INDIAN SOCIETY OF HYPERTENSION

Hypertension Journal

Published: 28th March 2026

REVIEW ARTICLE

Role of Salivary Biomarkers in Hypertensive Patients: An Oral Pathologist's Perspective

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ABSTRACT

Hypertension is a major global health burden associated with cardiovascular morbidity and mortality. Early detection and monitoring remain challenging because the disease often remains asymptomatic until complications develop. Saliva has recently emerged, as a promising non-invasive diagnostic medium reflecting systemic physiological change. This review explores the role of salivary biomarkers—including electrolytes, autonomic markers such as salivary alpha-amylase, inflammatory mediators, oxidative stress indicators, and hormonal markers like cortisol and aldosterone—in the context of hypertension. These biomarkers mirror underlying neurohormonal, inflammatory, and metabolic pathways involved in blood pressure regulation. Integrating salivary diagnostics with oral health evaluation may support early cardiovascular risk assessment and interdisciplinary preventive healthcare strategies.

doi: 10.61081/htnj/26v12i105

INTRODUCTION

Hypertension remains one of the most significant global contributors to cardiovascular morbidity and mortality, predisposing individuals to stroke, ischemic heart disease, heart failure, and chronic kidney disease.[1-6] Despite improvements in diagnostic accessibility, a substantial proportion of patients remain undiagnosed, or inadequately controlled, often because hypertension remains asymptomatic until end-organ damage occurs. Conventional diagnosis and monitoring rely on sphygmomanometry and serum-based investigations. However, the increasing shift toward preventive and predictive medicine has prompted exploration of non-invasive diagnostic alternatives. In this context, saliva has emerged as a biologically rich and clinically valuable diagnostic fluid.

Saliva is a complex biofluid containing electrolytes, enzymes, hormones, antibodies, nucleic acids, and metabolites that reflect both local and systemic physiological states. As emphasized in the base manuscript oral pathologists uniquely perceive the oral cavity not merely as a site of localized disease, but as a window into systemic health. Salivary glands are highly vascularized, allowing systemic biomarkers to enter saliva through passive diffusion, active transport, and ultrafiltration across acinar and ductal cells. This biological exchange underpins the concept of saliva as a "liquid biopsy." Recent narrative reviews have reinforced saliva's expanding diagnostic role in chronic degenerative and cardiovascular diseases.[7,8] In hypertension, alterations in autonomic regulation, endothelial function, inflammatory signaling, and renin–angiotensin–aldosterone system activity are reflected in measurable salivary biochemical shifts, supporting its adjunctive diagnostic potential.

Emerging evidence further highlights the complex interrelationship between systemic cardiovascular disorders and oral health, reinforcing the potential value of saliva-based diagnostics. Chronic inflammatory oral conditions such as periodontitis have been increasingly recognized as contributors to systemic vascular dysfunction through sustained inflammatory signaling and microbial dissemination, thereby linking oral pathology with cardiometabolic disorders including hypertension and stroke. Recent clinical studies evaluating periodontal interventions have demonstrated measurable improvements in inflammatory indices following targeted antimicrobial therapy, emphasizing the systemic implications of oral disease control.[9]

In parallel, contemporary research has underscored how hypertension frequently coexists with metabolic disorders such as diabetes, creating a pathophysiological milieu characterized by endothelial dysfunction, oxidative stress, and neurohormonal activation that predisposes individuals to acute vascular events including stroke and hypertensive crises.[10-13]

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Clinical observations also indicate that patients admitted with various systemic illnesses may develop in-hospital ischemic strokes due to the interaction of multiple vascular and inflammatory risk factors, highlighting the importance of early detection and comprehensive risk stratification.[14]

Collectively, these insights strengthen the rationale for exploring easily accessible biological matrices such as saliva, which may capture early biochemical signals of systemic inflammation, vascular stress, and metabolic dysregulation. Incorporating salivary biomarkers into cardiovascular risk assessment could therefore offer a non-invasive adjunct for identifying individuals at risk of hypertensive complications before overt clinical manifestations occur.

Salivary Electrolytes and Autonomic Markers in Hypertension

The pathophysiology of hypertension is intimately linked to sodium balance, renal handling of electrolytes, and neurohormonal activation. Early foundational in this field demonstrated that the salivary sodium–potassium ratio correlates with plasma renin activity in hypertensive individuals, suggesting that salivary electrolytes mirror systemic hemodynamic regulation.[15] Elevated salivary sodium and chloride concentrations have been reported in hypertensive patients, reflecting systemic sodium retention and altered ductal reabsorption mechanisms. Conversely, reduced salivary potassium levels may be observed in patients receiving diuretics or in conditions such as primary hyperaldosteronism.

Long-term antihypertensive therapy itself influences salivary composition. Significant alterations in calcium, bicarbonate, and phosphate ion concentrations among individuals receiving chronic antihypertensive medication, highlighten therapy-related biochemical modulation.[16] Such electrolyte disturbances may influence oral ecological balance and contribute to enamel demineralization or mucosal sensitivity.

Beyond electrolytes, salivary alpha-amylase (sAA) has gained recognition as a surrogate marker of sympathetic nervous system activation. Essential hypertension is frequently associated with increased sympatho-adreno-medullary (SAM) axis activity. sAA levels correlate with catecholamine release and acute stress responses.[17] Chronic sympathetic overactivity, a hallmark of early hypertensive dysregulation, may therefore manifest as persistently elevated salivary alpha-amylase concentrations. This non-invasive marker offers practical advantages over plasma catecholamine measurements, which are susceptible to venipuncture-induced stress artifacts.

Salivary flow rate and pH are also altered in hypertensive individuals. Significantly reduced salivary flow rates and altered salivary pH among elderly hypertensive patients, were associated with compromised oral health status.[18] Reduced salivary secretion may result from autonomic imbalance or medication effects and predisposes patients to xerostomia, dental caries, candidiasis, and impaired mucosal defense. These findings underscore the interplay between cardiovascular regulation and oral gland physiology.

Salivary electrolyte indices (notably Na+/K+) and autonomic proteins (e.g., salivary alphaamylase and chromogranin A) may offer a noninvasive signal of RAAS–mineralocorticoid activity and autonomic imbalance relevant to hypertension, but only under rigorous control of medications and sampling conditions-.[19-21] Aldosterone shifts extrarenal epithelial electrolyte transport so that salivary Na+ falls and salivary K+ rises, consistent with mineralocorticoid receptor–dependent ductal Na+ reabsorption/K+ secretion in salivary tissue. In vitro evidence supports a direct, steroidresponsive pathway: in a rat submandibular epithelial cell line, hydrocortisone and aldosterone increased ENaC expression and -amiloridesensitive Na^+ transport, providing a mechanistic bridge from RAAS hormones to salivary Na^+ handling-.[22] However, ductal modification is strongly flow and -stimulationdependent, so concentration-based metrics (including Na^+ /K^+) must be interpreted alongside flow rate (or analyte output per time) and clearly defined unstimulated versus stimulated collection-.[23,24] Antihypertensive drugs can confound salivary electrolytes both systemically (via. volume/electrolyte effects) and locally (via. neural or cellular effects on secretion): in a randomized crossover study, therapeutic furosemide or bendroflumethiazide produced modest changes in flow overall but reduced electrolyte output (especially from submandibular–sublingual secretion) and increased xerostomia tendencies.[25] Betablockade can alter the salivary protein matrix and amylase activity and is accompanied by measurable changes in ionic composition, implying that autonomic receptor antagonism can shift biomarker baselines even when blood pressure is controlled-.[26] Calcium channel blockers may reduce resting salivation by blocking Ca^{2+} entry mechanisms important for basal fluid secretion, a plausible mechanism for dry- mouth complaints and secondary concentration artifacts-.[27] For ACE inhibitors and ARBs, evidence remains limited and inconsistent; a PRISMA guided systematic review found too few, heterogeneous studies to attribute xerostomia/hyposalivation or salivary flow changes confidently to any specific antihypertensive class, underscoring the need for better-controlled trials-.[21] Autonomic regulation itself shapes saliva quantity and composition: parasympathetic cholinergic drive evokes high volume- watery secretion, while sympathetic noradrenergic drive preferentially promotes protein exocytosis, with synergistic crosstalk between intracellular Ca^{2+} -and cAMP pathways.

These mechanisms motivate autonomic biomarkers as cardiovascular adjuncts; in older adults, diurnal salivary alphaamylase patterns differed by blood pressure status and antihypertensive drug use, supporting sAA as a noninvasive- index of autonomic dysregulation in hypertension research, and chromogranin A–like immunoreactivity is stored in submandibular gland cells and is secreted into saliva in response to noradrenaline and acetylcholine, supporting salivary CgA as a quantitative index of glandular sympathetic activity.[28] Methodological priorities include fixed collection times, standardized stimulation/collection devices, assays sensitive in the low-concentration range, and structured capture of confounders (oral inflammation, diet, smoking/caffeine, hydration, and co-medications), because each can shift flow and concentration-based readouts.

Overall, salivary Na^+/ K^+ and autonomic markers are best viewed today as research grade- phenotype adjuncts rather than standalone diagnostics, and key gaps are longitudinal, medication- stratified cohorts linking standardized salivary panels to ambulatory blood pressure and cardiovascular outcomes.-

Inflammatory, Oxidative, and Hormonal Biomarkers

Hypertension is increasingly recognized as a chronic low-grade inflammatory and oxidative stress–mediated disorder. Elevated inflammatory mediators contribute to endothelial dysfunction,

vascular stiffness, and atherogenesis. Salivary C-reactive protein (CRP) has been shown to correlate with serum CRP levels and may serve as a surrogate marker of systemic inflammatory burden.[7] Elevated salivary CRP levels in hypertensive individuals reflect the systemic inflammatory milieu that underpins vascular pathology.

Nitric oxide (NO), a potent vasodilator synthesized by endothelial nitric oxide synthase, plays a central role in vascular tone regulation. Impaired NO bioavailability is a hallmark of endothelial dysfunction in hypertension. Salivary nitrate and nitrite concentrations provide indirect insight into systemic NO metabolism. Altered salivary nitrate levels in hypertensive patients, with correlations to lipid profile abnormalities, reinforce the interconnected nature of vascular and metabolic dysregulation.[29]

Oxidative stress markers, including salivary uric acid, further contribute to the biomarker landscape. Hyperuricemia has been implicated in the pathogenesis of hypertension through mechanisms involving renal microvascular injury and reactive oxygen species generation. Elevated salivary uric acid levels have been observed in hypertensive cohorts, correlating with systolic and diastolic blood pressure values.[8] These findings support saliva's potential role in reflecting systemic oxidative burden.

Hormonal biomarkers offer additional diagnostic promise. Salivary cortisol measurement provides a reliable assessment of free, biologically active cortisol and reflects hypothalamic–pituitary–adrenal (HPA) axis activity. Chronic psychosocial stress and HPA axis dysregulation are recognized contributors to sustained blood pressure elevation. Studies have demonstrated associations between elevated salivary cortisol and hypertension severity, particularly in stress-reactive individuals.[30] Unlike serum cortisol assays, salivary sampling avoids stress-induced fluctuations caused by needle phobia or procedural anxiety.

The renin–angiotensin–aldosterone system (RAAS) remains central to blood pressure regulation. Salivary aldosterone levels have shown significant correlation with serum concentrations and may serve as a screening tool for primary aldosteronism.[31] The feasibility of non-invasive aldosterone measurement presents value in outpatient and community screening settings.

Clinical Implications and the Expanding Role of the Oral Pathologist

The clinical relevance of salivary biomarkers extends beyond molecular quantification to tangible oral manifestations of hypertension and its treatment. Xerostomia is commonly reported among patients receiving diuretics, beta-blockers, and ACE inhibitors, leading to increased susceptibility to dental caries and opportunistic infections. Gingival overgrowth is notably associated with calcium channel blockers such as nifedipine, while lichenoid reactions may occur secondary to antihypertensive medications. Distinguishing medication-induced changes from primary mucosal pathology requires careful histopathological evaluation, reinforcing the importance of oral pathologists in systemic disease management.

Emerging evidence also highlights the bidirectional relationship between periodontal inflammation and blood pressure regulation. Chronic periodontal inflammation may amplify systemic cytokine release, contributing to endothelial dysfunction and vascular stiffness. Thus, oral health evaluation and salivary biomarker assessment may together enhance cardiovascular risk stratification.

Despite its promise, salivary diagnostics faces challenges including variability due to circadian rhythm, hydration status, and local oral inflammatory conditions. Many biomarkers exist in lower concentrations in saliva than in serum, necessitating high-sensitivity assays. Standardized collection protocols and validated reference ranges remain areas requiring further development.[8] Nevertheless, advances in microfluidics, biosensor technology, and point-of-care platforms are rapidly addressing these limitations.

From an oral pathologist's perspective, the integration of salivary diagnostics into routine dental and oral health evaluations represents a paradigm shift from reactive treatment toward predictive and preventive healthcare. In regions with limited access to laboratory facilities, non-invasive salivary screening could enhance early detection of hypertension and improve referral pathways. As interdisciplinary collaboration between dentistry and internal medicine strengthens, saliva may emerge as a cornerstone of integrated cardiovascular surveillance.

DISCUSSION

Hypertension remains one of the most prevalent and consequential non-communicable diseases worldwide and continues to be a leading contributor to cardiovascular morbidity and mortality. Persistent elevation of blood pressure predisposes individuals to myocardial infarction, stroke, heart failure, and chronic kidney disease. Although hypertension is frequently asymptomatic during its early course, the underlying pathophysiological processes involve complex interactions among vascular dysfunction, metabolic abnormalities, neurohormonal activation, and chronic low-grade inflammation. Contemporary research increasingly emphasizes the need for improved strategies for early detection and risk assessment, particularly through the identification of biological markers that reflect systemic vascular stress before the development of overt complications.

The clinical significance of hypertension becomes particularly evident in acute cardiovascular events. Patients presenting to emergency departments with chest pain require rapid triage and diagnostic evaluation to identify potentially life-threatening myocardial infarction. Studies assessing patients using structured triage tools such as the Emergency Severity Index highlight the importance of systematic clinical assessment in prioritizing care and improving outcomes in emergency settings.[32,33]

Hypertension frequently coexists with other systemic risk factors such as diabetes, smoking, and metabolic disorders, all of which contribute to the severity and prognosis of acute coronary syndromes. In addition, the presence of infectious comorbidities such as hepatitis B, hepatitis C, and HIV among patients presenting with myocardial infarction further illustrates the complex interplay between cardiovascular disease and systemic inflammatory states.[34] These interactions reinforce the concept that cardiovascular pathology is often influenced by broader biological and metabolic processes rather than isolated hemodynamic abnormalities.

In this context, the search for reliable biomarkers capable of reflecting cardiovascular risk has gained considerable attention.

Metabolic indicators such as uric acid and osteocalcin provide insight into the biochemical pathways linking metabolic dysfunction and hypertension. Elevated uric acid levels have been associated with obesity, insulin resistance, and visceral adiposity, all of which contribute to endothelial dysfunction and vascular stiffness.[35]

Similarly, osteocalcin, a hormone secreted by osteoblasts, has emerged as an important regulator of glucose metabolism and insulin sensitivity. Reduced osteocalcin levels in individuals with type 2 diabetes have been associated with impaired glycemic control and increased insulin resistance, further emphasizing the interconnected nature of metabolic and cardiovascular disease.[36] While, these biomarkers are traditionally measured in blood, increasing interest has been directed toward alternative biological fluids that may provide comparable diagnostic information in a less invasive manner.

Saliva has recently emerged as a promising diagnostic medium capable of reflecting systemic physiological and pathological changes. Salivary glands are highly vascularized, allowing various circulating molecules—including electrolytes, hormones, inflammatory mediators, and metabolic by-products—to diffuse into saliva. As a result, salivary biomarkers may provide a non-invasive window into cardiovascular and metabolic health. In hypertension, alterations in salivary electrolyte concentrations, oxidative stress markers, inflammatory proteins, and neurohormonal indicators may mirror the systemic processes that drive elevated blood pressure. The use of saliva for biomarker analysis offers several practical advantages, including ease of collection, minimal patient discomfort, and suitability for repeated measurements or large-scale population screening. Such characteristics make salivary diagnostics particularly attractive for preventive cardiovascular medicine.

In addition to biomarker research, complementary strategies aimed at improving blood pressure control are also being explored. Nutritional and plant-derived interventions have received increasing attention due to their potential to influence vascular function, oxidative stress, and inflammatory pathways. Himalayan raspberries, for example, contain polyphenols and flavonoids that enhance nitric oxide production, promote vasodilation, and reduce systemic vascular resistance, thereby contributing to improved blood pressure control.[37]

Similarly, celery seed extract has demonstrated antihypertensive potential through mechanisms including antioxidant activity, calcium channel modulation, and vascular relaxation.[38] Such interventions may complement conventional pharmacological therapy by targeting multiple physiological pathways involved in blood pressure regulation.

Hypertension also represents one of the most important modifiable risk factors for stroke, a leading cause of long-term disability worldwide. Advances in artificial intelligence are increasingly being applied to stroke rehabilitation, allowing clinicians to develop personalized rehabilitation programs, monitor patient progress through wearable sensors, and expand access to therapy through tele-rehabilitation platforms.[39] These innovations illustrate how technological advancements can improve recovery outcomes and quality of life for individuals affected by hypertension-related cerebrovascular events.

Overall, current evidence underscores that hypertension is a multifaceted systemic disorder influenced by metabolic, inflammatory, and neurohormonal processes. Emerging research on salivary biomarkers offers a promising avenue for non-invasive cardiovascular risk assessment, potentially enabling earlier detection of hypertensive pathology and improved monitoring of disease progression. When integrated with advances in metabolic biomarker research, nutritional therapeutics, and digital health technologies, salivary diagnostics may contribute to a more comprehensive and preventive approach to cardiovascular care.

CONCLUSION

Salivary biomarkers represent a compelling adjunct in the assessment and monitoring of hypertension. Electrolytes, autonomic indicators such as salivary alpha-amylase, inflammatory mediators, oxidative stress markers, and hormonal analytes including cortisol and aldosterone collectively reflect the multifactorial pathophysiology of elevated blood pressure. While salivary diagnostics cannot replace traditional blood pressure measurement and serum investigations, it offers substantial advantages in accessibility, patient comfort, and feasibility for large-scale screening. The oral cavity serves not only as a site of local pathology, but as a mirror of systemic vascular health. Harnessing salivary diagnostics may enable earlier detection, improved risk stratification, and more comprehensive cardiovascular care, positioning oral pathologists at the forefront of interdisciplinary preventive medicine.

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How to cite this article: Singh M, Sinha N, Jaisal V. Role of Salivary Biomarkers in Hypertensive Patients: An Oral Pathologist's Perspective. Hypertens J. 2026;12(1): 20-24

Source of support: Nil, **Conflicts of interest:** None