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REVIEW ARTICLE

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Cardiovascular Diseases and Adipokines: The Role of Visfatin in Coronary Atherosclerosis

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Abstract

Coronary artery disease (CAD) is a leading cause of cardiovascular disease-related mortality globally. Traditional risk indicators for CAD, such as age, gender, hypertension, and cholesterol levels, may not reliably predict the existence and severity of the disease in all individuals. Furthermore, these risk variables may not provide information regarding the long-term prognosis and survival of the patients with stable CAD. The limitations of present screening approaches suggest the need to develop novel prognostic biomarkers for the detection of coronary atherosclerosis.

This review focuses on the significance of adipokines in the pathophysiology of coronary atherosclerosis. The article discusses the role of various cytokines, focusing on visfatin in developing and progressing coronary atheroma and its potential to improve risk stratification, increase diagnostic accuracy, and guide therapy decisions. Clinical evidence supporting visfatin's role as a diagnostic marker for CAD is already available, with elevated levels observed in patients with significant coronary atherosclerosis. However, the paper acknowledges certain limitations, such as the need for more extensive longitudinal studies to validate its potential use in clinical practice to improve early diagnosis and prognosis, ultimately enhancing strategies for preventing cardiovascular disease.**(International Journal of Biomedicine. 2024;14(1):9-14.)**

Keywords: visfatin • coronary artery disease • adipokines • biomarkers • screening

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Abbreviations

ACS, acute coronary syndrome; **CAD**, coronary artery disease; **CVDs**; cardiovascular diseases; **NAMPT**, nicotinamide phosphoribosyltransferase.

Introduction

Coronary artery disease (CAD), sometimes called coronary heart disease or ischemic heart disease, is one of the most diagnosed cardiovascular diseases (CVDs) among the general population. Epidemiological data for 2016 show that it remains a leading cause of mortality worldwide, affecting 154 million people and representing 32.7% of the global burden of CVDs.[1,2] Both current epidemiological data on the disease and prognostic trends for the coming years are cause for concern.[3-5]

A major clinical problem in this context is primary and secondary prevention and effective screening, especially in the subclinical stage of atherosclerosis. This has led to many studies in recent years, with a growing focus on developing and discovering new risk scores and laboratory markers for predicting the clinical course and manifestation of CAD. These markers should be more accessible and cost-effective without losing their predictive value. They should possess high specificity and sensitivity, be easily reproducible, and meet the accepted definition of a biomarker: "a characteristic that is objectively measured and evaluated as an indicator of normal biological or pathogenic processes, or pharmacologic responses to a therapeutic intervention."[6,7]

To date, several biomarkers reflect disturbances in the structure, function, or various regulatory mechanisms at the cellular or tissue level.[8,9] Such laboratory indicators

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include cytokines, small signaling molecules whose primary function is intercellular communication.[10] In 1979, a family of cytokines called "interleukins" was differentiated. They are secreted and expressed primarily by leukocytes, playing a key role in immune processes. Subsequently, with the discovery of leptin, the subgroup of adipokines was formed—molecules produced by adipose tissue that participate in the evolution of metabolic syndrome and numerous CVDs. One of the representatives of the adipokine population is visfatin, a cytokine with a proven role in the pathogenesis of ischemic stroke, insulin resistance, and more.[11-13] Further research is needed to explore its potential prognostic value in CVDs, particularly CAD.[14-16]

Characteristics of Adipokines as a Subgroup of the Cytokine Family

Cytokines are small signaling molecules whose primary function is intercellular communication. The term encompasses a large and diverse family of regulatory molecules produced throughout the body by cells of different embryonic origins. Adipokines are a specific type of cytokines released by adipose cells. In the 1990s, interest in adipose tissue surged following the discovery of leptin. Over the past few decades, various molecules with hormonal activity have been isolated from adipose tissue. Adipocytes produce and release various proinflammatory and anti-inflammatory agents into circulation, including adipokines, cytokines, and chemokines.[11] The functional pleiotropy of adipose tissue is also determined by the distinction between two types, white and brown adipose tissue, which exhibit differences in the execution of various tissue functions.[17-19]

The accumulated data to this moment show that molecules with a proinflammatory nature produced by adipose tissue play an active role in the development of insulin resistance[13] and in increasing the risk of CVDs and obesity.[16] The significance of adipokines is underlined by the fact that adipose tissue is perceived as the largest endocrine "organ" in the human body. Despite the small number of molecules produced by individual adipocytes, the total volume produced by fat cells significantly influences the functions of the entire organism.[20,21] Levels of certain adipokines directly correlate with specific metabolic states and can potentially influence systemic metabolism's homeostasis directly. Dysregulation in adipokine function is implicated in the pathophysiological mechanisms of various diseases such as diabetes, obesity, atherosclerosis, and many others.[22]

The Role of Chronic Inflammation in Pathophysiology of Atherogenesis

Just a few decades ago, atherosclerosis was considered a seemingly straightforward proliferative process, according to which, extending the well-known classic Virchow's triad, endothelial damage leads to platelet aggregation and the release of platelet-derived growth factor, stimulating the proliferation of smooth muscle cells in the vascular intima, thereby forming the core of the atherosclerotic plaque. Subsequently, in addition to vascular smooth muscle cells, active immune cells and mediators were identified within atheromas, suggesting the involvement of proinflammatory mechanisms in the evolution of the disease.[6]

The immune mechanisms for combating inflammation are generally based on two types of immunity: innate and acquired (adaptive). The chronic inflammatory reaction in atherosclerosis involves elements of both types of immune responses. A significant body of evidence supports the role of the monocyte-macrophage system in atherogenesis, particularly the migration of monocytes into the vessel intima, expressing proinflammatory cytokines such as TNF-α, metalloproteinases, IL-1, and others. Activated platelets also release preformed proinflammatory cytokine mediators in response to endothelial damage.[23]

Numerous systemic anti-inflammatory strategies are applied in other diseases, such as corticosteroid therapy, non-steroidal anti-inflammatory drugs, or anti-cytokine agents. However, these treatments come with a range of unwanted side effects, which place them far from the position of ideal candidates for modulating the course of atherogenesis.[24]

Inflammation Markers as Potential Predictors of Coronary Artery Disease

Contemporary literature provides increasing evidence of the relationship between various inflammatory biomarkers and prospective CAD risk, both in asymptomatic individuals and those with already established heart failure or coronary atherosclerosis.[25-28] The clinical benefit of using such biomarkers for risk prediction in practice depends directly on their practicality, ease of measurement, cost, reproducibility of measurements, and the ability to add predictive value to existing biomarkers, such as IL-6, CRP, natriuretic peptides, myeloperoxidase, etc.[29]

Inflammatory molecules appear to have significant predictive value in individuals with known cardiovascular disease. They may be beneficial for identifying seemingly healthy persons without established CAD who cannot be diagnosed using standard risk factors. They may also effectively detect apparently healthy people without documented CAD who may be at a higher risk than established risk factors suggest.[30]

Combining such molecules may enhance CAD clinical diagnosis and prediction. More research on the discovery of new CHD-specific variables is necessary. However, no marker has firmly established itself in clinical practice at this stage. In this context, the focus in recent years has been on discovering a biomarker that meets these criteria and provides an opportunity for effective screening of individuals with an unclear coronary status and undiagnosed CAD. The goal is to initiate statin therapy earlier and prevent the development of CAD and future CAD events.

Visfatin – Adipokine with Many Faces

According to data from numerous publications over the last decade, adipokines are crucial in various aspects of systemic homeostasis.[31] However, these molecules do not share a

common denominator regarding their regulatory functions and the processes they guide. In recent years, adipokine visfatin has emerged among the diverse cytokine family. Accumulating evidence suggests that circulating levels of this molecule, also known as nicotinamide phosphoribosyltransferase (NAMPT), play a role in the pathogenesis of several conditions, including obesity, chronic inflammation, and lipid profile alterations in humans.[32,33]

Visfatin is primarily found in visceral adipose tissue and mimics the action of insulin in lowering plasma glucose levels. It is produced by various lines of immune cells (neutrophils and macrophages) and induces the expression of TNF-α and IL-6 in human monocytes, further supporting the proinflammatory qualities of this adipokine.

Clinical research data show elevated levels of visfatin in patients with type 2 diabetes, metabolic syndrome, and coronary atherosclerosis. There is also evidence that increased concentrations of this molecule raise the risk of pre-eclampsia and worsen the outcome of different types of malignancies.[34,35] Additionally, it is believed that, aside from regulating homeostasis, this cytokine is involved in disrupting atherosclerotic plaques[36] and stimulating angiogenesis.

Structure and Role of Visfatin in the Evolution of Coronary Artery Disease

Data exist regarding the participation of visfatin at various stages of atherogenesis, from endothelial dysfunction to plaque destabilization and rupture. It has been shown to be a proinflammatory mediator with a direct role in the atherosclerotic process, being involved in atherosclerotic plaque disruption, and is found in high concentrations in foam macrophages that constitute unstable plaques.[37]

Visfatin is a protein secreted by visceral adipocytes and activated lymphocytes localized in bone marrow stromal cells. It synergistically promotes B-cell proliferation in combination with IL-7 and stem cell factor (SCF). The adipokine, formerly known as Pre-B-cell colony-enhancing factor (PBEF), is also identified in an intracellular form and plays a key role in nicotinamide adenine dinucleotide (NAD) synthesis. There are two forms of visfatin/NAMPT in mammals: intracellular and extracellular (iNAMPT and eNAMPT). The intracellular form is primarily responsible for NAD+ production, while eNAMPT is associated mainly with cytokine function and an insulin-like effect in addition to its regulatory role in NAD+ biosynthesis.

To date, the importance of inflammation and the role of leukocytes at various stages of the atherogenic process has been recognized in the literature. Different types of macrophages express various effects regarding the appearance, development, and maintenance or, conversely, the remission, of inflammation. Both pro- and anti-inflammatory macrophages are present in atherosclerotic plaques, and the balance between these cellular fractions determines the fate of atheromas.[38] Macrophage polarization represents a process by which individual macrophages acquire various new functional capabilities in response to signals from their microenvironment. Polarization is regulated by multiple factors in atherosclerosis, and while numerous studies highlight its significance in atherogenesis, the regulation of the process itself remains unclear.[39,40]

In this context, visfatin has been found to be expressed in lipid-laden macrophages in the heart of the atherosclerotic plaque and may regulate lipid accumulation and the inflammatory state of these foam cells. Moreover, abnormal lipid metabolism, in combination with chronic inflammation, are key elements in atherogenesis, and this adipokine may serve as the link between these two pathological processes. Elevated concentrations of visfatin in peripheral blood are an independent factor contributing to the evolution of stable CAD into acute coronary syndrome (ACS) and increasing the risk of ischemic stroke.[41] Supporting this assertion, Zhang et al.[42] studied the levels of NAMPT in patients with confirmed ACS and a control group, demonstrating increased marker concentrations in the patient group compared to the controls.

NAMPT is a rate-limiting enzyme in NAD+ production, a substrate for the protein Sirtuin 1 (SIRT1), also known as the NAD-dependent deacetylase Sirtuin-1. This enzyme, mainly located in the cellular nucleus, is involved in the deacetylation of numerous transcription factors, thus playing a role in cellular regulation, stress response, and cellular longevity. The study results indicate an upregulation in the expression of the NAMPT/NAD+/SIRT1 signaling pathway in peripheral blood in subjects with ACS, suggesting the critical role of NAMPT in the evolution of atherosclerosis. In this context, the increased expression of eNAMPT in ACS patients likely plays a protective role precisely by regulating this signaling pathway.

Visfatin in the Diagnosis of Coronary Atherosclerosis

Several clinical studies conducted so far have reported significant results regarding the diagnostic role of visfatin in patients with CAD, from those with stable asymptomatic coronary atherosclerosis to subjects with confirmed ACS.

Kadoglou and colleagues [43] compared the serum levels of NAMPT in a cohort with established stable CAD and a control group. They found that marker concentration was significantly higher in patients with coronary atherosclerosis than in healthy individuals. However, this study was cross-sectional and not randomized, and the absence of coronary atherosclerosis in the healthy group was based on clinical data and non-invasive imaging methods, making it impossible to exclude angiographically pronounced coronary atherosclerosis.

Lu et al.[44] investigated the dynamic changes in adipokine levels in patients with ST-segment elevation myocardial infarction (STEMI), confirming the hypothesis that serum visfatin is significantly elevated in the setting of ACS, compared to patients with angina during physical exertion and healthy controls. Furthermore, the concentrations of this marker peaked approximately 24 hours after percutaneous coronary intervention (PCI) and declined to levels like those in the control group within the first week after revascularization. The authors also observed a correlation between baseline

serum levels of NAMPT and the peak levels of troponin-I, the peak levels of creatine kinase-MB fraction, total leukocyte count, and B-type natriuretic peptide. Limitations of this study were the small cohort and the short-term follow-up of the subjects, which doesn't allow dynamic tracking of the changes in visfatin levels over longer periods of time.

Other studies have also shown elevated visfatin levels in patients with in-stent restenosis following PCI[45] and those with symptomatic carotid plaques, where the biomarker is detected in the highest concentrations, particularly in lipid-laden macrophages.[36]

All this suggests that adipokines should be treated as immunomodulators, primarily localized in foam cells within unstable atherosclerotic plaques, playing a crucial role in their destabilization.

Limitations and Future Potential in the Application of Visfatin as a Biomarker for Coronary Atherosclerosis

Considering the aforementioned scientific studies, a question of particular interest arises: can circulating visfatin mark the progression of CAD and even predict its progression, potentially forecasting future ACS? Current understanding regarding this adipocytokine suggests it will shortly have potential use as part of routine laboratory indicators. However, the clinical studies discussed here contain certain drawbacks and limitations in their design or the hypotheses they investigate.

To date, no studies are tracking the marker's levels dynamically over longer periods, especially in patients for whom revascularization has not been performed for one reason or another. In most cases, subjects have been followed during their hospitalization but not in the months thereafter to determine potential fluctuations or dependencies of the adipokine on other factors. This limitation necessitates the conduct of larger, longitudinal studies.

In this context, no publications establish how visfatin concentrations react to statin or antidiabetic therapy, given the cytokine's role in the pathophysiology of both CAD and diabetes. Furthermore, the cohorts in most clinical trials are too diverse in their characteristics. The connection between insulin resistance, diabetes, obesity, and elevated levels of circulating visfatin is well known. Still, at this stage, individuals with these comorbidities have not been excluded from the study designs, compromising the "purity" of their results.

Another limiting factor in studying this adipokine is its persistently high cost of tests. It is a significant drawback from an economic standpoint and would hinder its widespread use as a potential screening method for subclinical coronary atherosclerosis, especially in regions with resource shortages for primary cardiovascular disease prevention.

Conclusion and Outlook

At the foundation of contemporary understanding of the evolution of the atherosclerotic process and plaque disruption lies a systemic inflammatory process, subject to constant regulation by numerous cytokines, one of which is the adipokine visfatin. Visfatin is found in the composition of coronary atherosclerotic plaques and has been discovered circulating in higher concentrations in the setting of acute coronary syndrome.

This molecule holds promising potential as a marker for CAD, especially in individuals with an unclear coronary status and subclinical coronary atherosclerosis. However, additional studies in this area are necessary. Such screening could significantly enhance the prevention of future cardiovascular events by initiating statin therapy and aspirin intake earlier, thus altering the long-term prognosis for these patients.

Competing Interests

The authors declare that they have no competing interests.

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