Review / Derleme
Akdeniz Medical Journal / Akdeniz Tıp Dergisi

Oxidative Stress, Atherosclerosis and Dietary Recommendations

Oksidatif Stres, Ateroskleroz ve Diyet Önerileri

Ayşe Betül DEMİRBAŞ, Burcu YEŞİLKAYA

Okan University, Nutrition and Dietetics, Istanbul, Turkey

Yazışma Adresi
Correspondence Address
Ayşe Betül DEMİRBAŞ
Okan University, Nutrition and Dietetics, Istanbul, Turkey

betulldemirbas@gmail.com

Geliş tarihi / Received : Aralık 17, 2020
Kabul tarihi / Accepted : Mart 30, 2021
Elektronik yayın tarihi : Ocak 01, 2022
Online published

Bu makalede yapılacak atıf:
Cite this article as:
Demirbaş A. B, Yeşilkaya B.
Oxidative Stress, Atherosclerosis and Dietary Recommendations.

Akd Med J 2022; 8(1):101-108.

Ayşe Betül Demirbaş
ORCID 0000-0003-2765-2677
Burcu Yeşilkaya
ORCID 0000-0001-9986-6119

ABSTRACT

Atherosclerosis, a chronic inflammatory disease, refers to the thickening and hardening of the vascular endothelium with plaque accumulation in the arteries. In the disease pathogenesis, the formation of oxidized LDL (ox-LDL) by oxidation of lipoproteins due to oxidative stress is seen as the first stage. Oxidative stress is defined as an imbalance in the direction of the increase in reactive oxygen species (ROS) and / or the decrease in the antioxidant defense systems of the body. Ox-LDL which is occurs as a result of oxidative stress, causes to deterioration in endothelial function, proliferation of adhesion molecules such as Intracellular Adhesion Molecule-1 (ICAM-1), Vascular Cell Adhesion Molecule 1 (VCAM-1), and causes a decrease in nitric oxide (NO).With the increase in adhesion molecules, monocytes enter the vascular intima and turn into macrophages with ox-LDLs. The next stage is the migration of smooth muscle cells and foam cell formation. Plaque formation occurs as foam cells collapse in blood vessels. Oxidative stress that initiates all this atherosclerosis process occurs naturally due to metabolism in the body, and various diseases and environmental factors can further escalate this situation. Diet is one of the most important environmental factors such as diet, smoking and alcohol that play a role in the development of oxidative stress and atherosclerosis. In the prevention of oxidative stress and atherosclerosis, it will be beneficial with the polyphenols, antioxidants, dietary fiber and healthy fats coming from the foods in the Mediterranean diet.

Key Words: Oxidative Stress; Atherosclerosis; Antioxidant; Nutrition

ÖZ

Ateroskleroz, arterlerin içerisinde plak birikimiyle birlikte damar endotelinde kalınlaşma ve sertleşmeyi ifade eden kronik inflamatuar bir hastalıktır. Hastalığın patogenezinde oksidatif stres sonucunda lipoproteinlerin oksidasyonuyla okside LDL (ox-LDL) oluşumu ilk aşama olarak görülmektedir. Oksidatif stres, reaktif oksijen türlerinin (ROS) artması ve/veya vücudun antioksidan savunma sistemlerinin azalması yönünde dengesizlik olarak tanımlanmaktadır. Oksidatif stres sonucunda oluşan ox-LDL, endotel fonksiyonunda bozulma, Intracellular Adhesion Molecule-1 (ICAM-1), Vascular Cell Adhesion Molecule-1 (VCAM-1) gibi çeşitli adezyon moleküllerinin çoğalması, nitrik oksidin (NO) azalmasına sebep olmaktadır. Artmış adezyon molekülleri sonucunda monositler damar intimasına girmekte ve burada ox-LDL'ler ile makrofajlara dönüşmektedirler. Sonraki aşamada düz kas hücrelerinin göçü ve köpük hücre oluşumu görülmektedir. Köpük hücrelerin kan damarlarında çökmesiyle plak oluşumu gerçekleşmektedir. Tüm bu ateroskleroz sürecini başlatan oksidatif stres vücutta doğal olarak metabolizma sonucunda oluştuğu gibi çeşitli hastalıklar ve çevresel etkenler bu durumu daha da arttırabilmektedir. Oksidatif stres ve ateroskleroz gelişimde rol oynayan diyet, sigara, alkol gibi çevresel etkenler içerisinden en önemlilerinden biri diyettir. Oksidatif stres ve ateroskleroz gelişiminin önlenmesinde Akdeniz diyeti içeriğindeki besinlerden gelen polifenoller, antioksidanlar, diyet posası ve sağlıklı yağlar ile yarar sağlayacaktır.

Anahtar Sözcükler: Oksidatif Stres; Ateroskleroz; Antioksidan; Beslenme

DOI: 10.53394/akd.1037799

INTRODUCTION

Atherosclerosis is known as one of the most common cardiovascular diseases in societies and it is among the first causes of death in the world with its complications (1,2).

The word atherosclerosis is a combination of two Greek words. In Greek, "adhere" means gruel, "scleros" means hard (3). The artery walls begin to get covered with soft sediments resembling gruel, and then these start to harden, causing the vessel to narrow and decrease blood flow (4). Atherosclerosis, also known as "arteriosclerosis", is a chronic inflammatory disease that refers to the thickening and hardening of blood vessels (5).

Oxidative stress refers to a condition that occurs due to the increase of reactive oxygen species (ROS) and the decrease in antioxidant defense. The balance between ROS and antioxidants deteriorates in favor of ROS (6,7).

Causing oxidative stress, ROS can naturally occur as a result of metabolic processes in the body. In addition, it may increase as a result of various diseases such as diabetes, hypertension, insulin resistance, obesity, dyslipidemia, inflammation, or environmental factors such as smoking and alcohol (8). Various studies have revealed that oxidative stress caused by ROS increased as a result of dyslipidemia causes the development of atherosclerosis and complications such as heart attack and stroke (9,10).

In this review, the effect of oxidative stress on the development of atherosclerosis and the importance of nutrition against modifiable risk factors to prevent the development of this process will be discussed.

1. Oxidative Stress and Free Radicals

Free radicals are known as highly reactive molecular products that contain unpaired electrons in their structure (11). They are naturally formed as by-products in the body as a result of enzymatic and non-enzymatic reactions (12,13). However, their overproduction can cause tissue damage, or further stages can cause cell death, apoptosis, and necrosis (2).

The most biologically damaging reactive oxygen species (ROS) are known as free radicals. ROS contains radicals, mainly superoxide (O2-), hydrogen peroxide (H2O2) and hydroxyl (OH •), which occur naturally in small amounts during oxygen metabolism (14).

There are various enzyme systems such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), xanthine oxidase (XO), uncoupled endothelial nitric oxide synthase (eNOS), lipoxygenases, and mitochondrial electron transport chain that cause the production of ROS in the body (5,8,10,15). The most important of these is the NOX system, which causes the formation of superoxide anion (16). NOX activity plays a part in oxidized low-density lipoprotein (ox-LDL) formation and Vascular Smooth Muscle Cell (VSMC) proliferation (17). Xanthine oxidase increases ROS formation in macrophages and VSMCs (5,10). Mitochondrial electron transport chain enzymes produce a certain level of superoxide anion. However, superoxide anion production can become harmful with excessive ROS production or deterioration of antioxidant defense (18). Leukotrienes are the end products of lipoxygenases. While being another ROS-generating system, they activate foam cell formation (19).

ROS react with compounds such as lipids, proteins and nucleic acids, causing changes to these compounds (12). ROS are kept under control by antioxidants in the body to prevent these effects. Enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px) and selenium, vitamin C, vitamin E, β-carotene, vegetable flavonoids are known as antioxidants that act as protectors (20). If ROS is overproduced, it causes cellular damage, and if this overproduction exceeds antioxidant capacity, it is called oxidative stress (21).

The effect of oxidative stress on lipids and proteins in plasma lipoproteins is particularly closely related to cardiovascular diseases (CVD). In the case of oxidative stress, LDL is oxidized, and ox-LDL is formed. Oxidized LDL cannot be recognized by LDL receptors, and this is considered a risk factor for the formation of atherosclerotic plaques (7).

2. Oxidative Stress and Atherosclerosis Progress

Arterial walls consist of three different layers: the outer layer, which is the connective tissue that gives shape to the vessels, the middle layer composed of smooth muscle to provide blood flow and pressure, and the inner layer (intima), which is the endothelial layer consisting of endothelial cells (9).

The endothelial layer provides structural and functional integrity, acts as a protector for the vascular wall and circulating blood, and ensures the bidirectional passage of blood gases and macromolecules (22). It also regulates vascular homeostasis. Vascular homeostasis occurs by the release of bioactive substances from endothelial cells that provide vasodilation and vasoconstriction (23). Nitric oxide (NO) is known as an essential gas that plays a role in vasodilation in endothelial cells to provide vascular homeostasis synthesized from the arginine amino acid (23,24). Also, it prevents NO thrombocyte aggregation and plays a role as a neurotransmitter and in macrophage functions (25). NO predominates in healthy endothelial layer compared to constricting factors (24). NO production is made by endothelial nitric oxide synthase (eNOS) found in the endothelium (26). However, in the case of inflammation, inducible nitric oxide synthase (iNOS), which has low activity under normal conditions, activates in macrophages and smooth muscle cells and forms superoxide radicals, and since the half-life of NO is very short (about 3-10 seconds), it reacts with oxygen and superoxide radicals and transforms into peroxynitrite (ONOO-), a type of reactive nitrogen species (RNS) (25,26).

Many diseases such as inflammation, diabetes, dyslipidemia, insulin resistance, obesity, hypertension, and environmental factors such as smoking and alcohol cause oxidative stress to occur (27). Oxidative stress is also known to be closely related to the increase in ROS production. ROS types, which increase due to oxidative stress, cause a decrease in the amount of NO in the endothelial layer and providing homeostasis (4). Reduced NO causes impairment of vascular homeostasis, increased vasoconstriction factors, and thus endothelial damage (9). It is known that endothelial cell

dysfunction as a result of endothelial damage has a significant role in the formation of sepsis, inflammatory diseases, hypertension and especially atherosclerosis (3).

The stages of atherogenesis in the process of atherosclerosis, which is a progressive disease that can begin even before adulthood (28), include various complex mechanisms such as endothelial dysfunction, vascular proliferation, matrix degradation, apoptosis, oxidative stress, inflammation, and thrombosis (29,30). The first phase in the development of atherosclerosis is the occurrence of endothelium damage as a result of the decrease of NO bioavailability together with the production of superoxide anion, which - occurring as oxidative stress-borne - is a type of ROS (31). This situation causes LDL to leak into the vascular intima and accumulate there. Under such pathological conditions, LDL is oxidized and Ox-LDL formation occurs (14). Ox-LDLs increase the number of cell adhesion molecules Vascular Cell Adhesion Molecule-1 (VCAM-1), Intracellular Adhesion Molecule-1 (ICAM-1), Leukocyte-Selectin (P selectin) and Endothelial-selectin (E selectin) in endothelial cells (30). Increased adhesion molecules reduce the capacity to produce endothelial NO and other molecules, and thus increase cytokines such as macromolecules, thrombocytes and monocytes' Monocyte Chemotactic Protein-1 (MCP-1), Tumor Necrosis Factor-α (TNF-α), Interleukin -1, -4, -6 (IL-1, IL-4, IL- 6) and Interferon-γ (INF-γ) to provide a transition to vascular intima (4,5,14,22). Monocytes are transformed into macrophages in the veins through proteins such as MCP-1, Macrophage-Colony Stimulating Factor (M-CSF), and IL-8. Afterward, macrophages start to recognize and incorporate Ox-LDL molecules by stimulating scavenger receptors such as cluster of differentiation 36 (CD36), serotonin-release assay (SRA) and oxidized low-density lipoprotein receptor-1 (LOX-1) (32). These lipid-loaded macrophages form foam cells (33). The formed foam cells gather on the artery walls and form the "fatty streak" structure (4). If lipid accumulation continues in the next stage, T-lymphocytes and mast cells also enter the endothelium and secrete cytokines. These secreted cytokines stimulate the migration of vascular smooth muscle cells (VSMC) and collagen accumulation, leading to "atherosclerotic plaque" formation (30).

The formation of an atherosclerotic plaque occurs as a result of dead foam cells, circulating inflammatory and immune cells, endothelial smooth muscle cells, and connective tissue elements, as the fibrous plate surrounds a necrotic lipid core (32,34). After this situation, the macrophages in the plaque formed by the accumulated foam cells accelerate the development of atherosclerosis by aggravating the inflammation with calcification and bleeding, leading to more complex plaques (30).

The most advanced thrombotic complications of atherosclerosis occur with the rupture of the fibrous plate surrounding the necrotic nucleus resulting from endothelial cell apoptosis (32). The destruction of the fibrous plate turns the stable plate into an unstable state. This situation increases the triggering of atherothrombotic occlusion and also the risk of thrombosis with the release of excess thrombogenic contents in the necrotic nucleus called plaque repetition into the lumen (22,35). Clinical symptoms of the advanced stage of atherosclerosis manifest as coronary heart disease, ischemic attack, peripheral artery disease, heart failure, or sudden death (36).

3.Atherosclerosis, Antioxidants and Nutritional Relation

Oxidative stress, which plays an important role in the development of atherosclerosis, develops due to the imbalance between ROS and antioxidant defense. For this reason, antioxidant defense are known as molecules that can neutralize ROS (20). Antioxidant defense occurs in two ways: primary defense in which endogenous enzymes play an important role, and secondary defense consisting of vitamin C, vitamin E and uric acid (37).

Antioxidants can be categorized as enzymatic and non-enzymatic. Superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx), thioredoxin (Trx) are known as enzymatic antioxidants. Glutathione, coenzyme Q (CoQ), bilirubin, uric acid and lipoic acid are known as endogenous, and vitamin E, vitamin C, vitamin A and carotenoids, B vitamins, and polyphenols are known as exogenous non-enzymatic antioxidants (37).

SOD acts as an essential enzyme in different varieties. There are varieties such as copper-zinc SOD (CuZn-SOD), manganese SOD (Mn-SOD) in the body. CuZn-SOD, the most abundant type, is located in the cytoplasm. SOD neutralizes the superoxide (O-) radical by reducing it to hydrogen peroxide (H2O2). Thus, SOD prevents the formation of the hydroxyl (OH-) radical (37,38). In addition, SOD has a vital role in preventing the atherosclerotic process by preventing MCP-1 and VCAM-1 adhesion molecules from participating in the atherosclerotic state and reducing the levels of F2-isoprostanes and isofurans in the aorta (29). Next, glutathione peroxidase (GPx), which is dependent on catalase and selenium, also reduces this H2O2 to H2O, a harmless molecule (38,39). Glutathione peroxidase prevents the expression of VCAM-1 and MCP-1 by means of H2O2 by oxidizing glutathione and converting H2O2 to H2O (39). Meanwhile, oxidized glutathione is made harmless again by glutathione reductase (GR) (38). Catalase also reduces VSMC proliferation. Thioredoxin increases NO bioavailability, reduces hydrogen peroxide, suppresses Trx1 VCAM-1 and ICAM-1 expression, and thus contributes to the prevention of atherosclerosis (40,41).

One of the non-enzymatic endogenous antioxidants, glutathione acts as a cofactor for various antioxidant enzymes such as glutathione peroxidase (GPx). The main effect of glutathione in the process of atherosclerosis is to reduce atherosclerotic lesions by scavenging hydroxyl (OH-), hypochlorous acid (HOCl-) and peroxynitrite (ONOO-) (42). Coenzyme Q (CoQ) is known as an antioxidant that has an important role in the electron transfer chain in mitochondria (22). As a result of an in vivo study on mice, the CoQ antioxidant was found to reduce LDL oxidation and foam cell formation (42). Bilirubin, another non-enzymatic antioxidant, protects endothelial and smooth muscle cells from the harmful effects of H2O2. In various in vitro studies, it has been shown that bilirubin prevents lymphocyte migration caused by the increase in the VCAM-1 adhesion molecule. In addition, it prevents the oxidation of lipoproteins, which is an important

cause of atherosclerosis (43). Studies on uric acid, the end product of purine catabolism, are contradictory (31,37,44,45). Although the increase in plasma levels is associated with cardiovascular diseases such as atherosclerosis, it is not fully known whether it increases as a cause of the disease or as a protective antioxidant against increased oxidative stress (44). There is also a study showing that uric acid may have activity against atherosclerosis with its ability to remove oxidants such as OH- and HOCl- (31). Yet additionally, there is also a study suggesting that it stimulates the VSMC proliferation, while, on the other hand, leading to endothelium cell dysfunction, and also that the decreasing of increased uric acid levels relieves the inflammation (45). Therefore, more studies are needed to be conducted about uric acid. Dihydro lipoic acid (DHLA), the reduced form of lipoic acid, and α-lipoic acid have been identified as antioxidants (46). It acts as a cleaner for lipoic acid, ONOO-, HOCl- and peroxyl radicals. It also reduces endothelial dysfunction and increases eNOS activity (20,31,37).

There are studies showing that vitamin E, one of the non-enzymatic exogenous antioxidants, reduces the development of atherosclerosis when used as a long-term low-dose supplement along with a low-cholesterol diet (44,47,48). Vitamin E shows this effect by reducing intima and media thickness with the expression of VCAM-1 and MCP-1 molecules (48). In addition, one of the most important effects of vitamin E is to prevent the oxidation of LDL (44). Vitamin C also acts as an important antioxidant similar to vitamin E. The most important feature of vitamin C is to prevent the formation of ox-LDL while recycling the oxidized vitamin E itself. In addition, it has effects such as increasing NO bioavailability, preventing endothelial dysfunction, providing vasodilation, and scavenging various ROS (20,49). B vitamins are a cofactor in homocysteine metabolism (50). It functions by removing OH and lipid peroxyl radicals and improving endothelial function in the process of atherosclerosis (20). Vitamin A can be synthesized in the intestine from β-carotene. Much research has been done on lycopene, the most common carotenoids. In studies, it has been found that lycopene is a very powerful singlet oxygen scavenger. Vitamin A and carotenoids function as radical scavengers in preventing atherosclerosis, preventing LDL peroxidation, inflammation and endothelial cell dysfunction (37,51). Lastly, polyphenols, another non-enzymatic antioxidant, and foods rich in polyphenols such as red wine, catechins, dark chocolate, resveratrol, curcumin, tea flavonoids, pomegranate juice, ellagic acid and cocoa are effective in the development of endothelial dysfunction, ox-LDL formation. It functions in processes such as VSMC proliferation, inflammation process of monocyte / macrophage and T lymphocytes, platelet aggregation (26,52).

The research on the antioxidants mentioned above have mostly been carried out on animals. Observation of positive effects in studies on humans is minimal.

For the benefit of antioxidants in preventing the development of atherosclerosis due to oxidative stress and their recommendations regarding their use as supplements, more research is needed.

One of the environmental sources of free radicals that cause oxidative stress is diet (12). Therefore, diet has an important place in the development of oxidative stress and atherosclerosis.

Mediterranean diet is a nutritional model with proven effects on cardiovascular diseases (4,53). The Mediterranean diet is a nutritional habit that mainly uses fruit and vegetables and olive oil (4). Diet includes an average of 8 servings / day of whole grain sources, 4-6 servings / day of vegetables and fruits, 4-5 servings / week of legumes, 30-45 grams / day of nuts, 25-50 ml / day of olive oil, 4-5 servings / week fish and moderate red wine are consumed (54).

The Mediterranean diet is thought to protect from oxidative stress that contributes to the development of atherosclerosis and strengthen the antioxidant defense system. (54-56). Polyphenols such as resveratrol, catechin and quercetin provided by the ingredients of the Mediterranean diet have been shown to have anti-inflammatory effects that improve damage caused by endothelial dysfunction (26,56). It has also been shown that some components of the diet, such as monounsaturated fatty acids and phenols, contained in olive oil, improve microvascular endothelial dysfunction (55). In addition, there are several studies suggesting that carotid intima-media thickness, an indicator of pre-clinical atherosclerosis and future cardiovascular disease, may decrease with the Mediterranean diet (57,58). In a study, it has been shown that it reduces the formation of ox-LDL, which has an important role in the development of atherosclerosis (59).

In summary, it is seen that the Mediterranean diet that is rich in monounsaturated fatty acids, low saturated fat consumption, antioxidant compounds provided by the consumption of fruits and vegetables, polyphenols provided by moderate red wine consumption, resveratrol and quercetin is a healthy and protective diet model in preventing the development of atherosclerosis. However, it would be useful to do more research for its long-term effects.

4.DISCUSSION and RESULT

Atherosclerosis is a chronic inflammatory disease caused by oxidative stress resulting from an imbalance between ROS and antioxidant defense due to increased reactive oxygen species (ROS) or decreased antioxidant capacity (4,5,9).

The first step in the development of atherosclerosis is that oxidative stress causes the oxidation of low-density lipoprotein (LDL) to form oxidized-LDL (ox-LDL). In the later stages, endothelial cell damage, decrease in NO production, and the transformation of monocytes to macrophages by entering into the endothelium due to the increase of endothelial adhesion molecules, the incorporation of macrophages into their structure by recognizing ox-LDL, and the formation of foam cells occur. If the migration of smooth muscle cells and lipid accumulation continue after foam cell formation, T-lymphocytes and mast cells also enter the vascular intima. In the last stage of atherosclerosis, fibrous plaque formed around a necrotic nucleus ruptures as a result of apoptosis, and thrombogenic content in the necrotic nucleus is released into the lumen. Clinical signs seen at this stage are coronary heart disease, ischemia, peripheral artery disease, heart failure or sudden death (14,30-36).

There are various enzymatic and non-enzymatic antioxi-

dant defense systems in atherosclerosis, such as SOD, CAT, GPx, Trx, glutathione, CoQ, bilirubin, uric acid, lipoic acid, vitamin E, vitamin C, B vitamins, polyphenols, vitamin A and carotenoids (37).

The Mediterranean diet is a healthy diet low in saturated fat, consuming fruits and vegetables, fish, nuts and moderate amounts of red wine. Beneficial components such as polyphenols, dietary fiber, antioxidants provided by the foods consumed will be beneficial for the prevention of oxidative stress and atherosclerosis development.

5. CONCLUSION

Oxidative stress that leads to the development of atherosclerosis may be caused by various diseases such as diabetes, dyslipidemia, insulin resistance, inflammation, and environmental factors such as smoking and alcohol. For this reason, lifestyle changes and, if any, treating diseases such as insulin resistance and dyslipidemia are important to reduce or prevent oxidative damage.

Nutritional therapy plays an important role in preventing oxidative damage and atherosclerosis. Maintaining a healthy body weight, Mediterranean diet is recommended as general recommendations. The polyphenols, dietary fiber, antioxidants and healthy oils provided by the Mediterranean diet will be beneficial to protect heart health and prevent the development of atherosclerosis.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has no financial support.

REFERENCES

1. Tanrıverdi B, Savaş Ş. Aterosklerozun Patofizyolojisi ve Risk Faktörleri. Marmara Pharmaceutical Journal 2017; 1:1-9.
2. Khosravi M, Poursaleh A, Ghasempour G, Farhad S, Najafi M. The effects of oxidative stress on the development of atherosclerosis. Biological Chemistry 2018; 1-44.
3. İlerigelen B. Ateroskleroz ve Obezite. Obezite Dergisi 2014; 2:6-8.
4. Alphan E. Kardiyovasküler Hastalıklar ve Beslenme Tedavisi. Hastalıklarda Tıbbi Beslenme Tedavisi. 5.Baskı. Ankara: Hatipoğlu Yayınevi, 2020:375-380.
5. Kattor AJ, Pothineni NVK, Palagiri D, Mehta JL. Oxidative Stress in Atherosclerosis. Curr Atheroscler Rep 2017; 19:42.
6. Pelusoa I, Morabitob G, Urbana L, Ioannonea F, Serafinia M. Oxidative Stress in Atherosclerosis Development: The Central Role of LDL and Oxidative Burst. Endocrine, Metabolic & Immune Disorders - Drug Targets 2012; 12:351-360.
7. Macit S, Akbulut G. Diabetes Mellitus ve Oksidatif Stres. Beslenme ve Diyet Dergisi 2015; 43(1):59-65.
8. Förstermann U, Xia N, Li H. Roles of vascular oxidative stress and nitric oxide in the pathogenesis of atherosclerosis. Circulation research 2017; 120(4):713-735.
9. Mahan LK, Raymond JL. Kardiyovasküler Hastalıklarda Tıbbi Beslenme Tedavisi. Krause Besin ve Beslenme Bakım Süreci. 14.Baskı. Ankara: Nobel Tıp Kitabevleri 2017; 646-658.
10. Manea A, Simionescu M. Nox enzymes and oxidative stress in atherosclerosis. Frontiers in Bioscience 2012; 4:651-670.
11. Perrotta I, Aquila S. The role of oxidative stress and autophagy in atherosclerosis. Oxidative Medicine and Cellular Longevity, 2015.
12. Konukoğlu D. Sorularla Konu Anlatımlı Tıbbi Biyokimya. 1.Baskı. Ankara: Nobel Tıp Kitabevleri; 2016.
13. Özcan O, Erdal H, Çakırca G, Yönden Z. Oksidatif stres ve hücre içi lipit, protein ve DNA yapıları üzerine etkileri. 2015.
14. Sies H, Berndt C, Jones D. Oxidative Stress. Annu. Rev. Biochem 2017; 86:715-748.
15. Di Pietro M, Filardo S, Falasca F, Turriziani O, Sessa R. Infectious agents in atherosclerotic cardiovascular diseases through oxidative stress. International journal of molecular sciences 2017; 18(11):2459.
16. Drummond GR, Selemidis S, Griendling KK, Sobey CG. Combating oxidative stress in vascular disease: NADPH oxidases as therapeutic targets. Nat Rev Drug Discov 2011; 10(6):453–71.
17. Matthews AT, Ross MK. Oxyradical stress, endocannabinoids, and atherosclerosis. Toxics 2015; 3(4):481-498.
18. Yuan T, Yang T, Chen H, Fu D, Hu Y, Wang J, Xie X. New insights into oxidative stress and inflammation during diabetes mellitus-accelerated atherosclerosis. Redox biology 2019; 20:247-260.
19. Kasikara C, Doran AC, Cai B, Tabas I. The role of non-resolving inflammation in atherosclerosis. The Journal of clinical investigation 2018; 128(7):2713-2723.
20. Malekmohammad K, Sewell RD, Rafieian-Kopaei M. Antioxidants and atherosclerosis: Mechanistic aspects. Biomolecules 2019; 9(8):301.
21. López-Domènech S, Martínez-Herrera M, Abad-Jiménez Z, Morillas C, Escribano-López I, Díaz-Morales N, Bañuls C, Víctor MV, Rocha M. Dietary weight loss intervention improves subclinical atherosclerosis and oxidative stress markers in leukocytes of obese humans. International Journal of Obesity 2019; 43(11):2200-2209.
22. Marchio P, Guerra-Ojeda S, Vila JM, Aldasoro M, Victor VM, Mauricio MD. Targeting early atherosclerosis: A focus on oxidative stress and inflammation. Oxidative medicine and cellular longevity. 2019.
23. Tousoulis D, Psaltopoulou T, Androulakis E, Papageorgiou N, Papaioannou S, Oikonomou E, Synetos A, Stefanadis C. Oxidative stress and early atherosclerosis: novel antioxidant treatment. Cardiovascular Drugs and Therapy 2015; 29(1):75-88.
24. Tousoulis D, Kampoli AM, Tentolouris Nikolaos Papageorgiou C, Stefanadis C. The role of nitric oxide on endothelial function. Current vascular pharmacology 2012; 10(1):4-18.
25. Ferrier D. Pentoz Fosfat Yolu ve Nikotinamid Adenin Dinükleotid Fosfat. Lippincott Görsel Anlatımlı Çalışma Kitapları: Biyokimya. 7.Baskı. İstanbul: Nobel Tıp Kitabevleri; 2019. p.150-151.

26. Cheng YC, Sheen JM, Hu WL, Hung YC. Polyphenols and oxidative stress in atherosclerosis-related ischemic heart disease and stroke. Oxidative Medicine and Cellular Longevity. 2017.

27. Pignatelli P, Menichelli D, Pastori D, Violi F. Oxidative stress and cardiovascular disease: new insights. Kardiol Pol 2018; 76(4):713-722.

28. Torres N, Guevara-Cruz M, Velázquez-Villegas LA, Tovar AR. Nutrition and atherosclerosis. Archives of Medical Research 2015; 46(5):408-426.

29. Yang X, Li Y, Ren X, Zhang X, Hu D, Shang H. Oxidative stress-mediated atherosclerosis: mechanisms and therapies. Frontiers in Physiology 2017; 8:600.

30. Salvayre R, Negre-Salvayre A, Camaré C. Oxidative theory of atherosclerosis and antioxidants. Biochimie. 2016;125:281-296.

31. Lönn ME, Dennis JM, Stocker R. Actions of "antioxidants" in the protection against atherosclerosis. Free Radical Biology and Medicine 2012; 53(4):863-884.

32. Gimbrone Jr MA, García-Cardeña G. Endothelial cell dysfunction and the pathobiology of atherosclerosis. Circulation research 2016; 118(4):620-636.

33. Zheng S, Du Y, Peng Q, Fan X, Li J, Chen M. Trimetazidine protects against atherosclerosis by changing energy charge and oxidative stress. Medical science monitor: international medical journal of experimental and clinical research 2018; 24:8459.

34. Chistiakov DA, Melnichenko AA, Myasoedova VA, Grechko AV, Orekhov AN. Mechanisms of foam cell formation in atherosclerosis. Journal of Molecular Medicine 2017; 95(11):1153-1165.

35. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. N Engl J Med 2013; 368:2004-2013.

36. Casas R, Castro-Barquero S, Estruch R, Sacanella E. Nutrition and cardiovascular health. International journal of molecular sciences 2018; 19(12):3988.

37. Goszcz K, Deakin SJ, Duthie GG, Stewart D, Leslie SJ, Megson IL. Antioxidants in cardiovascular therapy: panacea or false hope?. Frontiers in cardiovascular medicine 2015; 2:29.

38. Çaylak E. Hayvan ve bitkilerde oksidatif stres ile antioksidanlar. Tıp Araştırmaları Dergisi 2011; 9(1):73-83.

39. Cheng F, Torzewski M, Degreif A, Rossmann H, Canisius A, Lackner KJ. Impact of glutathione peroxidase-1 deficiency on macrophage foam cell formation and proliferation: implications for atherogenesis. PLoS One 2013; 8(8):72063.

40. Kirsch J, Schneider H, Pagel J, Rehberg M, Singer M, Hellfritsch J, Chillo O, Schubert KM, Qiu J, Pogoda K, Kameritsch P, Uhl B, Pircher J, Deindl E, Müller S, Kirchner T, Pohl U, Conrad M, Beck H. Endothelial dysfunction, and a Prothrombotic, Proinflammatory phenotype is caused by loss of mitochondrial Thioredoxin reductase in endothelium. Arterioscler Thromb Vasc Biol 2016; 36(9):1891–9.

41. Chen B, Wang W, Shen T, Qi R. Thioredoxin 1 downregulates oxidized low-density lipoprotein-induced adhesion molecule expression via Smad 3 protein. PLoS One 2013; 8(9):76226.

42. Moss JW, Ramji DP. Nutraceutical therapies for atherosclerosis. Nature Reviews Cardiology 2016; 13(9):513.

43. Kang SJ, Lee C, Kruzliak P. Effects of serum bilirubin on atherosclerotic processes. Annals of medicine 2014; 46(3):138-147.

44. Gagliardi AC, Miname MH, Santos RD. Uric acid: a marker of increased cardiovascular risk. Atherosclerosis 2009; 202(1):11-17.

45. Kimura Y, Yanagida T, Onda A, Tsukui D, Hosoyamada M, Kono H. Soluble uric acid promotes atherosclerosis via AMPK (AMP-Activated Protein Kinase)-mediated inflammation. Arteriosclerosis, Thrombosis, and Vascular Biology 2020; 40(3):570-582.

46. Shay KP, Moreau RF, Smith EJ, Smith AR, Hagen TM. Alpha-lipoic acid as a dietary supplement: molecular mechanisms and therapeutic potential. Biochimica et Biophysica Acta (BBA)-General Subjects 2009; 1790(10):1149-1160.

47. Siti HN, Kamisah Y, Kamsiah J. The role of oxidative stress, antioxidants and vascular inflammation in cardiovascular disease (a review). Vascular pharmacology 2015; 71:40-56.

48. Meydani M, Kwan P, Band M, Knight A, Guo W, Goutis J, Ordovas J. Long-term vitamin E supplementation reduces atherosclerosis and mortality in Ldlr −/− mice, but not when fed Western style diet. Atherosclerosis 2014; 233(1):196-205.

49. May JM, Harrison FE. Role of vitamin C in the function of the vascular endothelium. Antioxidants & redox signaling 2013; 19(17):2068-2083.

50. Choe H, Hwang JY, Yun JA, Kim JM, Song TJ, Chang N, Kim YJ, Kim Y. Intake of antioxidants and B vitamins is inversely associated with ischemic stroke and cerebral atherosclerosis. Nutrition research and practice 2016; 10(5):516-523.

51. Mahmoudi MJ, Saboor-Yaraghi AA., Zabetian-Targhi F, Siassi F, Zarnani AH, Eshraghian MR, Shokri F, Rezaei N, Kalikias Y, Mahmoudi M. Vitamin A decreases cytotoxicity of oxidized low-density lipoprotein in patients with atherosclerosis. Immunological investigations 2016; 45(1):52-62.

52. Storniolo CE, Roselló-Catafau J, Pintó X, Mitjavila MT, Moreno JJ. Polyphenol fraction of extra virgin olive oil protects against endothelial dysfunction induced by high glucose and free fatty acids through modulation of nitric oxide and endothelin-1. Redox Biology 2014; 2: 971-977.

53. Estruch R, Ros E, Jordi S-S, Covas M-I, Corella D, Aros F, Enrique G-G, Ruiz-Gutierrez V, Fiol M, Lapetra J, Rosa M, Raventos L, Lluís S-M, Xavier P, Basora J, Munoz MA, Sorli JV, Martinez JA, Fitó M, Gea A, Hernán MA, Martínez-González MA. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N. Engl. J. Med 2018; 378, e34.

54. Alphan E, Güleç GS. Akdeniz Diyeti. Diyetler ve Gerçekler. 2. Baskı. Ankara: Hatipoğlu Yayınevi, 2019:123-133.

55. Torres-Peña JD, Rangel-Zuñiga OA, Alcala-Diaz JF, Lopez-Miranda J, Delgado-Lista J. Mediterranean diet and endothelial function: a review of its effects at different vascular bed levels. Nutrients 2020; 12(8):2212.

56. Stromsnes K, Mas-Bargues C, Gambini J, Gimeno-Mallench L. Protective effects of polyphenols present in mediterranean diet on endothelial dysfunction. Oxidative Medicine and Cellular Longevity. 2020.

57. Gardener H, Wright CB, Cabral D, Scarmeas N, Gu Y, Cheung K, Elkind MS, Sacco RL, Rundek T. Mediterranean diet and carotid atherosclerosis in the Northern Manhattan Study. Atherosclerosis 2014; 234:303–310.

58. Murie-Fernandez M, Irimia P, Toledo E, Martínez-Vila E, Buil-Cosiales P, Serrano-Martínez M, Ruíz-Gutierrez V, Ros E, Estruch R, Martínez-González MÁ. Carotid intima-media thickness changes with Mediterranean diet: A randomized trial (PREDIMED-Navarra). Atherosclerosis 2011; 219:158–162.

59. Tuttolomondo A, Simonetta I, Daidone M, Mogavero A, Ortello A, Pinto A. Metabolic and vascular effect of the Mediterranean diet. International journal of molecular sciences 2019; 20(19):4716.