Does the use of acetylsalicylic acid have an influence on our vision?

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Purpose: Acetylsalicylic acid (ASA) is one of the most commonly used drugs in the world due to its anti-inflammatory, analgesic, and antipyretic properties. This review aims to describe the relationship between acetylsalicylic acid and age-related macular degeneration (AMD) – a chronic disease that causes deterioration of visual acuity and is one of the most common ophthalmological diseases these days.

Methods: Data presented in this review were collected from both research and review articles concerning ophthalmology and pharmacology.

Results: The results of the studies analyzed in this review are not unambiguous. Moreover, the studies are not homogenous. They differed from one another in terms of the number of patients, the age criteria, the ASA dose, and the duration of control period. The reviewed studies revealed that ASA therapy, which is applied as a protection in cardiovascular diseases in patients with early forms of AMD and geographic atrophy, should not be discontinued.

Conclusion: On the basis of the present studies, it cannot be unequivocally said whether ASA influences people’s vision and if people endangered with AMD progression or who are diagnosed with AMD should use this drug. It may increase the risk of AMD, but it can also reduce the risk of life-threatening conditions. The authors suggest that in order to avoid possible risks of AMD development, people who frequently take ASA should have their vision checked regularly.

Keywords: acetylsalicylic acid, AMD, lipofuscin genesis, drusen genesis, retinal pigment epithelium cells, geographic atrophy

Introduction

Acetylsalicylic acid (ASA) is one of the most commonly used drugs in the world, due to its anti-inflammatory, analgesic, and antipyretic properties, as well as properties of inhibition of platelet aggregation. Moreover, it has been proven that a relationship exists between ASA consumption and a lower risk of cancer and that ASA has positive therapeutic applications in the adjuvant therapy of cancer (malignant tumors). It is estimated that 100 billion ASA pills are consumed worldwide per annum.

For short-term treatment of problems such as aches and fever, a typical daily dose of ASA ranges from 0.5 g to 1.0 g to a maximum of 4.0 g in divided doses. In the case of rheumatic fever, the daily dose may even amount to 8.0 g. However, in the prevention and the treatment of cardiovascular diseases, the daily dosage generally amounts to 75–150 mg (in some cases, up to 325 mg/d).

The basic mechanism of the ASA effect is nonenzymatic protein modification – acetylation – which results in cyclooxygenase (COX) blocking. As a consequence, inhibition appears in the formation of prostaglandins, which participate in inflammation, fever, and conduction of painful stimuli. The ASA effect is irreversible, and in
**Discussion**

Recently, there have been many controversial reports on the influence of ASA on one of the most common ophthalmological diseases these days – age-related macular degeneration (AMD). It has been stated that many patients with AMD use ASA chronically for cardioprotection.

The pathogenesis of AMD is still not sufficiently understood. Currently, it is believed that the occurrence of this disease entity is influenced by a number of modifiable and nonmodifiable factors. Nonmodifiable determinants embrace genetic factors, advanced age, sex, race, and iris color. Modifiable determinants, in turn, embrace cardiovascular diseases (hypertension, atherosclerosis), systemic diseases (for instance, diabetes), obesity, and smoking. Scientists put more pressure on the genetic aspects of AMD. All monozygotic twins (100%) are diagnosed with AMD if the first sibling suffers from AMD. A study performed by Klaiver et al revealed that 23% of patients with late AMD have inherited predispositions to disease occurrence. Genetic studies indicate many potential genes that may influence AMD development. Enormous progress has been made in identifying genetic susceptibility variants for AMD. Variants at chromosome 1q32 (in the region of complement factor H [CFH]) and 10q26 (LOC387715/ARMS2) have very important and scientifically certified influence on the development of AMD. In recent years, more and more attention has been paid to the inflammatory component in AMD pathogenesis. It has been proven that excessive activation of the complement system participates in AMD progression. The relationship between the development of AMD and gene encoding factors H, I, and B of the complement and also components 2 and 3 of the complement has been found.10,11

The first discovery was made during a study by Francis et al in a small case–control sample.12 There exists strong association between Y402H variant in the CFH gene and increased risk of AMD. A meta-analysis connecting outcomes from multiple association studies of CFH and AMD shows that heterozygote carriers of the risk allele have a 2.5-fold increase in developing AMD and homozygous carriers have a sixfold increase in developing AMD compared to the nonrisk allele.13 The most recent trials show not only genetic variants of AMD pathogenesis but also the very important role of gene–gene and gene–environment factor interactions for this disease appearance. The phenotype of AMD status is an essential aspect for genetic studies. The strongest candidate, according to studies, among all genes is apolipoprotein E gene (APOE), because it exhibits a strong association with macular degeneration. APOE is responsible for the transport and metabolism of lipids and cholesterol and in response to neuronal injury; thus, it shows us that it could be an important connector with environmental factors – our lifestyle and diet, for example.14 APOE has three common alleles: ε2, ε3, and ε4. Initially, two studies reported a reduction in the frequency of the ε4 allele in patients with AMD compared to controls, suggesting a protective effect. In addition, ε2 allele frequency was increased in AMD patients compared to controls. The correlation between APOE and AMD has now been replicated by several independent reports. Further scientific studies
about interactions between environmental factors and genetic variants will be necessary to solve the problems concerning the reason of AMD development.

AMD is a result of a number of processes that occur within the outer layer of the retina; lipofuscin genesis – gathering of lipofuscin lodgments within the retinal pigment epithelium (RPE); drusen genesis – creation of insoluble drusen (extracellular collection of glycoproteins, lipids, and cellular debris deposits), which gathers between the layer of the RPE and the Bruch’s membrane; and chronic local inflammatory process and neovascularization – as a result of proangiogenic factors (vascular endothelial growth factor [VEGF]) domination over antiangiogenic factors (pigment epithelium-derived factor)\(^{15,16}\). Two forms of AMD have been distinguished: 1) Dry form of AMD is the most common, which occurs in 90% of cases and is characterized by the appearance of drusen and/or hyperpigmentation/hypopigmentation of pigment epithelium. Drusen that occurred earlier may disappear (the so-called geographic atrophy [GA]); it appears in the advanced stage of dry AMD. 2) Wet (neovascular) AMD is the second type, which leads to significant impairment of vision. In case of neovascular form of AMD, there is formation of abnormal vessels in the macular region. New pathological vessels are weak and prone to cracking. Moreover, they lead to retinal or subretinal hemorrhage.\(^{17}\) Its main symptoms are choroidal neovascularization (CNV) and pigment epithelial detachment. It is possible for the dry form to develop into the wet form.\(^{18}\)

The authors of the Blue Mountains Eye Study (BMES) studied the relationship between the regular intake of ASA over a 15-year period and the occurrence of AMD, particularly its wet form. BMES is a cohort population study of eye diseases, which was conducted on a group of 2,389 Australians living in urban regions, aged older than 49 years. The research showed that regular intake of ASA doubles the risk of neovascular AMD, regardless of medical history (cardiovascular diseases, smoking). The frequency of appearance increases as the drug dose rises. The use of ASA was not related either to the occurrence of GA or to incidents of early AMD. Regular use of ASA was defined in this study as taking the drug at least once a week. In the majority of cases, the daily dose was 150 mg. According to BMES, increased risk of development of CNV was observed in patients who used the drug for 15 years, which suggests that in pathogenesis, the accumulated dose is crucial.\(^1\)

A European research study – European Eye Study – was conducted in seven centers on a group of 4,691 participants aged older than 65 years. In the group under examination, the patients took ASA with varied frequencies: one dose a month and one dose a week. It was proven that the intake of ASA was connected with significantly more frequent (double) occurrence of both the early and late forms of AMD, regardless of the risk factors. The frequency of AMD increased as the frequency of ASA use rose. Moreover, in the research, it was noted that people who take ASA every day are at a greater risk of hemorrhage (3.75 times more often). The bleeding was three times as much as in people who did not take the drug.\(^{19}\)

An American study – Beaver Dam Eye Study – was conducted on 6,243 people aged between 43 years and 86 years (at the beginning of the research). They were monitored every 5 years over a 20-year period. During the study, the frequencies of both the early and late forms of AMD were estimated with reference to the frequency, period, and dose of ASA intake. It was proven that a 5-year period of ASA consumption does not increase the risk of development of either the early or late form of AMD. A 10-year period of ASA intake, in turn, statistically has a significant influence on the development of wet AMD, in comparison to the group of people who do not use ASA. There was no stated relationship between the dose of ASA and the frequency of occurrence of early and late forms of AMD, regardless of the period of its intake.\(^{20}\)

In these three major studies, a substantially larger risk of wet AMD development was observed in people who take ASA. On the other hand, the relationship between ASA consumption and the appearance of GA was not observed.\(^1,19,20\)

Another large randomized piece of research project,\(^{21}\) which was conducted in the US on women working in the health service, aimed to investigate whether the consumption of low doses of ASA every second day has an influence on the frequency of AMD. The results of this research were published in 2009. The study embraced 39,876 healthy women aged at least 45 years, who were divided into two groups: one group of women who took 100 mg of ASA every second day and a second group of women who took a placebo. Throughout a 10-year observation period, it was evaluated and confirmed by ophthalmological examination whether any cases of AMD occurred in which visual acuity deteriorated to the degree of 20/30 or worse. After 10 years of observation, 111 cases of AMD were observed in the first group and 134 cases in the group of patients taking the placebo. It was proven that the use of low doses of ASA by women does not influence the risk of AMD development.

In the San Francisco Veterans Affairs Hospital Eye Clinic, a retrospective research\(^22\) was conducted that aimed
to determine whether the frequency of CNV development increased in patients with recognized AMD who took ASA and statins. The examination embraced 326 patients with AMD and aimed to compare the progression of diseases in patients who took and did not take ASA and statins over at least 6 months. The research revealed that in patients treated with ASA and statins, the risk of CNV development was lower. Researchers from the Department of Ophthalmology of Maria Sklodowska-Curie Memorial Hospital in Zgierz and Department of Internal Diseases and Cardiac Rehabilitation of the Medical University of Lodz, Poland, studied the impact of ASA on AMD development. The researchers state that patients with drusen and CNV used ASA more often, but the acid is not an independent risk factor of AMD development. The researchers found that the major risk factor of AMD is the occurrence of macular diseases in family members.\(^{23}\)

Meta-analysis conducted by Li et al.\(^{24}\) shows that there is a slight but significant correlation between ASA intake and the risk of AMD development, especially in very advanced stages of AMD.

Another important research project was presented by Aronow et al.\(^{25}\) The research investigated the association between ASA use and the progression of AMD. Age-Related Eye Disease Study 2 was a multicenter, randomized, controlled clinical trial. Participants aged 50–85 years with no GA and neovascularization were divided into two groups:

- ASA users (those patients who took ASA five times a week) and
- non-ASA users.

Progression of AMD was defined as the development of either GA or neovascularization during the study period (2006–2012).

The observations from this study suggest that the use of ASA has no statistically significant association with AMD progression. Scientists state that patients with AMD can use ASA, if taking it is necessary.

Completely contrary reports were presented by Kahawita and Casson.\(^{26}\) The aim of this review was to evaluate the impact of ASA on early stage of AMD. The review presented four studies involving 10,292 individuals and examining the correlation between ASA and AMD. The results showed that using ASA is associated with early stage development of AMD. The conclusion arising from this review shows that there is a small but statistically significant association between ASA use and AMD progression.

ASA effects are connected to, for example, the influence on vascular endothelium. ASA inhibition of COX-1 and prostaglandin-endoperoxide synthase 2 causes the decrease in the synthesis of prostacyclin (PGI\(_2\)), which shows vasodilation effects. As a result, retina hypoxia occurs, which is one of the causes of neovascularization and the development of wet AMD. Eventually, a hypoxia-induced factor 1 occurs, which stimulates the formation of proangiogenic factors.\(^{27}\)

It was also indicated that an influence of ASA on endothelial progenitor cells (EPCs) exists, which fulfils, primarily, angiogenic functions through the production of growth cytokines such as VEGF and stromal cell-derived factor 1 and which takes part in the formation of endothelial cells. It was proven that patients with increased cardiovascular risk and with risk factors of atherosclerosis have a smaller number of circulating progenitor cells, which is a cause of reduced immunity to thrombosis and inflammation in the vessels.\(^{28}\)

The study conducted in 2010 examined patients who chronically took a 325 mg dose of ASA in order to determine whether the ASA influences circulating EPCs. In patients who had not been previously treated with ASA but then started to take the drug, the number of EPCs decreased. It is assumed that this phenomenon is caused by the inhibitory effect of ASA on the COX-dependent pathway, especially COX-2. It turns out that PGE-2 is indispensable for the production and the correct operation of progenitor cells. The blocking of COX-2 leads to the blockage of angiogenesis and apoptosis of cells.\(^{29}\)

Additionally, ASA reduces blood viscosity, thus decreasing critical speed in vessels. In some circumstances, this causes turbulence of blood flow, which damages vascular endothelium. Studies indicate that laminar flow of fluids becomes the so-called turbulent flow after exceeding the critical speed, which depends on the type of fluid and the type (diameter) of vessel.\(^{30}\) During turbulent flow, fluid fractions do not move in a direction parallel to the vessel’s conductor axis. Instead, they perform chaotic movements with different directions of velocity. Such movements are accompanied by the formation of whirls.\(^{31}\)

It was proven that ASA has influence on the lipids reaction of lipid oxidation – particularly, low-density lipoproteins (LDLs).\(^{19}\)

In a study that was conducted on ten healthy, nonsmoking men, the influence of ASA on LDL oxidation was evaluated. Volunteers took 75 mg/d over 2 weeks. It was determined that sensitivity to plasma LDL oxidation increased after ASA consumption.\(^{32}\)

It is believed that salicylates may support LDL oxidation caused by the myeloperoxidase enzyme (the enzyme that
participates in the initiation and formation of some cardiovascular diseases, for example, through an increase in LDL oxidation and acceleration of atherogenesis.\textsuperscript{33}

Moreover, salicylates, as monophenyl compounds, in some pro-oxidant cases may create phenoxy radicals, which cause oxidative damage. However, it turns out that radical effects are effectively slowed down through ASA’s metabolite – gentisic acid.\textsuperscript{34}

It is possible that plasma concentration of gentisic acid, salicylate metabolite, which weakens LDL oxidation, was not high after the intake of a daily dose of 75 mg, which was applied in the aforementioned study.

Oxidized LDLs play a key role in early atherosclerosis. They have cytotoxic properties toward endothelial cells and macrophages. They also have prothrombotic and proinflammatory effects.\textsuperscript{32} Oxidized LDLs are responsible for the development of atherosclerotic plaque and its destabilization. Endothelial damage makes it easier for inflammatory cells and LDLs to move on, and they intensify platelet adhesion. Moreover, changed LDLs activate macrophages, which produce more chemotactic substances, inflammatory substances, growth factors, and free radicals of prothrombotic tissue factor and proteolytic enzymes (metalloproteinases). The appearance of oxidized LDL, that is, abnormal LDL in the inner membrane is a signal for monocytes circulating in the blood (or monocytes that occur in the walls of vessels’ macrophages) to destroy the abnormal LDL through phagocytosis. Macrophages that are filled with cholesterol (foam cells) and are gathered under the endothelium constitute the early phase of atherosclerotic changes. Then, foam cell atrophy and its lipid content gather extracellularly, thus creating the lipid nucleus of atherosclerotic plaque.\textsuperscript{35}

As a result of retina microenvironment damage, the progression of degenerative changes related to age occurs. It was proven that meclofenamic acid and other nonsteroidal anti-inflammatory drugs, including ASA, irreversibly block gap junctions between RPE cells.\textsuperscript{36} These junctions allow for direct communication with adjacent cells and enable inorganic ions and small hydrosoluble particles (up to 1,000 Da molecular weight) to move from one cell cytoplasm to another. This provides an electric and metabolic connection among cells.\textsuperscript{37} This kind of intercellular communication is indispensable for the proliferation, differentiation, and correct functioning of RPE.

Scientists from the institutional review board of the University of Chicago conducted research that involved 195 patients, and it was carried out over 73 months. The research revealed that anticoagulant and antiplatelet treatments, including therapy with ASA, are independent factors of intraocular hemorrhage development. This dependence was observed particularly in people with wet AMD in both eyes. The destruction of retina photoreceptors occurs due to a clot retraction, the toxic effects of iron, and the blockage of nutritious diffusion. In the end, a scar formation process occurs that causes permanent loss of vision.\textsuperscript{39} As the authors pointed out earlier, reports on the protective influence of ASA on the development of AMD also appear. In another research trial, researchers also studied the association between antiplatelet and anticoagulant drugs as well as retinal or subretinal hemorrhages in patients with AMD. Scientists stated that daily antiplatelet and anticoagulant therapy was not a statistical risk factor of occurrence of retinal hemorrhages, but this therapy was a risk factor in participants with hypertension.\textsuperscript{40} In the Physicians’ Health Study published in 2001, which was conducted in a group of 22,071 American male physicians aged between 40 years and 84 years, researchers asked themselves whether the doses of ASA (325 mg) and beta-carotene (50 mg), which are consumed every second day as part of cardiovascular diseases and tumor prophylaxis, influence AMD development. The research was a randomized double-blind trial with the control group receiving a placebo. The statistics were enlarged with new cases of AMD, confirmed by ophthalmological examination, which appeared during the study, with visual acuity worsening to the degree of $\geq 20/30$. Throughout 60.2 months of observation, 117 new cases of AMD manifested themselves within the group, in which 51 patients took ASA and 66 patients placebo. It turned out that in the group of patients who were consuming ASA, there were fewer cases of AMD occurrence. Nevertheless, the difference was not statistically relevant. What is important, however, is that the study exposed, statistically, extreme reduction (44%) in the risk of myocardial infarct appearance, and therefore, the study was stopped earlier than was originally planned. The conclusions from this research precluded the stimulating influence of ASA consumption in small doses within 5 years on the risk of earlier development of AMD.\textsuperscript{40}

The results of other studies\textsuperscript{41,42} revealed that in people with AMD, blood flow in choroidal vessels were reduced, which may suggest that primary vascular disease has some influence on AMD pathogenesis. Taking into account that cardiovascular diseases, as well as the presence of risk factors of their progression (for instance, lipid disorders), increase the risk of AMD development,\textsuperscript{33-34} the prevention of these diseases, through both improving systemic circulation and decreasing the risk of vascular incidents, may benefit in
preventing AMD development. This proves the favorable influence of ASA even in patients with recognized AMD.

Along with age, it comes down to the damage of RPE cells, which leads to the influx of dendritic cells DC1 presenting the antigen. This is one of drusen’s components.47 In drusen’s components, plasma proteins and proteins connected with the activity of the complement system are also found. Drusen’s composition also includes substances that cause activation of local complement system.48 It suggests that AMD progression is influenced by local inflammation in the subretinal space.49 This local inflammation, which begins subretinally, turns into chronic cytomegalovirus retinitis with the activation of the complement system and the migration of macrophages, T-lymphocytes, and mast cells into the retina.16

As a consequence, chronic cytomegalovirus retinitis leads to the death of the RPE and their dependent photoreceptors, thus leading to the development of GA. Therefore, the anti-inflammatory effects of ASA may be favorable for the inhibition of AMD progression, especially in its early form, and for preventing the progression of advanced dry AMD. ASA, through paths independent of platelets inhibition, may have positive effects in preventing AMD progression. It was proven that ASA initiates the production of 15-epi-lipoxin 4A in the endothelial vessel cells, which has local inflammatory effects.50 ASA may protect endothelial cells through antioxidizing activity,51 and it prevents peroxidation of lipids.52

The fundamental function of ASA is an easy chemical reaction – its molecule hydrolysis to acetic acid and salicylic acid. Products of this reaction show that ASA has twofold effect:
- provides acetylic group and
- provides salicylate.53

ASA influence on human organisms is an example of nonenzymatic protein modification. The function of ASA in our body is pleiotropic, but the pharmacological area of this function is addicted to possibility of getting through to the protein in certain places.53 We cannot ignore significant ASA influence on human short-lived cells, eg, on endothelial cells that includes the endothelial cells located in the human eye. ASA directly increases production of nitric oxide (NO) by endothelium causing 15-epi-lipoxin A4 creation (a mediator responsible for NOS activation).50,54

NO has the following influences on the cells:
- cytoprotective – due to its activation of guanylate cyclase51 and
- anti-inflammatory – due to its inhibition of leukocytes and interaction of endothelial cells.55

These mechanisms prevent hypoxia and pathological angiogenesis. It is proved that ASA may decrease endothelial proliferation through the influence on DNA synthesis, which is addicted to p53 protein expression. There is a strong correlation between these mechanisms and a lower secretion of VEGF, and due to this, the creation of new vessels is reduced. Scientists are trying to find a new derivative of ASA that will be more specific and thereby will cause reduction in side effects.54

**Conclusion**

In light of often contradictory reports on the influence of ASA on the development of early and late forms of AMD, it is difficult to give an unambiguous answer on whether patients with AMD should use this drug. Taking into account these reports and the fact that among people endangered with AMD progression or diagnosed with AMD there is a large group of patients who consume ASA, we all should ask ourselves the following questions:

- Is AMD progression directly connected to the consumption of ASA?
- May ASA delay AMD progression through its anti-inflammatory and antioxidant effects or quite the opposite?
- How does ASA influence the development of early and late stages of AMD?
- At what stage of AMD progression do the aspects of ASA use, which are unfavorable for maintaining visual acuity, begin to outweigh the undoubted systemic benefits derived from its usage?

If we want to answer the question “Does the use of ASA have any influence on our vision?”, we have to take into account all the research presented in this review. We cannot ignore the fact that it is difficult to determine unequivocally what is the exact impact of ASA on the human eye. Three of many studies (BMES, Europe an Eye Study, Beaver Dam Eye Study) show that ASA increases the risk of AMD development, particularly its wet phenotype.19,20 Furthermore, this research demonstrated that the dose of ASA, the frequency of administration, and the period of intake have a very important influence on AMD development. The higher and the more frequent the dose and the longer period of dosage, the higher the risk.19,20 Scientists have proved stronger correlation of ASA with CNV than with the dry form.29 However, in this review, we can notice some evidence that denies the destructive influence of ASA on macula lutea, what is more, a favorable influence on it, for example by blocking COX2 – it stops angiogenesis.29 ASA
decreases LDL oxidation and prevents blinding disease. A significant study proves that those who take ASA with statins are less exposed to the risk of AMD. ASA, due to its anti-inflammatory specificity, decreases the possibility of disease occurrence – if we take into account inflammatory pathogenesis of AMD.

Regarding all the research, including risk for AMD and benefits of reducing risk for cardiovascular events, we can be sure that ASA is really beneficial. It may increase the risk of AMD insignificantly, but it can really reduce the risk of life-threatening conditions. One thing is clear, if we do take ASA frequently for its other health benefits, it is very important to have our vision checked regularly.

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