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Low Dose Aspirin and Omega 3 Fatty Acids in the Pro Resolving Pathway of Cardiovascular Disorders

Jayavelan Ramkumar¹ and Nidhi Sharma^{2*}

¹Department of Cardiothoracic Surgery, Sri Ramachandra Medical College and University, Chennai-600116, India.

²Department of Obstetrics and Gynaecology, Saveetha Medical College, Saveetha University, Chennai-602105, India.

Authors' contributions

This work was carried out in collaboration between both authors. Author JR designed the study, designed the conceptual framework, wrote the protocol and wrote the first draft of the manuscript. Author NS managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Newer mechanisms of action of Acetyl Salicylic acid have been discovered in proresolving pathway of various disorders. Omega 3 fatty acids are also involved in the synthesis of resolvins via an aspirin triggered pathway. The present review aims to discuss the role of recently discovered aspirin triggered lipoxins, resolvins, protectins, maresins in understanding the pathophysiology of endothelial dysfunction in various cardiovascular disorders, especially hypertension. The concept of aspirin triggered lipoxins (15-epi-LXA₄ and 15-epi-LX₄) counteracting the action of LTB₄, PGE₂, and TXA₂ is discussed. Aspirin triggered lipoxins also block the expression of IL-8 gene. Aspirin is the only known NSAID to induce NO in a dose dependent manner. In this narrative review, we describe role of acetyl salicylic acid in the pro-resolution pathways that might prevent or reduce complications in patients with high blood pressure.

*Corresponding author: E-mail: drbonuramkumar@yahoo.co.in;

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ABBREVIATIONS

NSAIDS	: Non Steroidal Anti Inflammatory Drugs
COX	: Cyclooxygenase
LA	: Linoleic Acid
ALA	: Alpha Linolenic Acid
LX	: Lipoxin
LT	: Leucotriene
NO	: Nitric Oxide
PG	: Prostaglandin
TX	: Thromboxane
DHA	: Docosa Hexaenoic Acid
LOX	: Lipoxygenase
AT	: Aspirin Triggered
GPCR	: G protein coupled Receptor
PUFA	: Polyunsaturated Fatty acid
HETE	: Hydroxy Eicosa Tetraenoic Acid
FPR	: Formyl Peptide receptor
PMN	: Polymorphonucleocyte
IL	: Interleukin
TGF	: Transforming Growth Factor
TNF	: Tumor Necrosis Factor
Rv	: Resolvins
PD	: Protectins
HEPE	: Hydroxy Eicosa Pentanoic acid
Mar	: Maresins
NP	: Neuroprostanes
EFOX	: Electrophilic oxy derivatives
NF- κ B	: Nuclear Factor kappa-light-chain-enhancer of activated B cells

1. BACKGROUND

Aspirin, a term coined by Bayer Pharmaceuticals, is the acetylated form of salicylic acid. Salicylate is a common constituent of numerous medicinal plants that have been used for thousands of years to treat pain and rheumatic fever in Ayurveda. Ancient Egyptians used the leaves of Myrtle tree to treat rheumatic pain. Hippocrates treated eye infections with extracts from poplar trees and used extracts from willow bark in treating pain and fever associated with childbirth. Salicylate was first chemically synthesized in 1859 and was widely used as an anti-inflammatory in 1876. Salicylate is unstable, has an extremely bitter taste and causes gastric irritation. Hence, researchers set out to develop analogs with the same pharmacological benefits but easier to tolerate upon ingestion. In 1897 Felix Hoffman, at Bayer pharmaceuticals, discovered the mechanism of acetylation of salicylate and thus there was advent of aspirin (acetylsalicylic acid) [1,2].

Aspirin was in use for over 70 years and yet its mode of action remained unknown. In 1960, H.O. Collier and colleagues determined that aspirin worked through pathways involved in the synthesis of the prostaglandins. In 1971, it was discovered that aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) exerted their effects through the inhibition of PG synthesis by inhibition of the bifunctional enzyme cyclooxygenase (there are two forms COX-1 and COX-2). However, the ability of aspirin to limit leukocyte migration into sites of inflammation, thereby dampening the recruitment and march of host inflammatory responses could not be explained only later [3]. Aspirin and Fish oil are low cost interventions that can prevent and aid in the resolution of inflammation [4].

2. OMEGA 3 FATTY ACIDS AND THEIR CARDIOVASCULAR ACTIVITY

Linoleic acid (LA; 18:2 ω -6) and α -linolenic acid (ALA; 18:3 ω -3) are essential fatty acids that are not synthesized by the human body. Docosahexaenoic acid (DHA) is considered as conditionally essential because of its limited formation from ALA.

DHA and EPA are biologically active omega 3 fatty acids that help in the prevention of cardiovascular diseases [5,6]. A high intake of ω -3 PUFA (>3gms/day) has been associated with cardiovascular protective effects improving endothelial function and reducing atherosclerosis [7]. Beneficial effects have been observed on blood pressure (BP), lipid profile, and platelet aggregation and also by their anti-inflammatory and proresolution properties [8]. Clinical studies suggest that consumption of ω -3 PUFA may reduce blood pressure in hypertensive subjects and patients with other cardiovascular risk factors such as overweight, hyperlipidemia or in patients treated with hemodialysis [9,10,11]. Fig. 1 summarizes the clinical benefits of ω -3 PUFA (Fig. 1).

3. ASPIRIN IN THE PREVENTION OF CARDIOVASCULAR DISEASES

Cardiovascular Disease is a leading cause of morbidity and mortality worldwide. The pathology is believed to evolve in two stages with endothelial dysfunction and atherosclerosis leading to Hypertension, Myocardial Infarction and Stroke

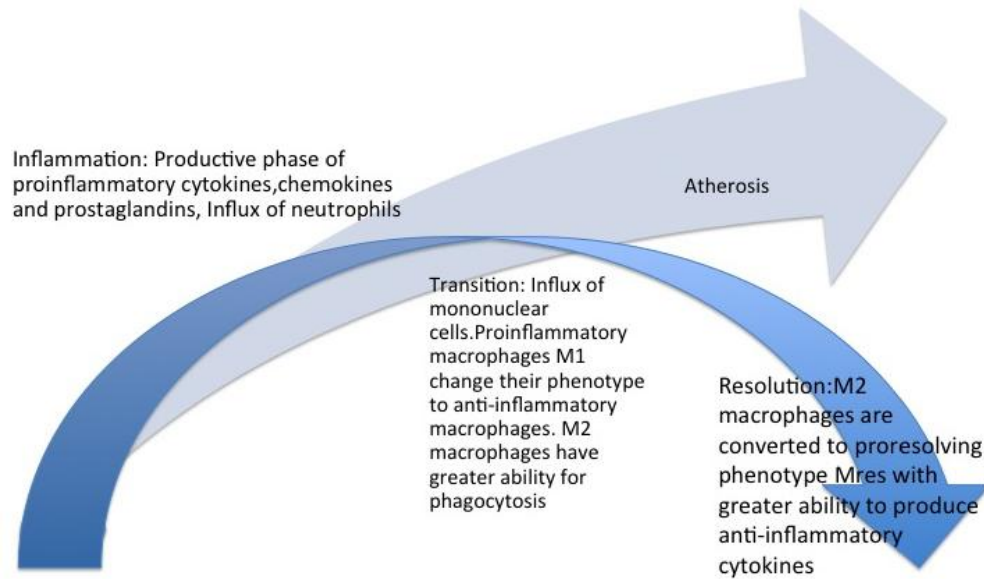


Fig. 1. The three phases: Inflammation, transition and resolution. Endogenous protective pathway resolves the initial inflammation leading to prevention of atherosclerosis in the transition phase endogenous protective pathway resolve the initial inflammation preventing atherosclerosis and leading to a normal vessel wall and blood pressure

as consequence of systemic inflammation, oxidative stress, and endothelial dysfunction [12-14]. Endothelial dysfunction is an exaggerated inflammatory response attributed to an unbalanced regulation of innate and adaptive immune responses. Atherosclerosis is deposition of subendothelial lipid-filled foam cells, fibrinoid necrosis of the arterial wall, perivascular lymphocytic infiltration, and it is similar to early atherosclerosis. In the transition phase, endogenous protective pathways resolve the initial inflammation preventing atherosclerosis and leading to a normal vessel wall and Blood pressure (Fig. 2). Resolution of inflammation is an ongoing process coordinated by mediators derived from Arachidonic acid, Eicosapentaenoic acid and Docosahexanoic acid. These include Lipoxins, Resolvins, Protectins and Maresins [15,16]. A lipoxin is an anti-inflammatory eicosanoid synthesized through the lipoxygenase interactions.

The LXs and Epi LXs also inhibit the actions of the leukotriene Lipoxins have been shown as an anti-inflammatory mediator in human endothelium in both in vivo and in vitro studies [17]. If the initial stage of inflammation is not controlled by immune regulation in endothelium, there is development of oxidative and endoplasmic reticulum stress, release of proinflammatory cytokines, increased anti

angiotensin antibodies in the circulation. This leads to endothelial and leukocyte activation in multiple organs. In the cardiovascular system, there is hypertension, peripheral edema, pulmonary edema and cardiac failure. In kidneys, there is glomerular endotheliosis resulting in proteinuria and renal failure. In brain, there is cerebral vessel ischemia and stroke [18].

4. ASPIRIN- CYCLOOXYGENASE INTERACTIONS

Aspirin is unique in that it not only has analgesic (pain), antipyretic (fever) and anti-inflammatory effects (exerted at the level of the PG and TX synthesis) but it also exerts beneficial effects on the cardiovascular system via anti-inflammatory pathways distinct from PG and TX inhibition mediated by the salicylate group and the acetyl group (Fig. 2). At high doses (300-325 mg three times a day) aspirin functions to block the PG and TX synthesizing activity of COX-1 which results in inhibition of the primary pro-inflammatory, pyretic and pain-inducing action of these eicosanoids [19]. At the site of coagulation there is a balance between the levels of platelet derived TXA₂ and endothelial cell derived PGI₂. This allows for platelet aggregation and clot formation but prevents excessive accumulation of the clot thereby maintaining blood flow around the site of the clot [20-22].

Possible Biological effects of omega3 Fatty Acids
Series 3 prostaglandin production with vasoactive ,antiplatelet and anti-inflammatory effects
Interaction with omega 6 pathways
Suppression of aldosterone secretion
Changes in intracellular signal transduction, reduction in plasma viscosity and in the activity of angiotensin converting enzyme
Increased production of endothelial Nitric oxide
Changes in ion channels with influence on the parasympathetic stimulation of vagus nerve reducing heart rate
Changes of myocyte cell membrane improving left ventricular diastolic function
Inhibition of transforming growth factor beta synthesis
Vascular smooth muscle apoptosis and prevention of vascular wall fibrosis and secondary hypertension development

Fig. 2. Omega 3 fatty acid: Biological effects

Endothelial cells regenerate active COX faster than platelets because mature platelets cannot synthesize the enzyme, requiring new platelets to enter the circulation (platelet half-life is approximately 4 days). Thus, PGI_2 synthesis is greater than that of TXA_2 . The effect of aspirin is more in favor of endothelial cell-mediated inhibition of the coagulation cascade [23-27].

5. CLASSICAL AND ASPIRIN TRIGGERED SYNTHESIS OF THE LIPOXINS

Lipoxin synthesis from arachidonic acid occurs through several different trans cellular interactions. An initial stimulus activates Phospholipase A_2 that hydrolyzes arachidonic acid from the membrane-associated phosphoinositide. Three pathways exist for the synthesis of the lipoxins. The "classic" pathway involves 5-lipoxygenase (5-LOX, encoded by the ALOX5 gene) activity in leukocytes followed by 12-lipoxygenase (12-LOX, encoded by the ALOX12 gene) action in platelets. The second pathway is the action of 15-lipoxygenase (15-LOX, encoded by the ALOX15 gene) in epithelial cells followed by the 5-LOX action in leukocytes.

The third pathway is that induced by aspirin-mediated acetylation of COX-2. Aspirin can trigger the synthesis of stereoisomers (epimers) of LXA_4 and LXB_4 identified as 15 epi- LXA_4 and 15 epi- LXB_4 (these compounds are also referred to as aspirin-triggered lipoxins (ATLs). In endothelial and epithelial cells the aspirin-

induced acetylation of COX-2 alters the enzyme such that it now converts arachidonic acid to 15R Hydroxy EicosaTetraenoic acid (15R-HETE). This is rapidly metabolized to the epi-LXs in monocytes and leukocytes through the action of 5-lipoxygenase (5-LOX). COX 2-enzyme initiation of leukotriene synthesis is prevented by acetylation [23,24].

6. ASPIRIN-LIPOXYGENASE INTER-ACTION

Only at low doses (75 mg) aspirin elicits its most important anti-inflammatory benefits. The low dose anti-inflammatory effects of aspirin are due to its ability to trigger the synthesis of the lipoxins (LXs: Epi LXA_4 and Epi LXB_4). Higher doses of aspirin have no significant effect on LX synthesis. [25].

The aspirin-triggered lipoxin synthesis pathway is initiated when activated circulating leukocytes (primarily neutrophils) adhere to the vascular endothelium leading to a tilt in balance towards resolution (Fig. 3). The lipoxins LXA_4 and 15 epi- LXA_4 elicit their effects by binding to a specific G protein-coupled receptor (GPCR) originally identified as ALXR. ALXR was originally identified as the formyl peptide receptor-like 1 (FPRL1) protein, a member of the formyl peptide receptor (FPR) family of receptors that bind N-formylated peptides derived by the degradation of bacteria or host cells. The ALXR/FPRL1 protein is encoded by the formyl peptide receptor

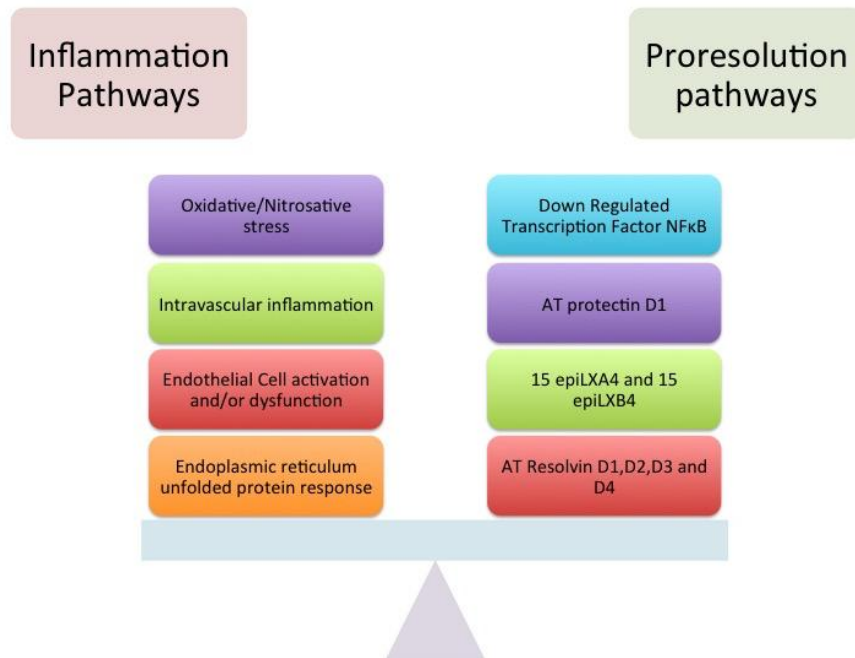


Fig. 3. Aspirin-triggered lipoxin synthesis pathway is initiated when activated circulating leukocytes (primarily neutrophils) adhere to the vascular endothelium and balance is tilted towards resolution

2 (FPR2) gene (26). The original member of the FPR family (FPR1) recognizes the N-formylated bacterial peptide formyl-Met-Leu-Phe. The FPRs are expressed predominantly in phagocytic leukocytes.

LXA₄ and LXB₄ promote the relaxation of the vasculature. Lipoxins and epi-LXs inhibit polymorphonuclear leukocyte (PMN) chemotaxis, PMN-mediated increases in vasopermeability, and PMN adhesion and migration through the endothelium. The LXs also stimulate phagocytosis of apoptotic PMNs by monocyte-derived macrophages. PMN phagocytosis represents the resolution phase of inflammatory events, thus aspirin promotes this process and increases the rate of return to the normal tissue state. This transition phase from inflammation to resolution is impaired in metabolic syndrome [28-30]. Lipoxins also lead to a reduction in swelling due to edema by regulating the actions of Histamine [31].

The actions of Epi LXA₄ lead to the production of prostacyclin (PGI₂) and Nitric Oxide (NO). The induction of NO by aspirin is correlated, in a dose-dependent manner, with a reduction in leukocyte accumulation at sites of inflammation. No other NSAID has been shown to exert this effect on NO production making aspirin unique

among this class of drugs [32,33]. Anti-inflammatory actions of the lipoxins and aspirin-triggered lipoxins include blocking expression of the IL-8 gene (a pro-inflammatory chemokine produced by macrophages and endothelial that stimulates neutrophil migration), inhibition of the release and actions of tumor necrosis factor- α (TNF- α), and stimulation of transforming growth factor- β (TGF- β)[34].

7. ASPIRIN INDUCED LIPID MEDIATORS FROM OMEGA 3 FATTY ACIDS

Aspirin also induces synthesis of an additional class of anti-inflammatory lipid mediators known as the resolvins (Rvs) and the protectins (PDs)[35,36,37,38]. These immune modulating EPA and DHA derivatives are referred to as Specialized Proresolving Mediators, SPM. Numerous studies have reported the role of omega-3 PUFAs, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in prevention of cardiovascular diseases [39]. A combination of aspirin and omega-3 PUFAs is an effective prevention strategy in cardiovascular diseases [40]. The Rv and PD molecules do not inhibit the onset of inflammation but stimulate the resolution pathways. Nine resolvin molecules and two protectins have been characterized.

The resolvins promote the resolution of the inflammatory cycle. The resolvins are divided into two classes with the E-series resolvins (RvE1, RvE2, and RvE3) being synthesized from EPA and the D series resolvins (RvD1–RvD6) being derived from DHA. The resolvins family members share a 17-hydroxy residue that is introduced into DHA by the lipoxygenase, 15-LOX. Several of the resolvins are synthesized in epimeric form via the effects of aspirin. The levels of RvE1 increase spontaneously in individuals taking aspirin or consuming EPA. RvE1 is produced in a trans cellular manner involving endothelial cells and leukocytes. Within the endothelium EPA is converted to 18R-HEPE (18R-hydroxyeicosapentaenoic acid) by the COX-2 enzyme following its exposed to aspirin (Fig. 4). The 18R-HEPE is released by the endothelial cells and taken up by adherent leukocytes where 5-LOX converts it to RvE1. The E series resolvins reduce inflammation, regulate PMN infiltration by blocking trans endothelial migration, regulate interleukin 12 production and lead to resolution of the inflammatory responses. RvE1 stimulates the phagocytosis of apoptotic PMNs by macrophages. RvE1 is also selectively disrupts thromboxane-mediated platelet aggregation.

The protectin identified as (N) PD1 (where the N refers to neuroprotectin) is derived from DHA through the actions of the lipoxygenase, 15-LOX and then enzymatic hydrolysis. Aspirin can trigger the formation of an epimeric PD1 molecule identified as AT-PD1. The protectins (N) PD1 and AT-PD1 have been shown to exert potent inflammation resolving actions by inhibiting T cell and PMN chemotaxis, by

promoting T cell apoptosis, by decreasing TNF α and INF- γ secretion, during ischemia-reperfusion injury. Thus an Aspirin and omega 3 fatty acid combinations not only prevents the onset of inflammation but also resolves it.

Maresins, named maresin 1 (MaR1) and maresin 2 (MaR2), are produced from DHA, when the lipoxygenase, 12-LOX acts on DHA. Maresins are produced by macrophages and so the name “maresin” means macrophage mediator resolving inflammation. Maresin 1 has anti-inflammatory, pro-resolving, analgesic and wound healing potencies. Maresin 1 mainly acts on vascular smooth muscle cells and vascular endothelial cells. In vascular smooth muscles and endothelium, Maresin 1 prevents the adhesion of monocytes to the endothelium induced by tumor necrosis factor alpha (TNF α). Maresin 1 also reduces the production of reactive oxygen species (ROS) by vascular smooth muscle cells and endothelial cells. The main pathway, through which Maresin 1 exerts its effects, is through down-regulation of the transcription factor, nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), in the vascular smooth muscles and vascular endothelium.

Maresin 2 has potent efferocytosis properties. It has been shown to reduce neutrophil infiltration and to enhance efferocytosis, the macrophage-mediated phagocytosis of dead and dying cells. The process of efferocytosis plays an important part in clearing of inflammation. In addition, when maresins produced by macrophages are released and acted upon by platelets, two related structures termed the maresin-like mediators (MaR-L1 and MaR-L2) are produced.

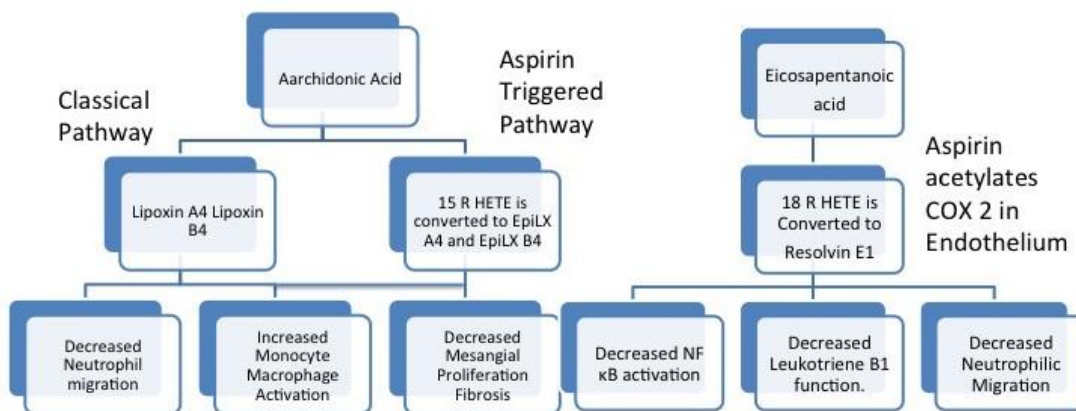
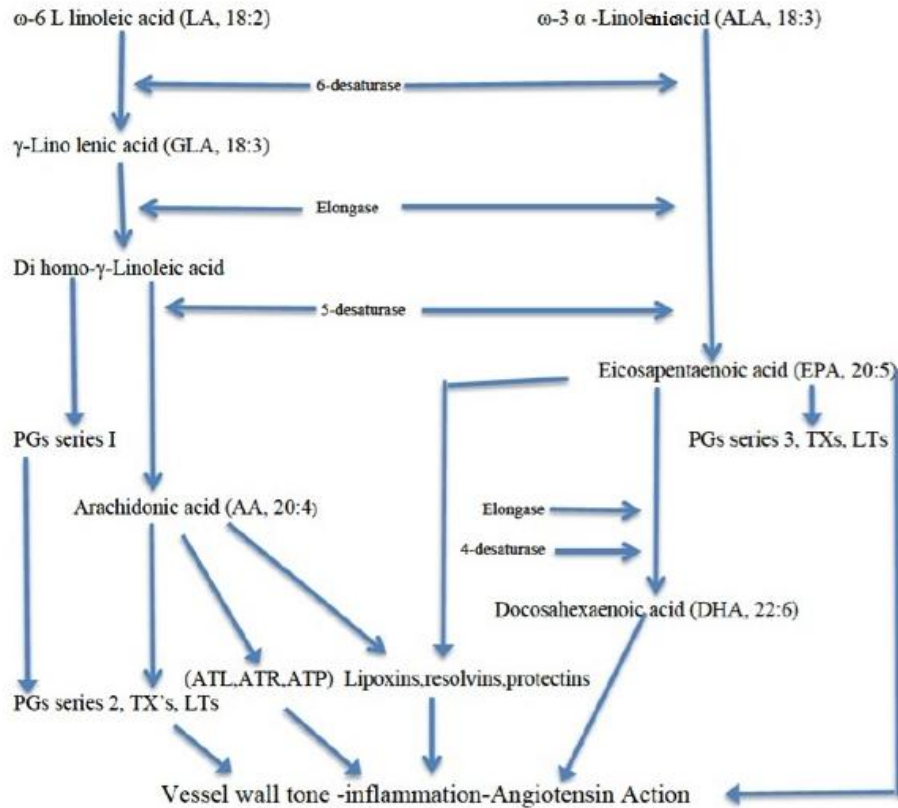


Fig. 4. Aspirin and Omega 3 fatty acids prevent the onset of inflammation by the release of Aspirin triggered Lipoxins, Protectins, Resolvins and Maresins



Scheme 1. Pathways to show how a diet rich in omega 3 fatty acids may have a role in improving vascular endothelial dysfunction

There are numerous DHA-derived bioactive lipid mediators in addition to resolvins, protectins, and maresins. Other DHA-derived Bioactive lipids are the electrophilic Oxo-derivatives (EFOX) which exert anti-proliferative and anti-inflammatory effects; the neuroprostanes (NP) which have wound healing and cardio protective effects; the epoxides which have analgesic and antihypertensive effects; the ethanol amines which exhibit neuromodulator, immune modulatory, and metabolic effects; the fatty acid esters of hydroxy fatty acids (FAHFA) which lead to inflammation proresolution and the *N*-acyl amides which have the neuroprotective and metabolic regulatory effects.

8. CURRENT RECOMMENDATIONS OF LOW DOSE ASPIRIN

The US preventive Task force recommends the use of aspirin for the primary prevention of cardiovascular diseases (CVD). Aspirin is recommended for men in the age group of 45-79 years to reduce the risk of myocardial infarction

when a net benefit is present. A net benefit means that the potential benefit from taking the aspirin outweighs the harms, mainly gastrointestinal (GI) bleeding. Aspirin is recommended for women age 55-79 to reduce the risk of ischemic stroke when a net benefit is prevented(39). The USPTF recommends against the use of aspirin in men <45 and women <55, and also in men and women aged more than 80. Online calculators can be used to predict the 10 year CHD risk in men (<http://hp2010.nlm.nih.gov/atp/iii/calculator.asp>) and women (<http://www.westrenstroke.org>).

Presently the American college of cardiologists and American Heart Association recommends aspirin at a dose of 75 to 100 mg/day in addition to warfarin in all patients with mechanical valves (Class I recommendation; Level of evidence: A) [40,41]. For the primary and secondary prevention of myocardial infarction in both men and women the American college of cardiologists and American Heart association Recommends aspirin for persons whose cardiovascular risk is

sufficiently high for the benefits to outweigh the risks associated with treatment (10-year risk of cardiovascular events greater than 6 – 10%) [42-44].

Another indication of aspirin is prevention of pregnancy-induced hypertension. The USPSTF recommends the use of low-dose aspirin (81 mg/d) as preventive medication after 12 weeks of gestation in women who are at high risk for preeclampsia. (B recommendation) [45-47]. If the woman is identified to be high risk later in pregnancy Aspirin still needs to be started as various multi centric stratified comparisons did not show that the timing of aspirin initiation (<16 weeks) or dosage had any effect on reducing the efficacy of aspirin for the prevention of preeclampsia [48,49]. Evidence does not suggest benefit of starting aspirin earlier (12 -16 weeks) rather than later in pregnancy. World Health Organization recommends the use of low dose aspirin (75 mg) as early as 12 -20 weeks of gestation for high risk women (previous preeclampsia, diabetes, chronic hypertension, renal or autoimmune disease, or multifetal gestation). There is limited evidence regarding the benefit of aspirin in low risk women [50].

The National Institute for Health and Care Excellence recommends that women at high risk for preeclampsia (i.e., those with a history of hypertension in a previous Pregnancy, chronic kidney disease, autoimmune disease, type 1 or 2 diabetes, or chronic hypertension) take 75mg/d of aspirin from 12 weeks until delivery. It recommends the same for women with more than one moderate risk factor (first pregnancy, age >40 years, pregnancy interval>10 years, body mass index >35 kg/m², family history of preeclampsia, or multifetal pregnancies) [51].

The American Heart Association and the American Stroke Association recommend that women with chronic primary or secondary hypertension or previous pregnancy related hypertension take low-dose aspirin from 12 weeks until delivery.

The American Academy of Family Physicians recommends low-dose aspirin (81 mg/d) after 12 weeks of gestation in women who are at high risk for preeclampsia.

Another clinical use of low dose aspirin (75-81mg/day) is diagnosed antiphospholipid antibody syndrome. Antiphospholipid antibody syndrome is characterized by clinical evidence of

vascular thrombosis and obstetrical complications like early pregnancy miscarriage, intrauterine growth restriction, preeclampsia and preterm births [52]. Serology study reveals persisting antiphospholipid antibodies on two occasions 6 weeks apart. The diagnosis of obstetric antiphospholipid antibody syndrome includes presence of both clinical and serological criteria [53]. The pathophysiology involves activation of endothelial cells, platelets, monocytes and complement pathways [54]. The anticoagulant proteins are inhibited. It has been suggested that the obstetric complications are associated with placental ischemia and inflammation rather than thrombosis at the fetomaternal interphase [55-57]. Low dose aspirin with low molecular weight heparin is the preferred treatment in pregnancy with antiphospholipid antibody syndrome [58]. Recently low doses of aspirin 1mg/kg/day have also shown to reduce pulmonary artery hypertension in murine models [59].

Contraindications to aspirin prescription are documented allergy to aspirin, asthma, bleeding disorders and gastritis. G6PD enzyme deficiency is a relative contraindication though long-term low dose aspirin has been found to be safe [60].

9. CONCLUSION

Aspirin is a low cost intervention that can prevent the atherosclerosis of vessels by its anti-inflammatory, antiplatelet and proresolving abilities. Recent understanding of the pathophysiology of hypertension and proresolving pathways can help to understand the rational use of aspirin in prevention and reducing the complications of high blood pressure. A combination of aspirin and omega 3 fatty acids has potential benefits. DHA metabolites have been found to have potent role in the resolution pathway of inflammation. Future endeavors would focus on the identification of subset of high-risk hypertensive patients who will benefit most from aspirin, omega 3 fatty acids and DHA. Different dosage and time of initiation in various high-risk groups needs to be identified. Further research is also required to identify the correct time and the oral doses that will help in minimizing the long-term risk of future cardiovascular diseases.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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