2 mg/dl in the PFA group and 1.0 mg/dl in the control group, while the mean annual change in GFR was 1.4 ml/min in the PFA group and 3.0 ml/min in the control group. Only one patient in the PFA group (7%) and six patients in the control group (43%) developed end-stage renal disease within 4 years [39].

The above studies underscore the key role of EPA jointly with ASA in progressive immunoglobulin A-dependent nephropathy. Researchers have observed minimal hematuria, reduced urinary protein levels, stabilization of renal function, and remission of the disease [37,39]. Regrettably, this is one of the few reports describing the correlation of EPA acids with ASA in immunoglobulin-dependent nephropathy [37,39]. Furthermore, Hirahashi J *et al*. [37] studied only three cases, Alexopoulos E. *et al*. [39] fourteen patients, which limits conclusively answering whether ASA combined with omega-3 fatty acids can replace steroid therapies in immunoglobulin-A dependent nephropathy (Table 1). More clinical trials are needed, with a much larger group of patients, in a wider age range, to accurately determine the optimal dose of EPA and DHA in combination with acetylsalicylic acid or alone to compare whether lower dose regimens are less effective in protecting kidney function in the relation to higher dose regimens in clinical practice.

5. EPA in conjunction with aspirin, alone and in combination to prevent colorectal adenoma

A colorectal adenoma is a benign type of intestinal cancer with glandular dysplasia of the intestinal epithelium [40]. Epithelial dysplasia forms neoplastic polyps of varying severity and involves changes in the structure, differentiation, maturation, transformation of epithelial cells [40].

Hull MA *et al*., in their study, emphasize the key role of EPA in combination with aspirin in the prevention of colorectal adenoma [40]. The experiment involved 709 patients aged 55 to 73 at high risk of intestinal adenoma. Patients were divided into four research groups. The first group (176 people) received a placebo, the second group (179 people) was supplemented with only 2 grams of EPA, the third group (177 people) took 0.3 grams of aspirin alone, the fourth group (177 people) received 2 grams of EPA and 0.3 grams of aspirin daily [40]. Participants' follow-up colonoscopy was performed 12 months after the start of the study. Among the studied groups, the fewest colorectal adenomas were detected in people taking EPA combined with ASA in combination, which was particularly visible in left-sided lesions [40].

The benefits of EPA with aspirin in preventing colorectal adenomas have also been described by Wang IE *et al*. The authors showed that ASA (300 mg/day) combined with EPA reduced the burden of colorectal adenoma in terms of location or subtype [36]. Analysis of recent clinical trials has shown that the combination of omega-3 polyunsaturated fatty acid derivatives and aspirin prevents the formation of the left, and right-sided neoplastic lesions of the colorectal adenoma [36,40]. In the context of narrative review, it should be noted that the study done by Hull MA *et al*. [40] is the only that describes a valuable ASA/EPA/EPA + ASA combination. Future studies should be conducted with individuals at increased risk of CVD events, abdominal obesity, and chronic stress which may be related to the development of colorectal adenoma.

6. Combination of DHA with ASA as a new therapeutic option in Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder. The diagnosis of degeneration is based on motor slowing, resting tremor, muscle rigidity, and postural abnormalities [41]. PD results from the loss of neurons that produce a transmitter in the brain called ‘dopamine’ [41]. Unfortunately, it becomes increasingly difficult to treat over time due to the severity of the movement disorders, the risk of falls, and the addition of non-motor symptoms such as cognitive, mood, sleep, psychotic, or dysautonomia. Parkinson's disease does not mask an effective and consistent therapeutic approach that does not change over time [41].

The experiment proposed by Fu Y *et al*. evaluated the expression of PPARα, retinoid X receptor (RXRα), and microRNA-27 (miR-27) factors in PD patients [42]. RXRα is a nuclear receptor involved in retinoid acid-mediated gene activation, while miRNAs are important in regulating this receptor in humans. RXRα in humans is involved in several signaling pathways. For example, a study performed by Fu Y *et al*. showed that where miR-21 levels increased, the PPARα levels decreased in PD patients compared to controls [42]. In addition, DHA increases PPARα expression by inhibiting miR-21, whilst the combination of ASA with DHA activates RXRα, and PPARα, respectively [42]. Acetylosalic acid combined with DHA effectively enhances the heterodimeric formations of PPARα and RXRα. Moreover, aspirin combined with DHA could significantly increase brain-derived neurotrophic factor BDNF and glial-derived neurotrophic factor GDNF, while inhibiting NfkB and COX-2 [42].

The above *in vivo* study shows that the combination of docosahexaenoic acid and aspirin in appropriate concentrations can protect neurons by inhibiting miR-21 and activating PPARα, RXRα in patients with Parkinson's disease [42]. However, in this study, only DHA has been described. Consequently, it will be valuable for clinical practice to include the EPA derivative, which, according to the authors [42], has much wider applications.

7. Supplementation with omega-3 polyunsaturated fatty acids combined with low-dose aspirin in periodontitis

Periodontitis is one of the most common, non-communicable chronic diseases (NCD) in humans [42]. It manifests as heavy inflammation of the periodontium [43]. The aim of the study done by Castro Dos Santos NC *et al*. was

to determine the clinical and immunological effects of orally administered omega-3 fatty acids and ASA in the treatment of periodontitis in patients with type 2 diabetes mellitus [44]. The authors showed that interferon-γ (IFN-γ), and interleukin-8 (IL-8) levels decreased in all study groups treated with omega-3 fatty acids and aspirin [44]. As an outcome of the work, dietary supplementation with ω-3 PUFAs and ASA was found to improve clinical and immunological outcomes in the treatment of periodontitis in patients with type 2 diabetes [44].

Keskiner I *et al*. study showed that supplementation with low doses of omega-3 fatty acids reduces salivary levels of tumor necrosis factor-α (TNF-α) in patients with chronic periodontitis [45]. Thirty healthy subjects with chronic periodontitis were included in the study and randomly assigned to two groups. The control group (n=15) was treated with scaling and root planing (SRP), while the test group met with SRP only. Moreover, the test group was supplemented with low doses of omega-3 PUFAs [45]. Saliva samples were collected, then analyzed for TNF-α, and SOD. Parameters were measured at the beginning of the study, 3, and 6 months after treatment. Both groups showed changes in parameters in response to treatment compared to baseline values [45]. The level of TNF-α in saliva decreased significantly in the study group after 6 months compared to the control group. Furthermore, salivary (superoxide dismutase) SOD levels increased significantly after 3 and 6 months in the study group and after 6 months in the placebo group compared to baseline values [45]. Interestingly for clinical practice, in the study proposed by Keskiner I *et al*. [45], very small doses of EPA and DHA were applied (see Table 1). In contrast, the results presented by Castro Dos Santos NC. *et al*. [44] showed that higher doses of omega-3 PUFA and ASA supplementation bring benefits in the treatment of periodontitis. Therefore, additional studies are needed to standardize the dosage and determine the mechanism of administration of ASA or omega-3 PUFAs.

Table 2. Summary of a beneficial combination of omega-3 fatty acids and aspirin presented in different diseases with the description of the main functions and mechanisms of action

A beneficial combination of omega-3 fatty acids and aspirin	
Main functions	Mechanisms of action
As innovative treatments for sepsis as well as acute respiratory distress syndrome	ASA with PUFAs n-3 increases anti-inflammatory mediators and inhibits COX enzyme, thus properly as well as effectively inhibiting the inflammatory process in the body. A diet rich in omega-3 fatty acids, poor in omega-6 improves symptoms associated with ARDS and lowers pro-inflammatory biomarkers [25-28]
On platelet function and CVD	A synergistic effect on platelet function after low-dose aspirin combined with EPA + DHA was described. Decreased platelet aggregation was observed. In patients with resistant aspirin, it is recommended to include adequate amounts of omega-3 fatty acids in aspirin therapy, and not to repeatedly increase the dose of the drug used [29-33]
In patients with type 2 diabetes, on ApoA1 and HDL cholesterol on levels associated with cardiovascular disease – CVD	The results suggest that combining acetylsalicylic acid with omega-3 fatty acids, especially DHA has the most beneficial effect on levels of lipid mediators that increase the risk of CVD events. In conclusion, personalized dosing of DHA in patients taking aspirin may be a beneficial option for aspirin-resistant patients with type 2 diabetes [20,34-36]
Can stop progressive immunoglobulin A dependent nephropathy, a potential alternative in immunosuppressive diseases	A low daily dose of omega-3 fatty acids was effective in slowing the progression of kidney conditions in high-risk patients with IgA nephropathy, especially those with advanced kidney disease [37,39]
To prevent colorectal cancer	Based on the reviewed results, it was found that both drugs had a preventive effect on the formation of neoplastic lesions of the large intestine [36,40]
As a new therapeutic option for Parkinson's disease	The combination of DHA with aspirin can protect neurons by inhibiting miR-21, activating PPARα, RXRα in patients with Parkinson's disease. Moreover, the combination could significantly increase the expression of BDNF and GDNF, while inhibiting NFκB, COX-2 [41,42]
In patients with periodontitis	It was shown that the levels of IFN-γ, and IL-8 decreased in all study groups supplemented with omega-3 acids + aspirin. Dietary supplementation of ω-3 PUFAs and ASA improves clinical, immunological outcomes in the treatment of periodontitis [43-45]

LIMITATIONS AND CONCLUSIONS

The synergistic effect of omega-3 fatty acids in combination with aspirin in clinical practice has been presented for the innovative treatment of several common, difficult-to-treat diseases in society. These medical conditions include i.e. sepsis and ARDS, coagulation disorders, progressive IgA nephropathy, colorectal cancer, Parkinson's disease, periodontitis, diabetes related to cardiovascular disease (CVD) and cholesterol disorders as shown in simplified Table 2. As presented, decreasing the inflammatory and anti-inflammatory mediators during combination therapy with aspirin and EPA/DHA may generate different synergistic effects. There are only a few reports on innovative pharmacotherapy of ASA + omega-3 PUFAs in the aforementioned single disorders. Considering the complex aspects of these studies and the effects of aspirin with PUFAs, a summary in Table 2 was prepared.

Based on the above information, we suggest that combining omega-3 PUFA acids with aspirin could be a breakthrough in the treatment of acute, as well as chronic inflammatory conditions. The latter include many diseases of civilization that are serious medical problems. Unfortunately, there are still many uncertainties about the effects of omega-3 polyunsaturated fatty acids and aspirin in clinical practice caused in many cases by limitations of studies. First, the analyses were conducted on a very small number of patients, with different time lengths of drug administration and then observation. Second, the doses of ASA and PUFA also vary significantly. Third, reviewed studies lack drug combinations of ASA, ASA+EPA, EPA, ASA+EPA+DHA, and DHA. In addition, few reports concern omega-6 fatty acid derivatives such as gamma-linolenic acid (with anti-inflammatory, antiproliferative, vasodilator and hypolipemic properties) in combination with acetylsalicylic acid. This combination may have significant pro-drug benefits [46]. In addition, some of the reviewed studies were published many years ago [1,4,21,32,39]. Therefore, further research design on the synergistic effect of PUFAs with acetylsalicylic acid is important, as this will allow the use of a lower dose of the drug, reducing the number of side effects after ASA administration, and, consequently, allowing more effective and safer pharmacotherapy for the patient. In view of ASA administration side-effects, it would be very important to determine the target dose of omega-3 unsaturated fatty acid derivatives in combination with non-steroidal anti-inflammatory drugs (NSAIDs). Finally, future clinical trials of polyunsaturated fatty acids in combination

with non-steroidal anti-inflammatory drugs should be performed in different patient groups (of different race, gender and age).

ORCID iDs

Anna Zając-Grabiec https://orcid.org/0000-0003-1558-4777
Katarzyna Sroczyńska https://orcid.org/0000-0002-9978-0769
Justyna Miszczyk https://orcid.org/0000-0001-7226-1750

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