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Vitronectin and Fetuin-A: Newfangled Glycoproteins in Periodontits and Coronary Artery Diseases: A Narrative Review

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Abstract

Periodontitis, an intricate inflammatory condition impacting oral support structures, is increasingly recognized as a potential contributor to systemic ailments, notably cardiovascular diseases. Its pathophysiology involves the release of inflammatory molecules like cytokines and chemokines, exacerbating conditions like atherosclerosis. Within this complex web of inflammation, glycoproteins like vitronectin and fetuin-A have emerged as pivotal players, with vitronectin's multifunctional roles in cellular processes and fetuin-A's influence on metabolic pathways. Understanding their involvement in periodontitis and cardiovascular disorders offers promise in leveraging them as diagnostic biomarkers, potentially enhancing disease management and prevention.

Keywords: *Periodontitis, Vitronectin, fetuin-A, glycoproteins, cardiovascular diseases*

1. Introduction

Periodontitis is a multifactorial inflammatory condition that impacts the soft and hard tissues that support the teeth [1]. The pathophysiology of periodontitis involves the production of specific cytokines and chemokines, leading to the activation of host-derived proteinases. These proteinases play a crucial role at different stages of the disease as they are released over defined time periods [2].

Many systemic disorders, such as cardiovascular diseases, are thought to be mostly caused by inflammation [3]. Chronic periodontitis initiates a systemic inflammatory response that exacerbates cardiovascular disease. These two common pathologies, periodontitis and cardiovascular disorders, can mutually intensify their adverse effects on each other's pathophysiology [4]. Since its inflammatory nature has been well understood, atherosclerosis can affect the development and spread of other inflammatory diseases including periodontitis.The acute-phase response is one of the primary defence mechanisms to restore equilibrium and eliminate the toxin. Acute-phase proteins are primarily glycoproteins that exhibit a rapid increase in their serum concentration during the initial phases of an infection. This increase can be substantial, often reaching up to 100-fold higher levels, and it typically remains elevated throughout the course of the infection [5]. Salivary biomarkers are utilized for diagnosing and predicting both periodontal and systemic diseases. Recently, novel glycoproteins like

vitronectin and fetuin-A have been investigated for their role in periodontal and systemic inflammatory conditions such as cardiovascular diseases.

Vitronectin also known as serum-spreading factor or S-protein is one such biomarker found in the granules of blood platelets, extracellular matrix, and plasma. It is a member of the family of adhesive glycoproteins, which play a variety of roles in the body. These roles include complement activation, blood clotting, binding to proteoglycans, and matrix modification. Vitronectin regulates cell differentiation, proliferation, migration, and morphogenesis in addition to playing a critical function in securing cells to their matrix. One such cell adhesion molecule (CAM) plays a role in wound healing, where the reduction of inflammation is necessary, despite being essential for cell spreading. In directing the inflammation, it might play a pro-inflammatory role. Human atheromatous plaques contain vitronectin, which suggests that it may play a role in atherosclerosis and restenosis [6].

Fetuin-A [Alpha 2-Heremans Schmid Glycoprotein (AHSG)], is an additional cystatin superfamily member glycoprotein that is primarily produced by hepatic and adipose tissues. Fetuin-A has earned recognition as a versatile plasma agent because of its activity in the body's metabolic processes, insulin resistance, adipogenesis control, and mineralization [7]. It is a negative acute phase protein that is down-regulated by inflammatory mediators. It alters the expression of the atheroprotective adipokine adiponectin and decreases the uptake and storage of free fatty acids in adipocytes. Periodontitis and cardiovascular disorders are particularly interested in its role in preventing ectopic calcification, particularly in arteries, by regulating calcium and bone metabolism. Reduced fetuin-A levels brought on by prolonged periodontitis may encourage calcification and inflammation, which might increase the risk of various cardiovascular consequences [8].

Vitronectin and fetuin-A play a critical role in regulating the connection between cell adhesion and physiological proteolysis, especially in the context of bone metabolism and turnover. They are considered potent inhibitors of systemic calcification [7].

This article explores the potential action of vitronectin and fetuin-A as diagnostic biomarkers in light of their relationship to periodontitis and coronary artery diseases.

2. Materials And Methods

Search strategy

The articles were independently evaluated during the screening procedures in accordance with the eligibility requirements. The articles ranged from 2013 to 2023 were searched in various search engines such as PubMed, Scopus, Science Direct, Research Gate and Web of Science databases. MeSH terms used to find the articles were “Vitronectin,” “Fetuin-A,” “Periodontitis,” “Coronary artery disease,” “Inflammation” and “Glycoproteins.”

Inclusion criteria

The inclusion criteria include the following: studies written in English; studies published in Pub Med, Scopus, Science Direct, Research Gate, and Web of Science; narrative reviews, research articles, and other studies.

Exclusion criteria

Case reports/series, book chapters, articles published prior to the year 2013, and articles that are not relevant to biomarkers in dentistry were excluded from the current literature survey.

Study selection

Eligibility criteria, databases, and search strategies were used to identify relevant studies. Reviewers independently evaluated the study titles and abstracts during the screening procedures, reading, analyzing, and selecting abstracts in accordance with the eligibility requirements. A total of 30 papers were retrieved during the selection process and a thorough screening of full-text articles was performed. 16 were excluded, 11 were found to be out of scope, and 5 were found to have insufficient details. A total of 14 significant articles were generated. The articles underwent crucial findings and judgments in order to construct significant outcomes of vitronectin and Fetuin-A as potential biomarkers in periodontitis and coronary artery diseases. [Figure 1]

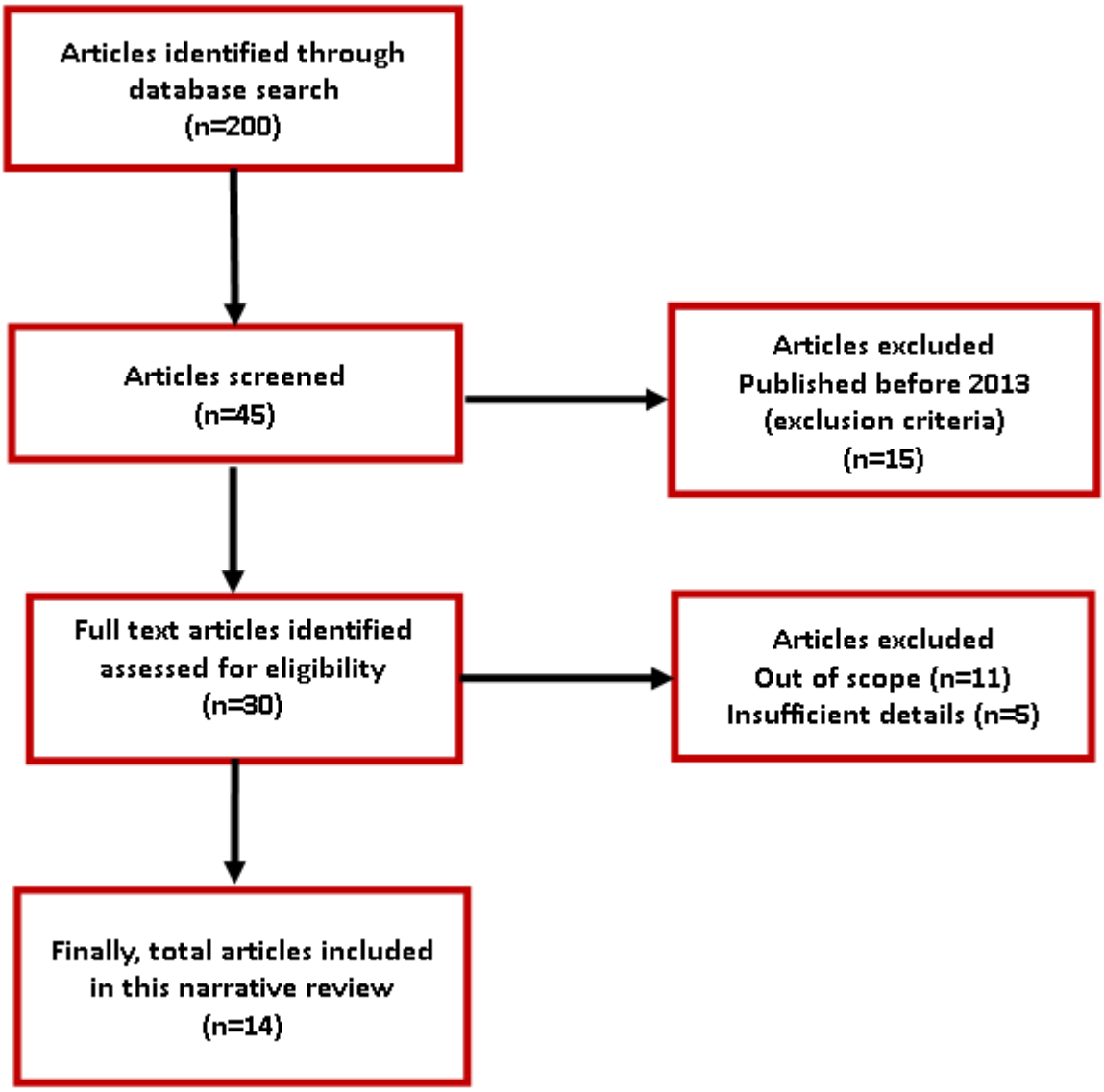

Figure 1: PRISMA flow diagram of articles screening and selection.

3. Results and Discussion

Out of the 200 files found, 28 articles showed the expression of Vitronectin and Fetuin-A in different inflammatory conditions, with 14 of them specifically focusing on the role of Vitronectin and Fetuin-A, particularly in coronary artery diseases. These articles were taken into consideration to explore the synergistic effect of both biomarkers associated with periodontal and cardiovascular studies. [Table 1 and Table 2].

Table 1: Animal studies related to vitronectin and fetuin-A as biomarkers in periodontitis and coronary artery disease.

Sl No.	Title	Reference	Study design	Findings
1	Vitronectin-binding PAI-1 protects against the development of cardiac fibrosis through interaction with fibroblasts.	Zhong J et al., [9]	Animal study (In vitro study)	Plasminogen activator inhibitor-1 (PAI-1) has a dual role in cardiac fibrosis: 1. It promotes cardiac fibrosis through its protease inhibitory pathway. 2. It can protect against cardiac fibrosis by binding to vitronectin.
2	Regulation of fetuin-A gene expression in the neonatal pig liver.	Ramsay TG et al., [10]	Animal study (In vitro study)	Hepatocyte experiments indicate that multiple hormones and cytokines play a role in regulating fetuin-A during the early growth of pigs.
3	Novel Vitronectin Variations and Their Comparative Analysis in Six Porcine Breeds.	Yan W et al., [11]	Animal study (In vitro study)	Porcine vitronectin gene was polymorphic and appears to have different genetic characteristics at vitronectin among six breeds.

4	Fetuin-A is a HIF target that safeguards tissue integrity during hypoxic stress.	Rudloff S et al., [12]	Animal study (In vitro study)	Fetuin-A serves as a multifaceted protective factor in the kidneys by: 1. Countering calcification. 2. Modulating macrophage polarization. 3. Reducing inflammation. 4. Attenuating fibrosis. 5. Preserving kidney function.
5	A vitronectin-derived peptide prevents and restores alveolar bone loss by modulating bone re-modelling and expression of RANKL and IL-17A.	Lee J et al., [13]	Animal study (In vitro study)	The study indicates that vitronectin-derived peptide-16 is a potent therapeutic agent for periodontitis by: 1. Regulating bone remodeling. 2. Modulating immune responses. 3. Controlling inflammatory reactions. 4. Preventing and treating the condition.

Table 2: Human studies related to vitronectin and fetuin - A as biomarkers in periodontitis and coronary artery disease.

Sl No.	Title	Reference	Study design	Findings
1	Vitronectin levels and coronary artery disease severity in acute coronary syndromes.	Aslan S et al., [14]	Human study (Randomized Controlled Trial)	VN levels are increased in patients with ACS and higher levels are associated with CAD severity.
2	Correlation of serum levels of vitronectin, malondialdehyde and Hs-CRP with disease severity in coronary artery disease.	Yaghoubi A et al.,[15[	Human study (Randomized Controlled Trial)	The relationship between VN (Vitronectin), MDA (Malondialdehyde), and hs-CRP (high-sensitivity C-reactive protein): - Suggests their involvement in atherosclerosis. - Indicates their potential as diagnostic and monitoring markers in coronary artery disease (CAD) patients. - Can serve as markers of disease severity in CAD.
3	Patients with dental calculus have increased saliva and gingival crevicular fluid fetuin-A levels but no association with fetuin-A polymorphisms.	Doğan GE et al., [16]	Human study (Randomized Controlled Trial)	- Fetuin-A c.742C > T and c.766C > G polymorphisms weren't linked to dental calculus presence. - Patients with dental calculus had higher levels of GCF and saliva fetuin-A. - This may indicate an adaptive mechanism to inhibit mineral precipitation and prevent calculus formation.
4	Fetuin-A levels are increased in the adipose tissue of diabetic obese humans but not in circulation.	Khadir et al., [17]	Human study (Randomized Controlled Trial)	- Fetuin-A levels increased in subcutaneous adipose tissue (SAT) with diabetes. - No significant increase was observed in circulating fetuin-A. - Physical exercise decreased fetuin-A levels. - Suggests that fetuin-A may function as a hepatokine impacting other tissues, like adipose tissue.
5	Do nonalcoholic fatty liver disease and fetuin-A play different roles in symptomatic coronary artery disease and peripheral arterial disease.	Nascimbeni F et al., [18]	Human study (Randomized Controlled Trial)	- Coronary artery disease (CAD) patients had higher fetuin-A levels than peripheral artery disease (PAD) patients. - NAFLD (non-alcoholic fatty liver disease) was less frequent in CAD patients. - NAFLD was positively associated with fetuin-A, but this association was observed in CAD patients only. - Fetuin-A levels were positively associated with both CAD and NAFLD.
6	Functional role of vitronectin in breast cancer.	Bera A et al., [19]	Human study (Randomized Controlled Trial)	- Serum vitronectin levels may serve as an early marker for breast cancer survival.

				- Research aims to identify cellular signaling factors that influence the expression and concentration of vitronectin.
7	Association of low fetuin-A levels with periodontitis in community-dwelling adults.	Furugen R et al., [20]	Human study (Randomized Controlled Trial)	- Participants with moderate to severe periodontitis had significantly lower fetuin-A levels than those with no or mild periodontitis. - There was a negative correlation between fetuin-A levels and periodontal clinical attachment loss, indicating an association between lower fetuin-A levels and more severe periodontal disease.
8	Serum Vitronectin and Related Molecules in Chronic Kidney Disease.	Hassan EA et al., [21]	Human study (Randomized Controlled Trial)	In chronic kidney disease (CKD): - Serum Vitronectin levels rise in early stages (1-2) but decline significantly as the disease progresses (stage 3). - Serum PAI-1 antigen levels increase significantly with CKD progression.
9	Evaluation of the effect of scaling and root planing on salivary and serum fetuin-A levels in patients with Stages II and III periodontitis.	Nair S et al., [22]	Human study (Randomized Controlled Trial)	- Salivary and serum fetuin-A levels decrease with worsening periodontal inflammation. - Non-surgical periodontal treatment (NSPT) significantly improves fetuin-A levels. - Fetuin-A levels have a significant positive correlation in healthy individuals and a positive but not significant correlation in patients with periodontitis.

Inflammation is a well-orchestrated, programmed signalling defensive reaction that occurs in response to an infection and/ or an injury, initiated to protect the host tissues thereby preventing further progression of the disease, thus leading to initiation of tissue healing. Though this natural response aims to revert the tissue homeostasis, it is considered to be destructive when it turns out to be uncontrolled and hyper-responsive [4]. Hence inflammation is considered as a double-edged sword where it plays both the role of protective and injurious response to the human body depending on its type and duration [3, 4].

The initial inflammation in the periodontal tissues is considered a physiologic defense mechanism against the microbial challenge, which on persistence leads to the development of chronic inflammation where the pre-existing innate immune response pathways are stimulated that will activate the adaptive immune response, resulting in the influx of immune and inflammatory cells such as the neutrophils and macrophages, that release chemical substances such as the cytokines to mediate the process of inflammation [3].

In response to inflammation the higher order of various glycoproteins is expressed in bone and periodontal ligament. Vitronectin and Fetuin-A are two such secreted proteins which play a crucial role in extracellular matrix structure and organization and especially in collagen assembly and hence have shown to play a critical part in inflammatory diseases such as periodontitis and cardiovascular diseases.

Vitronectin is one such multifunctional glycoprotein of 75 kD that binds to various biological ligands. Vitronectin was discovered in 1967 and initially called S-protein, but was later renamed by Hayman EG et al. It is an important component of the human extracellular matrix (ECM), and is synthesized in the liver and secreted into plasma. Vitronectin plays a crucial role in many biological processes including cell migration, adhesion and angiogenesis [8]. The interaction of vitronectin with the urokinase plasminogen activator–urokinase plasminogen activator receptor (uPA–uPAR) complex and integrin receptors is a part of the plasminogen activation system involved in old tissue degradation (pericellular proteolysis), reorganization and wound healing and is a key determinant in homeostatic processes [9].

The multifunctional human glycoprotein vitronectin plays a significant role in cell migration, tissue repair and regulation of membrane attack complex (MAC) formation. It also promotes neutrophil infiltration and, thus, enhances the inflammatory process during infection. There is a higher prevalence of coarse granular deposits of C3d, C9 and vitronectin in subepithelial tissues of patients with periodontitis. Vitronectin is involved in regulation of the terminal pathway of complement activation to

limit the self-reactivity of the innate immune response. This may indicate an increased turnover of complement in gingival tissues [13]. Hence complement activation is down regulated in periodontitis, at the expense of adequate local opsonic function. Vitronectin is also associated with the connective tissue of the marginal gingiva, the periodontal ligament, as well as the endosteum and periosteum with high staining intensity of vitronectin in the periodontal ligament. The concept that PDL responds to the mechanical stress produced by external forces such as orthodontic force induces a remodelling process. Various studies demonstrated that mechanical force applied to human PDL resulted in an increase in the synthesis of laminin, fibronectin and vitronectin in patients undergoing orthodontic therapy and suggested that alterations in the physical environment of cells found in the periodontium can affect biochemical processes, including those that govern the synthesis of structural macromolecules such as extra cellular matrix protein [13, 14].

Vitronectin has several binding domains which interact with a variety of plasma and cell proteins and bind with multiple ligands, including the soluble vitronectin receptor in the endothelial cells. A study demonstrated that anti-vitronectin antibodies inhibit the aggregation of platelets in vitro, indicating that vitronectin plays a role in platelet accumulation at the sites of endothelial injuries. Anti-vitronectin antibody prevents the second wave of platelet aggregation in both platelet-rich plasma and gel-filtered platelets [15]. Endogenous platelet vitronectin may serve to stabilize the platelet-platelet interactions when platelets are activated and platelet granule contents are released [14, 15]. In addition to its role in platelet interactions, vitronectin controls the thrombotic response evoked by vascular injury by regulating thrombin function. Studies have shown that vitronectin accumulated in human atherosclerotic plaques that are dependent on the vitronectin receptor-αVβ3 and αVβ5 play an important role of migration of smooth muscle cells into the intima layer which is a main contributor to intima thickening in atherosclerotic lesions [11, 15].

Fetuin-A, a cysteine protease inhibitor, is part of the cystatin superfamily. It's a serum glycoprotein weighing around 51-67 kDa, initially isolated from bovine fetal serum. The human counterpart is known as α2-Heremans-Schmid glycoprotein (AHSG). It's primarily produced in the liver, with some synthesis in the kidneys, placenta, and tongue. Fetuin-A has two cystatin domains, D1 and D2, followed by a 100-residue C-terminal segment, with a total of 367 amino acids [8].

Fetuin-A has shown the ability to inhibit the release of High Mobility Group Box-1 protein (HMGB-1) by macrophages, particularly in chronic inflammation. Moreover, its high abundance in bone, comprising 25% of non-collagenous proteins, indicates its role in mineralization. An in-vitro study demonstrated the role of fetuin-A in inhibiting the precipitation of hydroxyapatite from solutions supersaturated with calcium and phosphate by the subsequent formation of the fetuin-mineral complex. Hence it is suggested that fetuin inhibits phase separation in serum and modulates apatite formation during mineralization [10].

The protective function of fetuin-A has also been shown to have a cardio protective effect against cardiovascular diseases. First, fetuin-A can inhibit coronary artery calcification (CAC), which is a central characteristic of atherosclerotic cardiovascular disease, by increasing the blood solubility of calcium and phosphorus and preventing spontaneous mineral precipitation in the vasculature [12]. In addition to its role as a systemic calcification inhibitor, fetuin-A serves as a multifaceted protective factor. It counters local calcification, influences macrophage polarization, and reduces inflammation and fibrosis [18]. Fetuin-A has also been shown to have an effect on various pro-inflammatory cytokines in periodontal disease by down-regulation of several pro-inflammatory molecules, including tumor necrosis factor-α, interleukin-6, and interferon-γ. These cytokines are induced by periodontal inflammation and affect periodontitis pathogenesis. By regulating transforming growth factor and bone morphogenic protein, fetuin-A has potent osteogenic and differentiation effects and low serum fetuin-A level is correlated with worse periodontal status and could thus potentially serve as a marker of periodontitis [20].

Fetuin-A can be influenced by matrix metalloproteinases (MMPs), which play important roles in bone and periodontal diseases. Particularly, MMP-7, and to some extent, MMP-3, impact fetuin's ability to inhibit hydroxyapatite formation by cleaving it. This suggests that increased MMP levels in inflammatory diseases may disrupt mineralization regulation by fetuin-A, potentially elevating the risk of conditions like periodontitis [16, 20]. Fetuin appears to be a strong inhibitor of calcium-phosphate precipitation and calcification. Patients with dental calculus showed higher levels of GCF and saliva fetuin-A, possibly because the protein leaked from serum to inhibit calculus. Another reason for elevated fetuin-A in GCF and saliva could be its strong affinity for hydroxyapatite, the primary mineral in dental calculus. This suggests that fetuin-A levels increase in local circulations like GCF and saliva to prevent dental calculus formation [16].

Fetuin-A levels positively affect periodontal tissues following non-surgical periodontal therapy. The study showed that as the severity of periodontal inflammation increased, salivary and serum fetuin-A levels decreased, but non-surgical periodontal treatment significantly improved these levels. Fetuin-A levels had a significant positive correlation in healthy individuals and a positive, though not statistically significant, correlation in patients with periodontitis [22]. Fetuin-A levels serve as a significant and reliable biological marker in the development of periodontal disease.

Biomarkers have gained importance in identifying the risk for various inflammatory diseases. The various enumerated properties of vitronectin and fetuin-A proteins make them an upcoming and significant biomarker for systemic inflammatory conditions including periodontitis and coronary artery diseases. It is also evident that vitronectin plays an important role in periodontal tissue homeostasis during damage and destruction. Fetuin-A protein on the other hand has been a positive indicator for periodontal and cardiovascular diseases and has shown a significant response following periodontal treatment.

Hence, we can say that both vitronectin and fetuin-A has significant role to play in polymicrobial infection such as periodontitis which evokes an immune-inflammatory response in the host. Both these glycoproteins have shown significant improvement following periodontal therapy. Therefore, vitronectin and fetuin-A in saliva may prove to be non-invasive diagnostic biomarkers and a potential therapeutic tool guiding the clinician toward achieving efficient treatment results.

4. Conclusion

Overall, the literature review gives a telescopic understanding of the role of glycoproteins such as Vitronectin and Fetuin-A in periodontitis and cardiovascular diseases. The expression of Vitronectin and Fetuin-A unveils a new paradigm link between periodontal inflammation and cardiovascular events. Hence in near future, these novel glycoproteins can be used as diagnostic biomarkers in periodontal as well as cardiovascular diseases and the concept of early prevention can be taken into consideration for more holistic approach towards holistic health.

Conflict Of Interest

The authors report no conflicts of interest related to this study.

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