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Analysis of cytokines and CD68 in the aorta: new parameters for studying inflammation in type 2 diabetes mellitus

Análise de citocinas e CD68 na aorta: novos parâmetros para estudo da inflamação no diabete melito tipo 2

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ABSTRACT

Introduction: Atherosclerosis is a central element in the pathogenesis of contemporary cardiovascular diseases. Atherosclerosis can be defined as a slowly progressive inflammatory process associated with several causal factors. The pathophysiological process is characterized by a complex inflammatory cascade, initiated by vascular endothelial injury, leading to vascular narrowing and hardening.

Objective: To review the presence of a systemic inflammatory process through the analysis of interleukin-6 and tumor necrosis factor alpha (TNF-a) markers in the inflammatory tissue manifestations in different segments of the aorta.

Method: An integrative review was carried out in the PubMed and Scielo databases. The search used the following keywords: "inflammation, atherosclerosis, type 2 diabetes mellitus, CD68, IL-6, THFa, endothelium" and their English versions. Inclusion criteria included review articles, experimental studies, and preclinical and clinical research, written in Portuguese and English and available in full text. The selected articles were analyzed based on the technologies discussed, future prospects and challenges mentioned, and diseases related to the article's central idea.

Result: 63 articles were evaluated.

Conclusion: Pro-inflammatory cytokines are examples of inflammatory markers with serological expression. Tissue inflammatory markers, such as CD68, the macrophage activation glycoprotein, identified through immunohistochemical analysis, can allow the assessment of the vascular inflammatory process, especially in the context of atherosclerosis.

KEYWORDS: Inflammation. Atherosclerosis. Type 2 diabetes mellitus. CD68. IL-6, THFa. Endothelium.

Central Message

Among the most important risk factors for vascular inflammation, type 2 diabetes mellitus plays a crucial role. This inflammation, through oxidative stress, dyslipidemia, and insulin resistance, is strongly linked to the development and progression of atherosclerosis and, consequently, a significant increase in the risk of associated cardiovascular events

Perspective

Pro-inflammatory cytokines are examples of inflammatory markers with serological expression. Tissue inflammatory markers, such as CD68, macrophage activation glycoprotein - identified through immunohistochemical study - may allow the evaluation of the vascular inflammatory process, especially in the context of atherosclerosis.

RESUMO

Introdução: A patogênese das doenças cardiovasculares contemporâneas tem, na aterosclerose representação central. Elas podem ser definida como processo inflamatório de progressão lenta e associado a vários fatores causais. O processo fisiopatológico é caracterizado por complexa cascata inflamatória, iniciada por lesão do endotélio vascular, levando ao estreitamento e endurecimento vascular.

Objetivo: Revisar a presença de processo inflamatório sistêmico através da análise dos marcadores interleucina-6 e fator de necrose tumoral alfa (TNF-a) na manifestação inflamatória tecidual em diferentes segmentos da artéria aorta.

Método: Revisão integrativa realizada nas bases de dados PubMed e Scielo. A busca utilizou as seguintes palavras-chave: "inflamação. aterosclerose. diabete melito tipo 2, CD68, IL-6,THFa, endotélio" e suas versões ao inglês Os critérios de inclusão compreenderam artigos de revisão, estudos experimentais, pesquisas pré-clínicas e clínicas, escritos em português e inglês e disponíveis em texto completo. Os artigos selecionados foram analisados com base nas tecnologias abordadas, perspectivas futuras e desafios mencionados, doenças referidas relacionados à ideia central do artigo.

Resultado: Foram avaliados 63 artigos.

Conclusão: As citocinas pró-inflamatórias, são exemplos de marcadores inflamatórios com expressão sorológica. Marcadores inflamatórios teciduais, como por exemplo o CD68, glicoproteína de ativação de macrófagos, identificada através de estudo imuno-histoquímico, podem permitir a avaliação do processo inflamatório vascular, especialmente no contexto da aterosclerose.

PALAVRAS-CHAVE: Inflamação. Aterosclerose. Diabete melito tipo 2. CD68. IL-6,THFa. Endotélio.

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INTRODUCTION

The pathogenesis of contemporary cardiovascular diseases has a central representation in atherosclerosis. This disease can be defined as an inflammatory process of slow progression and associated with several causal factors.[1] The pathophysiological process of atherosclerosis is characterized by a complex inflammatory cascade, initiated by injury to the vascular endothelium, leading to vascular narrowing and hardening.[2]

The involvement of the inflammatory and atherosclerotic process occurs predominantly in large and medium-sized arteries, such as the aorta, coronary, carotid and iliac arteries. These arteries are more susceptible to injury due to the turbulent flow and hemodynamic stress that occurs at arterial bifurcations and curvatures.[3] Experimental studies with emphasis on the distribution of atherosclerosis along the aorta artery are still small, and have demonstrated heterogeneous activation of inflammatory pathways in its axis. Small-caliber arteries (resistance arteries) can also be affected, contributing to microvascular complications.[4]

Among the most important risk factors for vascular inflammation, type 2 diabetes mellitus (DM2) plays a crucial role. This inflammation, through oxidative stress, dyslipidemia, and insulin resistance, is strongly linked to the development and progression of atherosclerosis, and consequently a significant increase in the risk of cardiovascular events associated with it. Chronic hyperglycemia, characteristic of DM2, plays an important role in triggering and perpetuating the systemic inflammatory state.[5,6]

Experimental studies in rats, through the use of DM2 models with the use of streptozotocin (STZ), the most widely used substance for this purpose, have been fundamental to understand how chronic hyperglycemia leads to endothelial dysfunction, and subsequent inflammation, accelerating atherosclerosis in diabetics.[7,8] These models have served as substrates for the study of inflammatory, atherosclerotic, and DM2-related processes, aiming at glycemic control, inflammation reduction, and prevention of cardiovascular complications.

The analysis of inflammation, through inflammatory markers, is fundamental for scientific research. These markers allow molecular plasma analyses, and tissue analyses, in specific organs or segments, such as segments of the aortic artery.[9,10] While serological inflammatory markers may indicate a systemic manifestation of inflammation, tissue markers have the function of analyzing the occurrence of localized tissue inflammation.

Pro-inflammatory cytokines are examples of inflammatory markers with serological expression, with interleukin-6, tumor necrosis factor alpha (TNF-a) and interleukin-1 being some of the most relevant for the study of inflammation and atherosclerosis.[11,12]

Tissue inflammatory markers, such as CD68, a macrophage-activating glycoprotein, identified through immunohistochemical study, can allow the evaluation of the vascular inflammatory process, especially in the context of atherosclerosis.

Thus, the objective of this integrative review was to evaluate the presence of systemic inflammatory process through the analysis of interleukin-6 and tumor necrosis factor-alpha (TNF-a) markers in the tissue inflammatory manifestation in different segments of the aortic artery.

METHOD

This is an integrative literature review conducted in the PubMed and Scielo databases. The search used the following keywords: "inflammation. atherosclerosis. type 2 diabetes mellitus, CD68, IL-6, THFa, endothelium" and their Portuguese versions The inclusion criteria included review articles, experimental studies, preclinical and clinical research, written in Portuguese and English and available in full text. The selected articles were analyzed based on the technologies addressed, future perspectives and challenges mentioned, diseases referred to related to the central idea of the article, resulting in 63 articles

DISCUSSION

Cardiovascular diseases

The study called Framingham Score popularized the idea of cardiovascular risk factors, conditions or behaviors that increase the chances of acute myocardial infarction or stroke. The data obtained through this study generated more than 3,700 publications in indexed medical journals, and addressed several risk factors for cardiovascular diseases, such as hypertension, sedentary lifestyle and obesity. Studies have refined the idea of "good" and "bad" cholesterol and, as early as 1960, pointed to smoking as an important risk factor. This work continues to branch out from the heart to the brain, and even to the molecular level, adapting to the demands of science and being a valuable source of information on cardiovascular health.[13-16]

In order to analyze more recent data related to these diseases, the Cardiovascular Statistics – Brazil[17] which included chapters addressing 5 specific conditions: cerebrovascular disease, coronary artery disease, cardiomyopathy and heart failure, and atrial fibrillation. The publication follows the methodology used by the American Heart Association in the annual production of Heart Disease & Stroke Statistics Update[18], which also emphasizes epidemiological and public health data. The Cardiovascular Statistics – Brazil 2023[17] update, included more data on those diseases and brought new chapters on behaviors and risk factors for women.

Through the data mentioned above, it was found that 2 main cardiovascular diseases stand out from the others: 1) coronary artery disease in the first place in the ranking of the most fatal in Brazil, registering in the last 10 years an increase of more than 50% in hospitalizations for acute myocardial infarction, reaching an average of 90 thousand cases per year; and 2) in second place the stroke.[1] WHO data[19] on CVDs describe the repercussions on population morbidity and mortality, reduced life expectancy, and also on the individual's work disability.

The editorial board of The Lancet Neurology, in its 2024 publication, and in partnership with the World

Stroke Organization, emphasized the importance of behavioral attitudes in the prevention of stroke, which could cause up to 10 million deaths by 2050, recommending urgent actions to reverse this scenario.[20]

Inflammation and atherosclerosis

Some pioneering studies on the chronic inflammation of atherosclerosis have defined it as an accumulation of lipids, inflammatory cells, and connective tissue in the arteries. Through several publications, they have described the complex pathophysiological process of atherosclerosis, addressing the mechanisms of atheromatous plaque formation and the progressive narrowing and hardening of arterial walls, through the intricate interaction between the pathogenic components of the disease.[2,4,10,21-23]

The relationship between immunity and atherosclerosis was also addressed by several other authors, who praised the role of innate and adaptive immunity, and the participation of macrophages and lymphocytes in the formation of the atherosclerotic process, in addition to defining atherosclerosis as a response of immunocompetent cells against lesions that produce pro-inflammatory cytokines.[8,21,22]

Studies have described that the onset of the inflammatory process is characterized by endothelial dysfunction, which favors the infiltration and subendothelial retention of low-density lipoproteins (LDL) in the arterial intima layer.[24] These studies also highlight that the chronic inflammatory process begins soon after birth and persists throughout life. During this period, as didactically described by some studies,[8,25] this process is modulated by the spectrum of modifiable and non-modifiable risk factors. The modifiable ones are mainly represented by dyslipidemia, systemic arterial hypertension, smoking, DM2, sedentary lifestyle and obesity, and the non-modifiable ones by advanced age, male gender and genetic predisposition. The presence of these factors influences the establishment and also the evolution of inflammation.

Some authors have described that LDL, when retained in the subendothelial space, undergoes oxidative modifications, through a reduction in the bioavailability of nitric oxide, and significantly stimulates the evolution of the local inflammatory response through the recruitment of circulating monocytes to the arterial intima layer. Other authors have detailed the process in which circulating monocytes migrate to the subendothelial space, differentiate into macrophages and phagocytize the oxidized LDL, transforming them into so-called foamy cells, full of lipids. These authors also addressed that these cells are fundamental components in early atherosclerotic lesions, and detailed that this recruitment of circulating monocytes is facilitated through the expression of cell adhesion molecules in the endothelium, such as VCAM-1 (vascular cell adhesion molecule -1) and ICAM-1 (intercellular adhesion molecule-1).[26-30]

Several studies have reviewed the steps described by other authors in the formation of atherosclerotic plaques, citing the recruitment of monocytes, the differentiation into macrophages that phagocytize the oxidized LDL, and their transformation into foamy cells, key components of the initial atherosclerotic lesions. The participation of pro-inflammatory cytokines, such as TNFa, IL-1B and IL-6, which are released by immune and vascular cells and influence the proliferation of smooth muscle cells, perpetuating the evolution of the inflammatory state, was also highlighted.[26,31]

Researchers have described the progression of atherosclerotic plaque, with the formation of a necrotic nucleus, composed of apoptotic cells, cellular debris, and cholesterol crystals. The development of this plaque may favor neovascularization from the vasa vasorum, which may contribute to the instability of the lesion due to the fragility of these new vessels. The instability of this plaque can progress to rupture, which occurs more frequently in regions of greater vulnerability, such as the edges of the fibrous layer, leading to the exposure of thrombogenic material to the blood flow and triggering the formation of thrombi. These thrombi can partially or totally obstruct the arteries, and trigger acute thrombotic events, such as myocardial infarction or stroke. In addition to plaque rupture, calcification or ulceration may occur, which can also progress to acute thrombotic complications.[31-34]

Studies that evaluated the presence of topographic predisposition to the formation of atheromatous plaques observed a preference for sites of greater turbulence and shear of blood flow, determining a greater probability of vascular lumen obstruction and consequent cardiovascular complications in these sites. They emphasized the involvement of the coronary arteries, with repercussions on coronary artery diseases, and described the importance of the atherosclerotic process in the carotid arteries, responsible for the decrease in cerebral blood supply and increasing the risk of ischemic strokes. The inflammatory and atherosclerotic involvement of the arteries of the lower limbs - responsible for peripheral arterial diseases - is also well detailed in the literature.[31,35-37]

The aorta is described as a vessel frequently affected by atherosclerosis, particularly in its abdominal portion. The importance that chronic inflammation in the aortic wall determines for the occurrence of greater fragility and local dilation, and consequent formation of aortic aneurysms, potentially responsible for fatal hemorrhagic events, is emphasized.[38-40]

Studies have also demonstrated the presence of atherosclerosis without clinical manifestation, that is, without the occurrence of cardiovascular events, known as subclinical atheroclerosis. This phase can be characterized by a wide range of lesions, from early plaques to thin layers of high-risk fibroatheromas, with calcified plaques. In these studies, the gaps that still remain in the identification and treatment of those with subclinical atherosclerosis are emphasized, who, despite being apparently healthy, are at risk of developing atherosclerotic cardiovascular events.[12,41,42]

Inflammation and aortic artery

Recent studies have elucidated the molecular mechanisms by which systemic inflammation affects

the structural and functional integrity of the aorta. They demonstrated that chronic exposure to pro-inflammatory cytokines, such as TNF-a and IL-6, promotes the degradation of the extracellular matrix in the aortic wall, compromising its elasticity and resistance.[43,44]

Understanding the interaction between systemic inflammation and aortic health has important implications for prevention strategies. Recent research has proposed a risk stratification model for aortic diseases based on systemic inflammatory biomarkers, offering a potentially valuable tool for the early identification of individuals at high risk. In the context of therapeutics, anti-inflammatory approaches have been promising in the treatment of aortic diseases. A clinical trial revealed that the use of selective IL-1β inhibitors significantly reduced the progression of abdominal aortic aneurysms in patients with elevated markers of systemic inflammation.[45.46]

Inflammation and diabetes mellitus

T2DM is one of the most prevalent metabolic diseases in the world. It progressively evolves and is characterized by pancreatic β cell dysfunction and peripheral insulin resistance, leading to defects in glucose metabolism and chronic low-grade inflammation. The relationship between inflammation and T2DM involves multiple molecular and cellular mechanisms that contribute to the development and progression of the disease. Chronic inflammation can contribute to the development of T2DM and this, in a bidirectional way, can exacerbate inflammatory processes. The complexity and interconnectedness of these pathophysiological processes has gained increasing interest in the scientific community. There is an interrelationship between DM2 and inflammation, demonstrating molecular mechanisms that connect the altered state of glucose to the activation of inflammatory pathways. Chronic hyperglycemia induces the formation of advanced glycation end products (AGEs), which interact with their receptors (RAGEs), triggering signaling pathways that culminate in the activation of pro-inflammatory transcription factors, such as nuclear factor kappa B (NF-κB). These mechanisms perpetuate the presence of inflammation and promote a vicious cycle of metabolic dysregulation.[5,43,47]

Studies emphasize that in the process in which chronic hyperglycemia, with inadequate previous glycemic controls, induces an inflammatory state, it can lead to the perpetuation of diabetic complications - even after normalization of glycemic levels - due to the persistence of inflammation. This phenomenon, called "metabolic memory", was initially described by "The Diabetes Control and Complications Trial", in addition to describing chronic low-grade inflammation - also called "metainflammation" - as a subclinical state characterized by the persistent production of pro-inflammatory mediators, such as the cytokines interleukin-1β (IL-1β), necrosis factortumor-a (TNF-a) and interleukin-6 (IL-6). The activation of these inflammatory pathways in metabolic tissues, such as the pancreas and adipose tissue, contributes significantly to the dysfunction of pancreatic β cells and insulin resistance, central elements in the pathophysiology of DM2. This subclinical inflammatory state has been implicated in both the pathogenesis and progression of diabetes. In visceral adipose tissue, adipocyte hypertrophy and macrophage infiltration occur, leading to a chronic inflammatory state. This inflammatory microenvironment results in the increased secretion of adipokines and pro-inflammatory cytokines, exacerbating systemic insulin resistance.[48-50]

The role of the immune system in the pathogenesis of insulin resistance and DM2, as well as in atherosclerosis, is well highlighted in the literature. The discovery of the influence of a multiprotein complex called "inflammasome" (NLRP3) on the pathogenesis of these diseases has brought new perspectives to the study of the relationship between innate immunity and metabolism. Inflammasome activation is accomplished by several metabolic "danger signals," such as: free fatty acids, amyloid, advanced glycation products, urate crystals, including saturated fatty acids, and cholesterol crystals. After this activation, the production of potent pro-inflammatory cytokines, such as IL-1β and IL-18, is orchestrated. Chronic inflammasome activation not only contributes to insulin resistance, but is also implicated in pancreatic beta cell dysfunction and death.[51,52]

The role of the gut microbiota in modulating inflammation in metabolic diseases, especially T2DM, and changes in the composition of this microbiota (dysbiosis) have been associated with increased intestinal permeability, allowing the translocation of bacterial endotoxins, such as lipopolysaccharide, into the systemic circulation. This process, called "metabolic endotoxemia" activates Toll-type receptors, crucial components of the innate immune system for the initial detection of microbial invaders, in various tissues, amplifying the inflammatory response and insulin resistance. These studies bring new therapeutic possibilities in the treatment of DM2 and its complications, remodeling the intestinal microbiota through interventions such as medications, probiotics, prebiotics, fecal microbiota transplantation and diets.[53,54]

Experimental model of diabetes

Studies have reported important aspects regarding the induction of diabetes in animal models, which are important substrates for the study of several metabolic alterations, including inflammation. They described the use of toxic chemicals for induction, targeting pancreatic β cells. Aloxan was described as the first substance to be used, whose action occurred through the generation of free radicals, leading to the fragmentation of β cells. However, due to its low stability, short half-life, acidic nature of the solution (precluding intraperitoneal use), and increased renal toxicity, it has become the drug of second choice. Streptozotocin (STZ), an antibiotic derived from Streptomyces achromogene, and considered essentially analogous to nitrosourea, then became the most widely used substance. These authors detailed that the nitrosourea portion of the STZ is responsible for damage to β cells, while its deoxyglucose portion is responsible for the transport of

the native molecule across cell membranes. Since STZ uses glucose transporter 2 to access pancreatic β cells, other organs, which also express this transporter such as kidney, liver, and intestine, are also affected.[55,56]

Other authors have described that STZ can be used to induce type 1 diabetes and DM2. High doses of STZ severely impair insulin secretion, which can lead to the formation of ketone bodies and polyuria, a characteristic condition of uncontrolled type 1 diabetes. On the other hand, low doses of STZ cause slight impairment in insulin secretion, being more similar to the later stages of DM2. This same author addressed that there are no standardized protocols for the preparation and administration of the STZ. It is usually dissolved in saline solution or citrate buffer, adjusting the pH to 4.5, the most suitable for injection.[57]

Recent research has addressed the routes of administration of STZ, which can be subcutaneous, intracardiac or intramuscular; however, it is more commonly administered intraperitoneally or intravenously. Although STZ doses can vary greatly between sex and strain, STZ dosages > 65 mg/kg are considered high, 40-55 mg/kg moderate, and < 35 mg/kg low.[55,56]

One study used a model of T2DM induced by intraperitoneal injection of STZ to evaluate the effect of fish oil supplementation on metabolic, cognitive, and behavioral disorders associated with the disease. In this model, newborn rats received a single intraperitoneal injection of STZ at a dose of 100 mg/kg, solubilized in 10 mM citrate buffer (pH 4.5).[58] The diabetization model, in the neonatal period used, proved to be valid to mimic time-dependent aspects of DM2, without significant changes in the increase in mass, food and water intake, and urine and fecal volume, over time.[59]

Inflammatory markers

Pro-inflammatory cytokines

Pro-inflammatory cytokines participate significantly in the modulation of the body's immune and inflammatory response. These molecular mediators are low molecular weight proteins, secreted by various cells of the immune system, such as macrophages, T lymphocytes, and dendritic cells, as well as by non-immune cells, such as fibroblasts and endothelial cells.[1]

Interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-a) are examples of the most relevant pro-inflammatory cytokines in the study of inflammation. These molecules exert activation of the vascular endothelium, act on leukocyte adhesion and induce the expression of adhesion molecules, thus contributing to the progression of the atherosclerotic inflammatory process.

In addition, current research is exploring the therapeutic potential of modulating these cytokines in several diseases. Specific pro-inflammatory cytokine inhibitors, such as anti-TNF-a monoclonal antibodies, have shown efficacy in the treatment of chronic inflammatory diseases, such as rheumatoid arthritis and Crohn's disease.[60]

The modulation of the inflammatory response, as a strategy to prevent and treat atherosclerosis, was emphasized through a study called CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study). In this research, the inhibition of interleukin-1β, Pro-inflammatory cytokine, through the use of the monoclonal antibody canakinumab, significantly reduced the occurrence of recurrent cardiovascular events in patients with previous coronary disease. This study was a milestone in understanding the role of inflammation in atherosclerosis, and provided new direction for future research and treatments in cardiology.

CD68

The history of immunohistochemistry begins in 1942, when researchers used the direct fluorescence method to identify pneumococci in infected tissue, and, since its initial use, the use of this technique has grown exponentially. Variations of the initial protocol were incorporated into the method, increasing the sophistication and sensitivity of the technique, with the development of kits in laboratories for research and pathological diagnosis.[61]

The principle of immunohistochemistry involves the use of a specific antibody to the peptide studied, whose interaction can be identified by binding to a marker, which can be a fluorescent molecule or enzyme (peroxidase or alkaline phosphatase), whose activity will be used to produce a colored complex in the presence of chromogen. Immunohistochemistry can be performed by direct and indirect methods. In the direct method, which is more commonly used for diagnostic purposes, the labeled antibody reacts directly with the antigen, and is therefore a much faster method. The indirect method involves the formation of a complex at the antigenic site consisting of antibodies labeled directly with the fluorescent molecule or with a chromogen revealed by means of a peroxidase reaction. This method is more sensitive.[62]

The main "target" of immunohistochemistry is membrane proteins, which are called markers, since they identify and distinguish various cell types. In order to define the molecules present on the cell surface, and thus demarcate the cell lineage and type, the technique of cluster of differentiation or CD is used.[63]

CONCLUSION

Pro-inflammatory cytokines are examples of inflammatory markers with serological expression, with interleukin-6, tumor necrosis factor alpha (TNF-a) and interleukin-1 being some of the most relevant for the study of inflammation and atherosclerosis. Tissue inflammatory markers, such as CD68, a macrophage-activating glycoprotein, identified through immunohistochemical study, may also allow the evaluation of the vascular inflammatory process, especially in the context of atherosclerosis.

Authors' contributions

Luciane Bittencourt Carias de Oliveira – Conceptualization, methodology, validation, writing, revision and editing.
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Fernando Issamu Tabushi – Project management, writing – proofreading and editing.
Stephanie Rubianne Silva Carvalhal – Methodology.
Sérgio Ossamu Ioshii – Methodology, validation.
Rodrigo Schuh – Methodology, validation.
Laís Soares Rodrigues – Methodology, validation.
Thomas Horlem – Validation.
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