Role of Nutrition in Providing Pro/Anti Inflammatory Balance

The Process of Acute and Chronic Inflammation, Biomarkers and Their Relationship with Diseases

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ABSTRACT

Inflammation is a physiopathological process that has been known for a long time but its relation with acute and chronic diseases and its role in the development of diseases are becoming better understood. Diabetes, hypertension, ischemic heart disease, various organ cancers, rheumatologic diseases, the most common diseases of the liver, lungs and kidneys are either closely related to inflammatory processes or are caused by direct inflammatory processes. In one aspect, the aging process is a progressive inflammatory process. Is it possible to slow down or stop the course of chronic inflammation? How does changing the various environment and living conditions and diet affect this process? The correct answer to these questions is only possible by understanding what inflammation is and the mechanisms by which the inflammation occurs in the organism and by accurately identifying and following the clinical markers that show the course of inflammation. In this section, basic issues related to inflammation will be examined.

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Keywords: Inflammation, immune system, acute and chronic inflammation, cancer, aging, obesity, diabetes, atherosclerosis, laboratory markers, C-reactive protein, procalcitonin, interleukin

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Inflammation is a physiopathological process that has been known for a long time but its relation with acute and chronic diseases and its role in the development of diseases are becoming better understood. Diabetes, hypertension, ischemic heart disease, various organ cancers, rheumatologic diseases, the most common diseases of the liver, lungs and kidneys are either closely related to inflammatory processes or are caused by direct inflammatory processes. In one aspect, the aging process is a progressive inflammatory process. Is it possible to slow down or stop the course of chronic inflammation? How does changing the various environment and living conditions and diet affect this process? The correct answer to these questions is only possible by understanding what inflammation is and the mechanisms by which the inflammation occurs in the organism and by accurately identifying and following the clinical markers that show the course of inflammation. In this section, basic issues related to inflammation will be examined.

BACKGROUND

Inflammation is one of the oldest medical conditions defined in history. It is the process of plasma proteins and leukocytes coming out of the vessel wall in tissues and destroying the antigenic structure or microorganism which is recognized as harmful due to their activation. During this process, there is a strong physiopathological response to tissue damage in the organism at both cellular and humoral levels. Inflammation begins with the recognition of microorganisms or dead tissues. It can start with the natural immune system response and continue with the adaptive immune response. Inflammation can be defined as acute and chronic inflammation depending on time (Baştürk, 2017).

In all living things, a number of defensive mechanisms have been developed to protect the organism against living and inanimate harmful agents coming from outside for millions of years. In vertebrate and nonvertebrate organisms, it is aimed to defend the organism with acute and chronic responses to external factors through highly sophisticated, complex and detailed mechanisms. These defence mechanisms have been programmed to remove the alien from the organism in some way by the acute and chronic inflammatory responses of various cellular and chemical components through chain reactions.

The various components of the immune system protect the organism from outside and at the same time against a number of harmful substances and cells formed by a number of specific and nonspecific processes that are innate or acquired. Although acute and chronic inflammatory processes are mainly based on the logic of protection, they may also lead to undesirable consequences during these processes. Acute responses often result in symptoms of systemic disease and are often returned to normal physiological status.

Especially in the formation of chronic diseases and aging process, the main mechanism is usually chronic inflammatory processes. While these processes aim to defend the organism on the one hand, it also causes irreversible changes that lead to chronic tissue destruction and organ damage. Chronic inflammatory responses may lead to structural and functional changes in cells, resulting in diseases such as cancer, diabetes, and various chronic connective tissue diseases. In order to understand acute and chronic inflammation, cellular and chemical components of immune system and normal immune responses should be recognized (Barten at al. 2008)

IMMUNE SYSTEMS AND COMPONENTS

Human immunity is mainly created by two main elements.

1- Natural Immunity

2- Acquired Immunity

Natural Immunity: It is a naturally occurring immunity which occurs due to genetic factors during embryogenesis, carried from one generation to another.

Acquired immunity: These are the answers that we do not bring with birth but that the organism develops as we face pathogens over the years.

Both natural and acquired immunity are mainly accomplished by humoral and cellular components. In natural immunity, a variety of chemical mediators such as cells, complement and cytokines are present in the blood or tissues, such as macrophages, neutrophils and natural clays lymphocytes. Although the main cells of acquired immunity are t and b lymphocytes, the main humoral component is antibodies. Natural immunity consists of cellular and chemical defence mechanisms. It only responds to germs and damaged tissues.

Monocytes: the form of tissue macrophages in the peripheral blood, and they produce specific and nonspecific responses in many bacterial and virus infections.

Eosinophils and basophil cells: cells that are found mainly in the tissue in the peripheral blood.

Eosinophil cells are primarily responsible for the control of parasitic infections and they are also responsible for the development of allergic responses.

Basophil cells, also known as mast cells, regulate vascular permeability and provide eradication and immunization of allergic responses to bacterial, virus and parasitic infections.

Eosinophil basophil and mast cells are often responsible for allergic reactions caused by exaggerated immune responses (Barten at al. 2008)

CHEMICAL COMPONENTS OF THE IMMUNE SYSTEM:

Although both the natural and acquired immune system operate in part with different mechanisms, both systems have common pathways, common cells and chemical mediators. These structural elements have a common role in the formation of many diseases such as cancer and rheumatologic diseases, shaping of the aging process and long-term organ and tissue damage caused by acute and chronic inflammation. Determine the prognosis of the disease. In clinical practice, most of them are markers of inflammation that are used as laboratory tests.

Antigens: They are substances that can produce a reactive immune response in the organism. The antibodies and macromolecular substances which are specific to them are protein, polysaccharide, peptide, which may interact with the cell. They can be antigens. In some instances, nucleic acids may acquire antigenic properties.

Antibodies: Immune globulin mediators that are developed specifically for antigen and are composed of light or heavy chain proteins produced by B lymphocyte cells. When bacteria and other microorganisms are first encountered, the antigenic substances in their structures are perceived as foreign and specific antibodies are developed against each of them. The resulting antibodies combine with the antigen to form antigen antibody complexes. These complexes also provide the destruction of the cell to which they are attached. Unnecessary and excessive accumulation of antigen antibody complexes in tissues and vascular beds may cause tissue damage and cause many chronic organ diseases (White, 1999; Kuralay & Çavdar 2006; Wan, Haw, & Blackburn, 1989).

Table 1. Chemical mediators of inflammation

Vasoactive amines	Histamine Bradykinin
Plasma Proteases	Quinines: Brachinin Kallikrein Complement system Coagulation and fibrinolytic system products
Arachidonic acid metabolites	Thromboxane Prostaglandins Endoperoxides Leukotrienes …
Leukocyte products	Various lysosomal proteases Free oxygen radicals
Platelet activating factor	
Cytokines	
Growth factors	

Complemantary system: These chemical mediators in the blood plasma, activated by inflammatory processes and formed in various proteins, strengthen the inflammation process and destroy the foreign and harmful cells. During this process, they increase vascular permeability and provide vasodilatation. They also stimulate the secretion of vasoactive amines such as histamine from mast cells. They facilitate phagocytosis of macrophages. They attach to the foreign cell membrane and cause their sequence, allowing leukocytes to migrate to the inflammation site. The complement chain consists of a large number of sub-molecule structures and often performs their functions through chain reactions (Rus, Cudrici, & Niculescu, 2005).

Arachidonic acid metabolites: They are ansatured fatty acids formed from phospholipids in the cell membrane by various inflammatory stimuli. These metabolites follow two main pathways, leading to inflammatory processes. It is synthesized to prostoglandins (PG) by cyclooxygenase and to leukotrienes

(LKT) by lipoxygenase. PG and leukotrienes are responsible for most of the systemic effects of tumor necrotizing factor-alpha (TNF-α) and interleukin (IL).

Cyclooxygenase pathway: Arachidonic acid from the cyclooxygenase enzyme and arachidonic acid from PG G2 and then peroxidase effect PGH2 is formed. After several synthesis steps, they are converted to PGI2, Thromboxane A2, and other PG by the action of specific enzymes. While thromboxane A2 is a potent vasoconstrictor, some PG derivatives such as PGE2, PGD2, have vasodilatation and edema-enhancing effects.

Lipoxigenase pathway: In this way, the enzyme lipoxygenase, which is abundantly found in neutrophil leukocytes, forms leukotrienes through arachidonic acid. They are chemical mediators that play an important role in inflammatory processes in leukotrienes. They increase the adhesion and aggregation of leukocytes to vascular endothelium. In many acute and chronic diseases (chronic obstructive pulmonary disease, various skin and kidney diseases) as intermediate mediators affect the course and prognosis of the disease (Donowitz, 1985; Kuralay & Çavdar,2006; Parkin, & Cohen, 2001).

Leucocyte products: They are proteases and free oxygen radicals synthesized in leukocyte lysosomes. When stimulated by the immune stimulus, neutrophils and macrophages accompany the inflammation response by producing lysosomal enzymes and free oxygen radicals. In particular, free oxygen radicals have long-term adverse effects on the endothelial surface and vascular structure. They adversely affect vascular permeability and cause significant tissue damage. Free oxygen radicals are closely related to many chronic diseases and aging processes, especially atherosclerosis. Our tissue and organ systems have antioxidant defence systems that fight free oxygen radicals. When mediators such as elastase, collagenase, and leukocyte lysosomal proteolytic enzymes accumulate in the tissue, they break down other tissue proteins and cause tissue damage. For example, aging and skin elasticity are related to this process.

Thrombocyte activing factor: Platelet activating factor (PAF) is a phospholipid with strong physiological effects. 1-alkyl-2- (o) -acetyl-glycero-3-phosphocholine.

The source of basal PAF in plasma is the kidney. Other tissues in which PAF is synthesized are phagocytosis cells of the liver, spleen and blood. Many cells involved in inflammation or allergy, such as neutrophils, rnakrophages, lymphocytes, basophils and eosinophils, synthesize and release PAF when activated. Another source of PAF is human endothelial cells. Human endothelial cell cultures have been shown to synthesize PAF when stimulated with thrombin.

It causes activation of platelets, polymorphonuclear leukocytes, monocytes and rnakrophages. It also leads to increased vascular permeability, hypotension, decreased heart rate, glycogenolysis in the perfused liver, and stimulation of uterine contractions. It was found to function both in normal physiological events and to mediate some pathological events (Sarıahmetoglu & Çakıcı, 1996).

Cytokines: They are mediators formed in many cells such as CD4+ T lymphocytes and activated macrophrophages. CD4+ T lymphocytes are capable of evolving into T lymphocytes producing different cytokines. Cytokine secretion can be stimulated by bacterial products, immune complexes, various toxins, physical injuries and various inflammatory events. The most important of the polypeptide cytokines are IL and TNF-α. The three main effects are: triggering systemic acute phase reactants, leukocyte adhesion, procoagulant activity and Tenofovir alafenamide fumarate (TAF) activation from endothelial cells, increasing collagen synthesis and fibroblast production (Kishimoto, Taga, & Akira, 1994).

TNF-α and IL-8 are potent chemoattractive mediators and cause chemotaxis and activation of neutrophils. TNF-α plays an important role in acute inflammation and antitumoral activity and wound

healing IL play a critical role in the etiopathogenesis and prognosis of many acute and chronic diseases such as rheumatologic diseases, septic shock, malignancy, and AIDS (Dinarello, 2002).

The soluble IL-1 receptor has been developed for anti-inflammatory and immunosuppressive therapy in the stimulation of haematopoiesis, protection against lethal doses of radiation and inhibition of growth of cancer cells (Leiva, Gardner, McKinnon, & Poretta, 2003).

Growth factors: They are released from activated macrophages and act by binding to receptors in the cell membrane. Activated macrophages are capable of greater phagocytosis since cell volume and lysosomal enzyme levels are increased and secrete a variety of biologically active products that produce fibrosis, a characteristic of chronic inflammation. These are proinflammatory enzymes such as lysosomal proteases and plasminogen activator, coagulation and complement system fragments, reactive oxygen metabolites, AA metabolites, TAF and growth factors that affect proliferation of various cell types in addition to cytokines such as IL-1 and TNF (Sessle, 2001).

Nitric oxide: Nitric oxide (NO) is synthesized in endothelial cells. It is one of the most important mediators of vascular resistance and inflammatory processes in circulation. It is found in many cells in the body that play a role in cardiovascular physiology with its various isomers.

Once synthesized in endothelial cells, the vessel enters into smooth muscle cells by diffusion. Relaxation occurs in vascular smooth muscle cells. It is also secreted in the vessel lumen, thereby inhibiting the adhesion of platelets and leukocytes. Slows down the growth of smooth muscle. The release of NO is regulated by physical and humoral stimuli. NO plays an important role in the pathogenesis of hypertension and complications. Inhibition of NOproduction leads to decreased vasodilatation, contraction of arteries and decreased blood flow. Chronic NO deficiency disrupts tissue circulation leading to target organ damage. With similar mechanisms, NO plays an important role, especially in the formation of diabetes and organ damage due to diabetes (Gültekin, Ersanlı, & Küçükateş, 1996; Radi, 2018).

Histamine: Histamine is common in the body, mast cells in connective tissue are the main source. Various physical stimuli such as trauma, cold, autoimmune events and antigen antibody complexes, complement fragments, and a number of neutrophil products cause histamine release. Histamine increases vascular permeability and provides vasodilatation. Histamine is also a chemotactic factor for eosinophils (Parsons, & Ganellin, 2006; Branco, Yoshikawa, Pietrobon, & Sato, 2018).

Serotonin: Serotonin is a biogenic amine similar to epinephrine and norepinephrine. Serotonin, also known as 5-hydroxytryptamine (5-HT), has an important role in the central nervous system as well as platelet aggregation, smooth muscle and vascular tone, pulmonary artery pressure and intestinal motility. It is also a mediator in acute and chronic inflammation. They are stored in the periphery in platelets and in the granules of mast cells (Shajib & Khan, 2015)

Plasma Proteases: They are peptide-mediated mediators with various biological activities in the inflammatory response and originating from plasma. In this chain, precallikrein is converted to prekallikrein, which is its active form with the stimulation of Hageman Factor (Factor 12). Kallikrein converts kininogen to bradykinin. Bradykinin is an important vasoactive mediator. It causes vasodilatation, natriuresis and diuresis, endothelial cell contraction and increased vascular permeability. It also provides neutrophil aggregation (Campbell, 2013).

Other mediators: It has mainly examined mediators involved in chronic inflammation processes, substance P is involved in a number of mediators such as calpaines and hemigenigenase.

ACUTE AND CHRONIC INFLAMMATION FORMATION

As can be seen, acute and chronic inflammation processes are highly complex events with many cellular, humoral and chemical components. In fact, the main purpose of inflammation is to protect the organism from external and internal factors that cause cell damage, and to cleanse the necrotic tissues and cells and chemical substances of cell damage. However, this process may sometimes work against the organism in the chronic period and may cause some undesirable consequences and diseases. This condition takes place in the pathophysiology of many diseases seen in the clinic. In order to understand and define the pathological processes, it is necessary to examine how the physiological process works and how the above mentioned mediators form chain reactions and how these reactions turn into pathological processes.

The inflammatory pathway consists of inducers, sensors, mediators, and target tissues. Inducers initiate the inflammatory response and are detected by sensors. Sensors, such as Toll-like receptors (TLRs), are expressed on specialized sentinel cells, such as tissue-resident macrophages, dendritic cells, and mast cells. They induce the production of mediators, including cytokines, chemokines, bioactive amines, eicosanoids, and products of proteolytic cascades, such as bradykinin. These inflammatory mediators act on various target tissues to elicit changes in their functional states that optimize adaptation to the noxious condition (e.g., infection or tissue injury) associated with the particular inducers that elicited the inflammatory response. The specific components shown represent only a small sample of the myriad different sensors, mediators, and target tissues involved in the inflammatory response (Ruslan Medzhitov, 2010).

In acute inflammation, a series of events begins between the cellular and chemical components of the immune system, together with the factor that triggers inflammation. Acute inflammation develops in minutes and days, is characterized by extrapulmonary fluid and protein output and is characterized by more polymorphic neutrophils, while chronic inflammation is a process involving more lymphocytes and macrophages and mononuclear cells lasting for weeks and years. The role of chemical mediators in this process is more obvious and the determining factor of the process. Local temperature increase, Redness, Swelling, Pain and Loss of Function in acute inflammation are the five main clinical symptoms; when the organ damage caused by chronic inflammation exceeds a certain level, symptoms start.

In general, inflammation has three periods: induction, regulation and resolution. Period of initiation, regulation of the process with inducing factor and finally cleaning and resolution of waste material caused by inflammation.

It is emphasized that many diseases, especially type 2 diabetes, atherosclerosis, asthma, neurodegenerative diseases and cancer, may be related to chronic inflammation caused by some infections at an early age.

Several types of inflammation—differing by cause, mechanism, outcome, and intensity—can promote cancer development and progression. Persistent Helicobacter pylori infection is associated with gastric cancer and mucosa-associated lymphoid tissue (MALT) lymphoma. Infections with hepatitis B (HBV) or C (HCV) viruses increase the risk of hepatocellular carcinoma (HCC), and infections with Schistosoma or Bacteroides species are linked to bladder and colon cancer, respectively (Grivennikov, Greten, & Karin, 2010).

The relationship between chronic inflammation of non-infectious origin and these diseases and the course of the inflammation process in these diseases are known to determine the prognosis of the disease. Tissue damage during the inflammation process and a number of toxic substances occurring after injury are important causes of chronic inflammation (Hunter, 2012; Medzhitov, 2010).

CHRONIC INFLAMMATION AND ITS RELATIONSHIP WITH DISEASES:

Under this heading, both chronic inflammatory pathways on the basis of diseases and how this process has turned into disease will be examined.

Relationship between inflammation and cancer: The transformation of inflammatory processes into cancer is a common occurrence and a number of mediators involved in inflammation and inflammation, and more importantly, tissue destruction products and toxic substances that result from inflammation can stimulate the emergence of tumor in a healthy tissue. Inflammation can induce every step of tumorogenesis. Reactive oxygen metabolites produced by immune cells in the initial process can lead to DNA damage. DNA damage is the earliest stage of tumor formation. There is a clear relationship between tumor cells and the immune system. One of the important tasks of the immune system is the destruction of cells that tend to become cancerous in various ways. In the area of inflammation, on the one hand, metabolites resulting from inflammation disrupt the DNA structure and stimulate the formation of new cancer cells, while at the same time disrupting the eradication process of formed cancer cells. This transformation, which often starts on a single cell basis (initation), then leads to the promotional phase and malignant transformation by uncontrolled proliferation of the cell. This new tissue, which invades the local area, then reaches the vessel bed or different channels and spreads to near and distant tissues and metastasizes (Hunter, 2012).

Recent data suggest that an additional mechanism involved in cancer-related inflammation (CRI) is induction of genetic instability by inflammatory mediators, leading to accumulation of random genetic alterations in cancer cells.

Oxidative stresses can activate a variety of transcription factors such as the nuclear factor (NF)-κB, AP-1, p53, HIF-1α, PPAR-γ, β-catenin / Wnt, and Nrf2. Activation of this transcription can affect around 500 different genes and alter the formation and effects of inflammatory growth cytokines, chemokines, molecular, and anti-inflammatory molecules that regulate cell cycle (Reuter, Gupta, Chaturvedi, & Aggarwal, 2010).

On the one hand, the inflammation process is the trigger for tumorigenesis, while on the other hand genetic tendencies, carcinogenic environmental factors such as smoking in lung cancer, and comorbid diseases such as obesity, the tendency to become cancerous increases significantly, and a small chronic inflammation can be an important cancer trigger. Low-grade chronic inflammation in diabetes and similar diseases increases the tendency to various organ cancers in the long term, combined with environmental factors (Smith & Missailidis, 2004).

*Table 2. Chronic inflammation increases cancer risk (*Grivennikov et al., 2010).

Subclinical, often undetectable inflammation may be as important in increasing cancer risk (for instance, obesity-induced inflammation).
Various types of immune and inflammatory cells are frequently present within tumors.
Immune cells affect malignant cells through production of cytokines, chemokines, growth factors, prostaglandins, and reactive oxygen and nitrogen species.
Inflammation impacts every single step of tumorigenesis, from initiation through tumor promotion, all the way to metastatic progression.
In developing tumors antitumorigenic and protumorigenic immune and inflammatory mechanisms coexist, but if the tumor is not rejected, the protumorigenic effect dominates.
Signaling pathways that mediate the protumorigenic effects of inflammation are often subject to a feed-forward loop (for example, activation of NF-kB in immune cells induces production of cytokines that activate NF-kB in cancer cells to induce chemokines that attract more inflammatory cells into the tumor).
Certain immune and inflammatory components may be dispensable during one stage of tumorigenesis but absolutely critical in another stage.

Inflammation, obesity, diabetes and atherosclerosis: Type 1 Diabetes is a disease that usually occurs in childhood due to cellular mediated immune events and destruction of pancreatic Beta cells and loss of insulin production (Oever, Raterman, Nurmohamed, & Simsek, 2010).

Insulin resistance and Type II diabetes are not only metabolic components but also hyperuricemia, hyperleptinemia, obesity, microalbuminuria, more importantly endothelial dysfunction and inflammatory processes. There was a direct correlation between insulin resistance and CRP (C-reactive protein) elevation. CRP is an important inflammatory marker produced in the liver in response to IL-6 (Borazan, & Binici, 2010).

Hotamışlıgil and his friends with together Karasik and his friends Showed for the first time proinflammatory cytokines and TNFs that were formed in adipose tissue with potential systemic effects on increased metabolism (Hotamisligil, Shargill, & Spiegelman, 1993; Feinstein, Kanety, Papa, Lunenfeld, & Karasik, 1993).

Leptin, IL-6, resistin, monocyte chemoattractant protein-1 (MCP-1), Plasminogen activator inhibitor-1 (PAI-1), angiotensinogen, visfatin, retinol-binding protein-4, serum amyloid A (SAA) and others as stimulants and inducers of inflammatory events in adipose tissue determined. It has been understood that a number of inflammatory processes in adipose tissue increase the production of new adipose tissue and cause obesity. Increased adipocyte inflammatory in adipose tissue and liver.

MCP-1and play a major role in the migration of other chemokinning macrophages into adipose tissue. These cytokines and chemokines activate the intracellular pathways, leading to the formation of insulin resistance and Type 2 diabetes.

Systemic products of oxidative stress play an important role in the formation of obesity and insulin resistance by increasing adipocyte (Wellen & Hotamisligil, 2005).

Lipids regulate and coordinate inflammation and metabolism. Increased plasma lipid levels are closely related to obesity infection and other inflammatory processes. When obesity and hyperlipidemia include

peripheral insulin resistance, they produce acute phase responses that are proaterogenic in the long term, leading to atherosclerosis. There is a close relationship between macrophages, inflammation processes and metabolism. It is known that macrophages in adipose tissue are increased in obesity too. This helps us to understand the inflammatory changes in adipose tissue. Increased macrophages also play a role in the development of insulin resistance.

An important question is whether there are genetic differences between healthy individuals in terms of inflammation-induced insulin resistance. Genetic linkage and genetic predisposition have been demonstrated by different studies (Wellen & Hotamisligil, 2005).

Insulin resistance and inflammatory changes in the small vessel bed, which we will discuss in the next topic, are the most important causes and determinants of type 2 diabetes progression and end organ damage.

The local, portal and systemic effects of insulin resistance and atherogenesis, as well as diabetes and organ damage to diabetes occur (Shoelson, Lee, & Goldfine, 2006).

Other cell types in adipose tissue may also be involved in inflammatory processes. Multiple capialrization takes place by placing vascular cells in the adipose tissue. Thus, the adipose tissue is rapidly proliferating and increases the storage of nutrients. This increase in angiogenesis probably aggravates tumor development. Diabetes and obesity are among the reasons for the increase in the incidence of cancer.

Leukocytes, which cannot show adhesion on normal endothelium or show low adhesion, are more easily settled into vascular endothelium when high fat content is present.

IL-6 is a major inflammatory cytokine produced in many tissues, mainly activated leukocytes, adipocytes and endtelial cells. CRP is the most important indicator of inflammation among acute phase reactants. IL-6 is known to increase gluconeogenesis and compensate for hyperinsulinemia (Pradhan, Manson, Rifai, Buring, & Ridker, 2001).

Endothelial dysfunction is the most important factor in the pathogenesis of vascular disorders due to diabetes. Endothelium is a monolayer on the inner surface of the vessel, active tissue that forms a physical barrier between the circulating blood and the vessel lumen. In particular, it plays an important role in providing hemostasis and vascular tone. Regulates the balance between coagulation and fibrinolysis. An inflammatory activity in the endothelium also adversely affects cell proliferation and the function of other cell types such as smooth muscle cells, platelets, leukocytes, mesengial cells and macrophages through various chemical mediators. Endothelium is a tissue that is in continuous production and destruction, and disruption of this balance causes microvascular changes and microvascular apoptosis. This event is effective in the formation of early diabetic lesions (Oever, Raterman, Nurmohamed, & Simsek, 2010).

In physiological conditions, there is a balance between vascular expanding factors such as NO prostacyclin (PGI-2) released from the endothelium and contracting factors such as endothelin 1 (ET-1), prostaglandins, angiotensin2 (ANGT-II). Inflammatory processes, together with risk factors such as hypercholestrolemia, dyslipidemia, smoking and diabetes, lead to endothelial dysfunction and pave the way for atherosclerosis. Endothelial dysfunction, leukocytes lead to smooth muscle hypertrophy, vasoconstriction, impaired coagulation, vascular inflammation, thrombosis and lead to vascular complications. The most important mediator synthesized in endothelial cells is NO. The vasodilator plays an important role in preventing the adherence of NO leukocytes to the vascular endothelium, which reduces antithrombotic, anti-proliperative permeability and has antioxidant effects that reduce inflammation. Oxidative stresses are more effective because endothelial dysfunction brings with it the

benefit of low NO. Oxidative stresses result in increased oxidant formation, decreased antioxidant production and inability to repair oxidative damage. Free radicals, on the other hand, activate oxygen atoms containing reactive anions. For example, hydroxyl radical, superoxide, hydrogen peroxide and peroxy nitrate increase in the endothelium. Many cardiovascular risk factors increase oxidative stress (Oever et al.,2010; Badawi, Klip, Haddad, Cole, Bailo, El-Sohemy, & Karmali, 2010).

Apoptosis is an important process in cell death and can be called cell suicide. Apoptosis can be controlled and regulated in healthy cells and is different from tissue necrosis. Necrosis is an uncontrolled condition that usually results from inflammatory processes resulting from tissue inflammation and cell destruction. Apoptosis or programmed cell death is a controlled process that continues throughout life. Provides healthy regeneration of cells. Throughout his adult life, apoptosis causes the destruction of old useless and damaged cells. Apoptosis and cell reproduction are in balance in a healthy organism. Many chronic diseases are caused by the deterioration of this balance. There are several factors that increase the speed of apoptosis in cells. Cytotoxic substances that bind to cell surfaces, also called death receptors, accelerate apoptosis (Oever et al.,2010; Badawi at al., 2010).

Endothelial dysfunction in diabetes; proliferation, low barrier function, adhesion of circulating cells and increased apoptosis sensitivity. NO has been shown to inhibit apoptosis in many cells, particularly endothelial cells. Insulin resistance is one of the most important triggers of endothelial dysfunction. Diabetes accompanying hypertension, obesity, such as the explanation of the presence of diseases mentioned above is the result of endothelial dysfunction and fat tissue problems (Navarro, & Mora, 2005).

Atherosclerosis is now described as an inflammatory disease. High lipid levels, smoking, hypertension, diabetes and possibly high serum homocysteine levels or microorganisms cause inflammatory responses in the endothelium. Increased vascular permeability, increased procoagulant activity, formation of vasoactive amines, various cytokines and growth factors cause persistent and slowly progressive inflammation and produce atheromatous changes (Borazan & Binici, 2010).

Although atherosclerosis is an aging process, it is caused by unhealthy diet and lifestyle and other facilitating factors. Endothelial cells that normally cover the inner surface of the arteries are resistant to adherence of leukocytes, but high saturated fat diet, smoking, hypertension, hyperglycemia, obesity or insulin resistance facilitate the adhesion of leukocytes. This adhesion binds lymphocytes and monocytes. Migration of leukocytes into the endothelium initiates a chronic inflammation, primarily with the release of cytokines and other inflammatory mediators, leading to accelerated atherosclerosis processes. The placement of monocytes in intima causes the migration of lipoproteins and the accumulation of cholesterol esters. Macrophages also secrete different growth factors. This transformation and proliferation leads to the formation of atherosclerotic plaques. The arterial lumen may become clogged due to rupture of the plaques or platelets on the plaques. Acute complications in atherosclerosis are related to this condition. T lymphocytes of the adaptive immune system play an important role in atherogenesis. However, the onset and development of atherosclerosis is determined by fat products (Libby, 2006).

The process of atherosclerosis may cause cardiovascular diseases as well as systemic vascular involvement, cerebral vascular diseases and peripheral vascular diseases. Reducing oxidative stresses or administering antioxidant drugs externally may slow down the process of atherosclerosis. During atherosclerosis, the early accumulation of proatherogenic oxidized LDL in the vascular bed is the earliest process. This cumulation stimulates the migration of vascular endothelium of macrophages. LDL elevation is an important marker in atherogenesis. HDL is another potential biomarker. HDL particles have antioxidant and anti-inflammatory effect.

Neopterin, produced in macrophages and dendritic cells and is an important marker of immune system activation, can be used to determine cardiovascular risk. Increased neopterin concentrations have been

reported as an indicator of chronic immune activation from viral, bacterial, parasitic infections, autoimmune and malignant tumoral diseases. It is known that high neopterin concentrations in patients with atherosclerosis are accompanied by low levels of some antioxidant components and vitamins such as ascorbic acid (Mangge, Becker, Fuchs, & Gostner, 2014).

Many inflammation markers in plasma have been shown to be closely associated with heart disease and atherosclerosis. These include HS-CRP, serum amyloid A levels, IL-4, and intercellular allergy molecule type 1 (sICAM-1) (Ridker, Hennekens, Buring, & Rifai, 2000).

Oxidative stresses and free radicals in cardiac tissue play an important role in the prognosis of the disease. Oxidant and antioxidant balance in mitochondria (redox steate) adjusts energy use by changing the permeability of pores in mitochondria. Increased NO production in mitochondria is associated with early atherosclerosis and hypercholestrolemia. Coronary circulation is easily affected by disruption of this balance and causes myocardial hypoxia (Elahi, Kong, & Matata, 2009).

Factor VIII, a coagulation factor that promotes inflammation rather than hypercoagulability, can be used as cardiac risk markers in elderly patients and D-dimer, a marker of plasmin activation in elderly patients (Tracy, 2003).

Aging and inflamation: Aging is a complex phenomenon that is affected by environmental, stochastic, genetic and many factors throughout life. Human aging is associated with chronic, low-level inflammation, and this phenomenon is called inflamaging. Inflammation is a high predictor of morbidity and mortality in the elderly. CRP and IL levels in elderly patients are associated with morbidity and mortality. Under normal conditions, many toxic substances that arise as a result of immune system activities are easily eliminated and there is difficulty in eliminating residues in old age. Damaged cells and organelle components, oxidative stress-free radicals, metabolites such as extracellular ATP and many other tissue destruction products cannot be adequately eliminated. This means that a low-grade inflammation will persist. Low-level inflammation is a condition that significantly disrupts tissue dynamics during the aging process. This is the main mechanism underlying many chronic diseases such as type II diabetes, Alzheimer's, disease, cardiovascular disease, frailty, sarcopenia, osteoporosis, and cancer. There is overwhelming epidemiological evidence that a state of mild in ammation, revealed by elevated levels of in ammatory biomarkers such as CRP and IL-6 is associated and predictive of many aging phenotypes—for example, changes in body composition, energy production and utilization, metabolic homeostasis, immune senescence, and neuronal health.

Age-related changes to the immune system (immunosenescence) likely contribute to in_ammaging. Adaptive immunity declines with age, whereas innate immunity undergoes more subtle changes that could result in mild hyperactivity. These age-related changes most likely result from both lifelong exposure to pathogens and antigens, as well as intrinsic changes in immune cells and possibly genetic predisposition (Franceschi & Campisi, 2014; Fougère, Boulanger, Nourhashémi, Guyonnet, & Cesari, 2016; Ballou & Kushner, 1997).

Other conditions related to inflammation: It is a known fact that many infections affect and direct the inflammation process. It has been shown that sytomegalovirus (CMV), hepatitis C virus, HIV virus and many other chronic infectious agents provoke inflammation by stimulating chronic inflammatory processes (Tracy, 2003).

Osteoporosis is a condition characterized by low bone mass and increased bone fragility, putting patients at risk of fractures, which are major causes of morbidity substantially in older people. Osteoporosis is currently attributed to various endocrine, metabolic and mechanical factors. However, emerging clinical and molecular evidence suggests that inflammation also exerts significant influence on

bone turnover, inducing osteoporosis. Numerous proinflammatory cytokines have been implicated in the regulation of osteoblasts and osteoclasts, and a shift towards an activated immune profile has been hypothesized as important risk factor. Chronic inflammation and the immune system remodelling characteristic of ageing, as well as of other pathological conditions commonly associated with osteoporosis, may be determinant pathogenetic factors (Di Benedetto & De Martinis, 2005).

Bone loss occurs due to increased bone resorption, decreased bone formation, and often a combination of both. systemic bone loss is seen in inflammatory joint diseases, inflammatory bowel diseases and many inflammatory diseases. Many inflammatory diseases potentially lead to increased catabolism in the bone. In addition, malnutrition, general body weakness and corticosteroids often used in inflammatory diseases cause bone loss (Hardy & Cooper, 2009).

In many rheumatologic and autoimmune connective tissue diseases such as rheumatoid arthritis, SLE, Behçet's Disease systemic sclerosis (SSc), Sjögren's syndrome (SST), mixed connective tissue disease (MCTD), and various vasculitis, chronic inflammation processes play a role in the formation and progression of the disease. Chemotactic stochines play an important role in the development of both primary disease and complications by stimulating other mediators of inflammation.

Angiogenesis, the formation of new blood vessels, is a crucial process in a number of physiological processes, such as reproduction, development and tissue repair, as well as in disease states including, among others, rheumatoid arthritis (RA) and other inflammatory diseases (Bodolay, Koch, Kim Szegedi, & Szekanecz, 2002).

NO plays an important role in the pathogenesis of autoimmune diseases as it plays a role in the aging process and many other inflammatory processes. High amounts of NO, synthesized systemically and intra-articularly, play an important role in inflammatory joint diseases (Stichtenoth & Frölich, 1998).

Inflammatory processes play a role in many lung diseases, especially chronic obstructive pulmonary disease. Chronic obstructive pulmonary disease (COPD) is a major worldwide health problem with an increasing prevalence and incidence is characterized by chronic inflammation in the pulmonary tissue. The disease is associated with a switch from a self-limiting inflammatory response, mainly initiated by smoke inhalation, to a chronic persistent inflammatory response after prolonged interaction with cigarette smoke. The extent of the inflammatory reaction is correlated with the severity of the disease (Oudijk, Lammers, & Koenderman, 2003).

COPD is primarily characterised by the presence of airflow limitation resulting from airways inflammation and remodelling often associated with parenchymal destruction and the development of emphysema. However, in many patients the disease is associated with several systemic manifestations that can effectively result in impaired functional capacity, worsening dyspnoea, reduced health-related quality of life and increased mortality (Barnes & Celli, 2009).

Chronic inflammation is associated with a broad spectrum of neurodegenerative diseases of aging. Included are such disorders as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, the Parkinson-dementia complex of Guam, all of the tauopathies, and age-related macular degeneration (Mcgeer & Mcgeer, 2004).

Acute and chronic systemic inflammation are characterized by the systemic production of the proinflammatory cytokine TNF-α that plays a role in immune to brain communication. Previous preclinical research shows that acute systemic inflammation contributes to an exacerbation of neurodegeneration by activation of primed microglial cells (Holmes et al., 2009).

Ulcerative colitis (UC) and Crohn's disease (CD), the primary constituents of inflammatory bowel disease (IBD), are precipitated by a complex interaction of environmental, genetic, and immunoregulatory factors.

Inflammatory bowel diseases, which are very common in modern societies, are purely a chronic inflammation disease which is closely related to chronic inflammatory processes and even provoked by various other factors (Hanauer, 2006).

INFLAMMATION AND LABORATORY MARKERS

Acute and chronic inflammation, the occurrence, the course, to identify and monitor the damage caused by many different laboratory tests are used. Some of these may be cellular elements and various mediators directly involved in inflammation, and some are various chemical substances caused by tissue damage caused by inflammation. Theoretically, all cells and chemical mediators involved in the inflammation process are measurable and traceable. It is possible to identify and follow them with sensitive laboratory methods. However, many of these tests are not economically expensive, highly sensitive and specific. Laboratory markers used in the follow-up of inflammation processes should be easily identifiable, economically low-cost, highly sensitive to a disease or organ, that is, they should not be affected by other factors than inflammation.

Following years of clinical experience and numerous researches, the most widely used markers of inflammation in clinical practice are as follows.

CRP: CRP was first discovered in 1930 by Tillet and Francis in the serum of patients with S. pneumoniae pneumonia and is called an "C fraction protein akut. The infection was defined as a biomarker in the early periods as it was higher in the advanced infection periods than the baseline (Tillett & Francis, 1930).

CRP is a protein belonging to pentraxin family which is one of calcium dependent ligand binding plasma proteins and it is very low levels in healthy individuals (<1 mg / dl). Serum levels begin to rise 6-8 hours after the onset of inflammation, reach the highest value in about 48 hours and have a half-life of 4-9 hours.

Although CRP is considered as an acute phase reactant, it is used as a follow-up parameter to determine the severity and prognosis of the disease in many chronic diseases, especially cancer, diabetes and cardiovascular diseases.

Procalcitonin (PCT): Procalcitonin is a prohormone of 116 amino acids, the precursor of calcitonin, which is secreted from neuroendocrine cells in the lungs and small intestine, particularly in the C cells of the thyroid gland. Procalcitonin is an important marker of inflammation in the follow-up of acute inflammatory events, especially sepsis and septic shock (Becker, Snider, & Nylen, 2008).

Erythrocyte Sedimentation Rate (ESR): Erythrocyte sedimentation rate is a simple and inexpensive test that is often used to determine inflammatory activity. Blood erythrocytes with red cells that carry oxygen to the tissues through hemoglobin normally do not aggregate within the vessel due to the negative charges they carry in the vessel and collapse due to the fact that their densities are higher than plasma in vitro. However, since many plasma proteins are positively charged, the various proteins and chemical substances associated with inflammation reduce the repulsive forces of erythrocytes and increase aggregation and roll formation, thereby increasing the rate of collapse in plasma. This test, which is very simple, gives an important idea about the severity and progression of many chronic diseases.

In daily practice, total leukocyte count, neutrophil macrophages and monocytes, eosinophils, basophils, lymphocytes, such as the number and morphology of lower leukocyte cell groups are important tests that provide valuable information about inflammation.

Although most of the chemical mediators are used as markers, levels of IL-6, fibrinogen, angiotensin converting enzyme, complement levels, infection agents or antibodies against external and internal allergens are used in diagnosis and follow-up (Pradhan et al., 2001).

Measured values of various enzymes resulting from inflammation in tissues such as aspartate amino transferase, alanine amino transferase, amylase, lipase, creatine kinase take place in clinical practice as inflammatory markers.

CONCLUSION

Although it has examined the main examples here, it is known that many organ diseases, including liver and kidney diseases, are associated with chronic inflammatory processes and are actually a chronic inflammatory disease. Portal cirrhosis, alcoholic and nonalcoholic fatty liver, chronic hepatitis, acute and chronic nephritis, chronic renal failure can be considered in many clinical situations.

Diagnosis and follow-up of diseases in clinical practice is done by measuring inflammatory markers with various laboratory methods. Cellular and chemical mediators involved in chronic inflammatory process are used as markers of inflammation.

Good recognition and early diagnosis of signs and symptoms of ongoing inflammation, often at the subclinical level, will prevent the progression of many diseases and end-organ damage, save the patient in long and strenuous treatments, and provide significant economic savings. Knowledge of inflammation and its consequences is also very important in terms of preventive medicine and it can be prevented by some simple measures before many diseases occur. The most important factors preventing chronic inflammatory processes are; healthy environment, healthy eating and healthy living conditions.

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