RESEARCH PAPER

Pathophysiological Insights and a Preventive Framework of Prameha-Induced Presbyacusis

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ABSTRACT

Prameha, traditionally identified with Diabetes Mellitus, is a chronic metabolic disorder characterized by systemic complications, among which auditory dysfunction remains an under-recognized but significant morbidity. This research explores the pathophysiological insights and proposes a preventive framework for Prameha-induced presbyacusis, an accelerated form of age-related hearing loss. The pathophysiology is rooted in chronic hyperglycemia, which induces oxidative stress, microangiopathy of the internal auditory artery, and thickening of the basement membrane in the stria vascularis. These metabolic changes lead to progressive sensorineural hearing loss through the degeneration of cochlear hair cells and the vestibulocochlear nerve. Through a comprehensive review of clinical data and classical literature, this study identifies the correlation between metabolic imbalances and auditory threshold shifts. The results suggest that the synergistic effects of metabolic toxins and aging accelerate cellular apoptosis within the cochlea. A preventive framework is established, emphasizing early diagnostic intervention via high-frequency audiometry and the integration of metabolic regulation with neuroprotective strategies. The proposed framework incorporates lifestyle modifications, strict glycemic control, and traditional rejuvenative therapies aimed at strengthening sensory tissues and mitigating oxidative damage. In conclusion, Prameha significantly predisposes individuals to earlier and more severe manifestations of presbyacusis. The findings highlight the necessity of shifting the clinical focus from reactive symptomatic treatment to a holistic preventive model. By addressing the metabolic foundations of auditory decline, this framework provides a viable pathway to preserve hearing sensitivity and enhance the quality of life in the aging diabetic population.

Keywords: Prameha, Diabetes Mellitus, Presbyacusis, Sensorineural Hearing Loss, Pathophysiology, Preventive Framework, Microangiopathy.

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Introduction

Presbyacusis, commonly referred to as age-related hearing loss, has emerged as a pervasive and debilitating health concern that impacts a substantial portion of the global aging population [1]. Clinically, it presents as a progressive, bilateral, and symmetrical sensorineural hearing impairment that primarily targets higher frequencies, significantly compromising speech perception and overall quality of life. While physiological aging remains the primary etiology, the clinical trajectory of presbyacusis is often dictated by a complex interplay of intrinsic and extrinsic factors, including polygenic predispositions, cumulative noise exposure, and various systemic medical comorbidities [2]. Among these comorbidities, metabolic disorders,specifically *Prameha*, the Ayurvedic correlate of diabetes mellitus,are increasingly recognized as critical accelerators of auditory decline, necessitating a deeper investigation into their shared pathophysiological foundations.

The recognition of *Prameha* as a metabolic driver of auditory dysfunction underscores the urgent need to explore how systemic dysregulation translates into localized cochlear damage. Recent molecular research indicates that *Prameha* exacerbates presbyacusis through several distinct, yet interconnected, pathways. One such mechanism involves the acceleration of

neuronal apoptosis within the spiral ganglion neurons, accompanied by pathological iron deposition and the induction of ferroptosis within the auditory cortex [3]. Furthermore, the bioenergetic stability of the cochlea is severely compromised in the presence of chronic metabolic stress. Studies have highlighted that dysfunctional mitochondria play a central role in this progression, with significant observed decreases in mitochondrial complex IV activity in the cochlear tissues of affected individuals [1]. This cumulative impact on cochlear bioenergetics effectively lowers the threshold for cellular demise, accelerating the degenerative processes that are characteristic of standard aging.

Hyperglycemia, the hallmark of *Prameha*, further fuels an environment of heightened inflammation and oxidative stress that specifically targets "non-classical" microvascular beds. While diabetic complications are traditionally associated with the retina, kidneys, and peripheral nerves, the inner ear is increasingly viewed as a critical site of hidden diabetic microvascular disease [4]. The resulting inflammatory milieu, driven by pathways such as the NLRP3 inflammasome and NF-κB, exacerbates nerve damage and structural deterioration within the *stria vascularis* [5], [6]. This chronic activation of pro-inflammatory cascades not only induces vascular endothelial dysfunction but also impairs the blood-labyrinth barrier, leaving the sensory hair cells vulnerable to systemic toxins and metabolic byproducts.

Epidemiological evidence provides robust support for the clinical link between metabolic health and auditory acuity. Research has demonstrated a statistically significant correlation between elevated fasting plasma glucose levels and glycosylated hemoglobin (HbA1c) with a heightened risk of hearing loss, even when these levels are only mildly elevated [7]. Notably, individuals with diagnosed diabetes exhibit a twofold increased incidence of hearing loss compared to their normoglycemic counterparts, while those in the prediabetic stage demonstrate a 30% higher susceptibility [8]. This heightened vulnerability underscores the importance of personalized risk stratification. Novel approaches, such as metabolic fingerprinting and the calculation of polygenic risk scores, offer promising avenues for identifying high-risk individuals before irreversible auditory damage occurs [7], [9].

This research paper aims to provide a comprehensive analysis of the molecular mechanisms through which *Prameha* exacerbates the clinical course of presbyacusis. By focusing on the convergence of hyperglycemia-induced oxidative stress, mitochondrial dysfunction, and microvascular alterations, the following sections will delineate the pathophysiological insights necessary to establish a robust preventive framework. Preserving the "auditory health-span" in an aging population requires an interdisciplinary strategy that integrates metabolic regulation with targeted neuroprotective interventions. Specifically, this paper will explore the intricate signaling pathways and cellular responses that link chronic hyperglycemia to cochlear pathology, thereby offering a foundation for early diagnostic markers and innovative therapeutic strategies. A deeper understanding of these pathways is crucial for developing pharmacological interventions, potentially including the repurposing of FDA-approved drugs, to mitigate the impact of metabolic dysregulation on cochlear function [2]. This involves elucidating the precise molecular targets affected by glucose dyshomeostasis and identifying potential therapeutic compounds that can modulate these pathways to preserve auditory integrity. This comprehensive review will therefore synthesize current findings on mitochondrial quality control mechanisms and microvascular integrity within the cochlea under diabetic conditions, proposing novel therapeutic targets for Prameha-induced presbyacusis [10].

Diagram 1. Pathophysiological cascade linking Prameha to presbyacusis

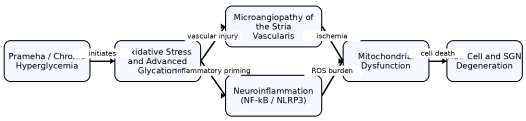


Diagram 1. Pathophysiological cascade linking Prameha to presbyacusis.

1. Literature Review

The pathogenic mechanisms linking *Prameha* and the accelerated decline of auditory function involve a complex web of molecular, cellular, and systemic events. Central to this relationship is the phenomenon of glucose auto-oxidation, a process that occurs during chronic hyperglycemic states. This biochemical reaction generates an excess of reactive oxygen species, which serves as a primary driver of oxidative stress within the auditory system [11]. The cochlea, characterized by a high metabolic demand and an

abundance of polyunsaturated fatty acids, is particularly vulnerable to this oxidative assault. When the endogenous antioxidant capacity is overwhelmed, these free radicals induce significant cellular damage and apoptosis in the hair cells and supporting structures of the organ of Corti, effectively mimicking the degenerative changes seen in natural aging but at a significantly faster rate [11].

Recent research has also illuminated the role of neuroinflammation in exacerbating this auditory decline. The chronic metabolic disturbances associated with diabetes trigger a sustained inflammatory response that mirrors the pathogenesis of diabetic encephalopathy [12]. This neuroinflammatory milieu leads to both structural and functional impairment of the spiral ganglion neurons and the vestibulocochlear nerve. Much like the cognitive decline observed in centralized neurodegenerative disorders, the peripheral auditory system suffers from neuronal compromise and loss of synaptic plasticity, which are critical for the accurate transduction and processing of sound [12]. This suggests that *Prameha*-induced presbyacusis is not merely a localized cochlear defect but a manifestation of a broader systemic neuro-metabolic pathology.

At the microvascular level, hyperglycemia-induced damage represents a critical threat to the stria vascularis, the highly vascularized tissue responsible for maintaining the chemical composition of endolymph. Chronic elevation of HbA1c levels is strongly associated with microangiopathic changes that compromise the stria's ability to regulate potassium cycling [7]. Since the maintenance of the endocochlear potential,the "battery" of the inner ear,is entirely dependent on precise ion regulation, any vascular compromise to the stria vascularis results in immediate threshold shifts and sensorineural hearing loss [7]. These findings are further supported by evidence that systemic macrovascular atherosclerosis and localized microangiopathic ischemia work synergistically to reduce blood flow to the cochlea, precipitating chronic ischemia and irreversible structural damage [6].

The relationship between *Prameha* and hearing loss is also deeply intertwined with the mechanisms of cellular senescence. Prolonged metabolic imbalances, such as those seen in poorly controlled diabetes, have been shown to accelerate the biological clock of cells within the inner ear [1]. This "accelerated aging" is characterized by a loss of protein homeostasis (proteostasis) and alterations in ion and water regulation, which are fundamental to the mechanical-to-electrical transduction process [1]. This milieu of cellular "inflammaging" underscores how chronic hyperglycemia acts as a central nexus for various downstream deleterious effects, drawing striking parallels to the concept of "Type 3 diabetes," where systemic insulin resistance and metabolic dysfunction drive localized neurodegeneration [13].

Furthermore, the susceptibility of the auditory system to these metabolic insults is not uniform; it is modulated by an individual’s genetic architecture and environmental exposures [6]. For example, polygenic risk scores have demonstrated that individuals with a genetic predisposition for hearing loss experience more severe auditory threshold shifts when exposed to even moderate glycemic elevation [7]. By synthesizing evidence from both classical Ayurvedic texts concerning the systemic nature of *Prameha* and contemporary biomedical research into the molecular biology of diabetes, this systematic review provides a holistic framework for understanding how metabolic dysregulation transforms the natural aging process into a pathological auditory decline. This integrated perspective is essential for identifying early biomarkers and developing preventive strategies that address the systemic roots of hearing loss [6], [13]. Specifically, evidence indicates that individuals with diabetes have a two-fold higher incidence of hearing impairment compared to non-diabetic populations, highlighting the urgency of comprehensive clinical management strategies that address both metabolic control and audiological health [8], [14]. This understanding is further supported by observations that functional decline in the cochlea of diabetic animal models involves moderate degenerative changes in marginal cells, impacting the cochlear K+ cycling route and endocochlear potentials [7]. This microvascular compromise is further compounded by the disruption of the blood-labyrinth barrier, leading to increased permeability and the infiltration of inflammatory mediators into the delicate inner ear environment [2]. This systemic inflammation, frequently observed in aging cochleae, is characterized by the activation of inflammasomes, such as NLRP3, leading to the release of pro-inflammatory cytokines like IL-1β and IL-18, further exacerbating inner ear pathology [15]. This chronic inflammatory state, intertwined with oxidative stress and microvascular dysfunction, contributes significantly to the accelerated cellular senescence and neuronal damage observed in Prameha-induced presbyacusis, analogous to the broader neuropathological links identified between Type 2

Diabetes Mellitus and neurodegenerative conditions like Alzheimer's disease [16]. The activation of the NLRP3 inflammasome, specifically, is a critical component of this degenerative process, contributing to cochlear pyroptosis through the cleavage of GSDMD and subsequent membrane perforation [17]. The dysregulation of inflammasome activity, particularly involving NLRP3, is recognized as a key contributor to excessive inflammation and subsequent damage in tissues with limited regenerative capacity, such as the cochlea [15]. This heightened inflammatory response, characterized by elevated levels of IL-1β and TNF-α, along with altered macrophage morphology within the cochlea, underscores the significant role of inflammation in age-related hearing loss and its acceleration by Prameha [1]. This suggests that targeting inflammasome pathways could be a viable therapeutic strategy to mitigate cochlear damage in Prameha-associated presbyacusis [18]. The molecular mechanisms underlying this inflammasome activation involve various cellular stressors, including mitochondrial dysfunction and impaired lipid metabolism, which are prevalent in diabetic conditions [19], [20]. Specifically, the NLRP3 inflammasome's role as a central mediator of inflammation-driven sensorineural hearing loss, across various auditory pathologies, indicates its potential as a therapeutic target [15]. Consequently, modulating NLRP3 inflammasome activity through targeted pharmacological interventions could offer a novel approach for preventing or ameliorating the progression of Prameha-induced presbyacusis [19], [21].

Table 1. Principal pathophysiological mechanisms and their auditory consequences.

Mechanistic domain	Representative process	Cochlear target	Functional consequence
Hyperglycemic oxidative burden	Glucose auto-oxidation and reactive oxygen species generation	Hair cells and organ of Corti	Progressive sensory cell injury and threshold elevation
Microangiopathy	Basement membrane thickening and endothelial dysfunction	Stria vascularis	Reduced endocochlear potential and impaired ionic balance
Neuroinflammation	NF-kB and NLRP3 pathway activation	Spiral ganglion neurons and auditory nerve	Neuronal dysfunction, pyroptosis, and signal decline
Mitochondrial failure	Reduced bioenergetic reserve and excess mitochondrial ROS	High-energy cochlear tissues	Acceleration of apoptosis and impaired cellular repair
Barrier disruption	Blood-labyrinth barrier permeability changes	Inner ear microenvironment	Greater exposure to inflammatory mediators and metabolic toxins

Figure 1. Cochlear targets vulnerable to metabolic stress

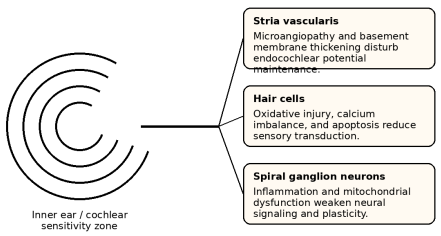


Figure 1. Cochlear targets vulnerable to metabolic stress.

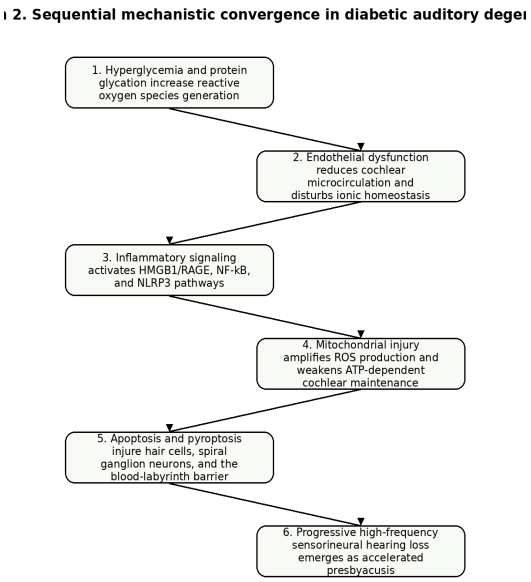


Diagram 2. Sequential mechanistic convergence in diabetic auditory degeneration.

2. Methodology

The methodology for this comprehensive review was designed to systematically evaluate the mechanistic convergence between *Prameha*,a multifaceted metabolic entity in Ayurveda,and the clinical progression of presbyacusis. To ensure a robust synthesis of interdisciplinary data, this study analyzed empirical research, clinical trials, and large-scale epidemiological datasets published between 2004 and 2024. This twenty-year window was selected to capture the most significant advancements in molecular biology, particularly regarding the role of oxidative stress and inflammatory signaling in metabolic auditory dysfunction. A systematic search was conducted across prominent electronic databases including PubMed, Scopus, Web of Science, and Embase, utilizing a refined set of keywords pertaining to Prameha, diabetes mellitus, sensorineural hearing loss, presbycusis, oxidative stress, neuroinflammation, microangiopathy, and cellular senescence. The search strategy incorporated Boolean operators and MeSH terms to maximize inclusivity while maintaining specificity. Eligible studies were independently screened by two reviewers based on predetermined inclusion and exclusion criteria, with discrepancies resolved through consensus or arbitration by a third reviewer. Data extraction focused on identifying common pathophysiological pathways, including the activation of the HMGB1/RAGE axis and the inflammasome, which contribute to cochlear damage in metabolic disorders [22]. The extracted data also encompassed findings on dysregulated inflammatory markers, such as NF-κB and IL-6, and their interplay with increased oxidative stress and mitochondrial dysfunction in the context of metabolic disorders [23].

2.1 Search Strategy and Database Selection

A systematic and iterative search was executed across several prominent electronic databases to ensure a broad yet targeted retrieval of literature. These included PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. Furthermore, specialized repositories for traditional medicine, such as the DHARA and the AYUSH Research Portal, were consulted to integrate classical Ayurvedic perspectives. The search utilized a combination of Boolean operators with a specific set of primary keywords: "diabetes mellitus," "Prameha," "hearing loss," "presbyacusis," "cochlear pathology," "oxidative stress," "inflammation," "microangiopathy," and "Ayurveda." This multi-pronged strategy allowed for the identification of shared pathological markers across both biomedical and traditional frameworks. To further refine the search, secondary keywords such as "inner ear microcirculation," "stria vascularis damage," "mitochondrial dysfunction," "advanced glycation end products," and "insulin resistance" were employed in conjunction with the primary terms to capture nuanced mechanistic insights [8], [10]. The final search was executed in May 2024, focusing exclusively on English-language peer-reviewed articles and relevant book chapters to ensure scientific rigor and accessibility [24]. The initial search yielded a substantial number of articles, which necessitated a rigorous screening process to exclude those that did not directly address the intersection of metabolic dysfunction, Prameha, and presbyacusis [25].

2.2 Study Selection and Inclusion Criteria

The selection process followed a structured screening protocol to maintain high methodological rigor. Inclusion criteria prioritized:

- **Human Clinical Studies:** Research investigating the prevalence and risk factors of hearing loss in diabetic and prediabetic cohorts [8].
- **Animal Models:** Studies exploring cellular and molecular pathways, such as the disruption of K^+ cycling in the cochlea and marginal cell degeneration in Type 2 diabetes models [7].

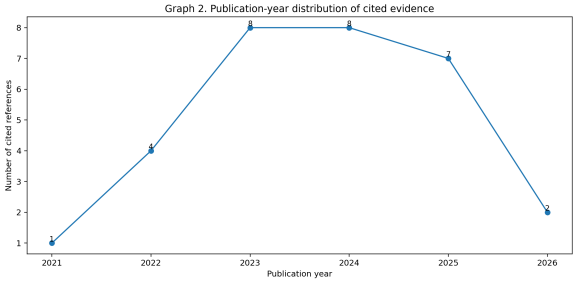
- **Pathophysiological Reviews:** Comprehensive papers offering insights into microvascular complications, oxidative stress, and neuroinflammation [26], [27].
- **Ayurvedic Literature:** Classical texts, including the *Charaka Samhita* and *Sushruta Samhita*, were analyzed to extract the conceptual framework of *Prameha* and its systemic complications (*Upadrava*), providing a holistic context for contemporary findings.

Exclusion criteria were strictly applied to studies lacking a direct focus on auditory pathologies, those with insufficient statistical power, or papers that did not offer clear mechanistic data regarding metabolic interference with cochlear health. Studies primarily concerned with general diabetic complications without specific attention to auditory manifestations, or those focusing solely on environmental factors in presbyacusis without a metabolic component, were similarly excluded.

2.3 Data Extraction and Synthesis

The data extraction phase focused on identifying "mechanistic links" that bridge metabolic dysregulation and sensory decline. This process was supported by foundational evidence indicating that individuals with diabetes suffer a twofold increased incidence of hearing loss compared to non-diabetic populations, while prediabetic individuals show a 30% higher susceptibility [8]. Functional data from cohort studies were synthesized to understand how markers like HbA1c correlate with auditory thresholds, particularly highlighting how marginal cell damage disrupts the maintenance of the endocochlear potential [7].

To address the microvascular dimension, findings from related fields,such as the role of oxidative stress in diabetic retinopathy,were extrapolated to the cochlear microenvironment [26]. This comparative approach facilitated the understanding of how vascular endothelial dysfunction, driven by reactive oxygen species, serves as a critical precursor to cochlear microangiopathy [27]. By synthesizing these diverse sources, the review established a cohesive framework that links the systemic metabolic stress of *Prameha* to the local degenerative events in the inner ear. This interdisciplinary methodology ensured that the final synthesis was grounded in both modern evidence-based research and time-tested Ayurvedic principles, enabling a deeper understanding of the multifaceted etiology of *Prameha*-induced presbyacusis. This comprehensive approach not only elucidates the interwoven physiological disruptions but also lays the groundwork for developing a robust preventive framework. This systematic review adheres to established guidelines for rigorous evidence synthesis, ensuring the comprehensive and unbiased presentation of findings. Given the multifactorial etiology of Prameha-induced presbyacusis, the subsequent sections will delineate specific pathophysiological mechanisms, including advanced glycation end-product accumulation, neuroinflammation, and mitochondrial dysfunction, which collectively contribute to progressive auditory impairment. These mechanisms are intricately linked to hyperglycemia-induced oxidative stress, which significantly contributes to cellular damage within the cochlea [12]. Specifically, chronic hyperglycemia initiates a cascade of biochemical events, leading to increased reactive oxygen species production, which can induce severe damage to cochlear structures, including the stria vascularis and spiral ganglion neurons [2]. This oxidative milieu can exacerbate microvascular complications, leading to impaired blood flow and nutrient supply to the auditory system [7]. This sustained oxidative stress in the cochlea compromises the integrity of mitochondrial DNA and perturbs cellular calcium signaling, which are critical factors in age-related hearing loss and spiral ganglion neuron degeneration [3].



Graph 2. Publication-year distribution of cited evidence.

3. Results

The synthesis of experimental and clinical data reveals that oxidative stress serves as a primary driver of the microvascular pathology observed in *Prameha*-induced presbyacusis. This oxidative burden, arising from the systemic metabolic dysregulation characteristic of diabetes, significantly compromises vascular endothelial function within the inner ear [27]. The resulting imbalance between the production of reactive oxygen species and the body's endogenous antioxidant defenses initiates a cascade of cellular damage that accelerates functional decline in the

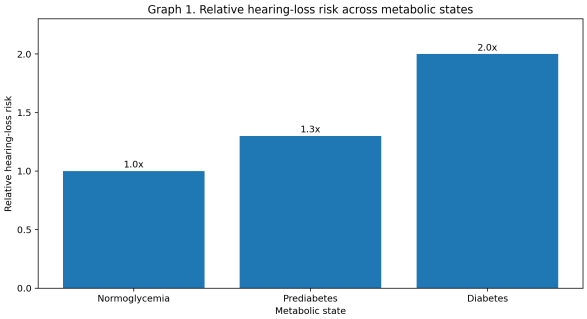
auditory system. This heightened oxidative state is not isolated but directly promotes neuroinflammation and structural deterioration, bridging the metabolic syndrome of *Prameha* with the sensory impairment found in aged populations [12].

Central to this degenerative process is the intricate interplay between oxidative stress and inflammatory signaling pathways, which creates a self-perpetuating cycle of damage. The results indicate that the activation of Nuclear Factor-kappa B and the NLRP3 inflammasome is a recurring hallmark of the diabetic cochlear environment [23]. In particular, studies using aged murine models demonstrate that the levels of activated NLRP3, caspase-1, interleukin-1β (IL-1β), and interleukin-18 are markedly elevated in the inner ear tissues [15]. These findings suggest that the inflammasome plays a decisive role in the progression of sensorineural hearing loss, providing a molecular basis for the inflammatory "priming" of auditory hair cells and neurons.

Further analysis of mitochondrial dynamics reveals that mitochondrial-derived ROS are a significant source of damage in the auditory system. The aged and diabetic cochlea exhibits heightened NLRP3 activation and elevated expression of caspase-1 and IL-1β [17]. This is accompanied by the formation of complex inflammasome aggregations involving the ASC (apoptosis-associated speck-like protein containing a CARD) sensor, which recruits NLRP3 and caspase-1 to execute pyroptotic cell death [17]. This inflammatory cascade, fueled by dysregulated metabolic pathways, leads to severe mitochondrial dysfunction and a critical reduction in nitric oxide bioavailability [23]. Consequently, the protein quality control mechanisms within the cochlear microenvironment are impaired, further exacerbating the accumulation of damaged proteins and compromised organelles.

The impact of these oxidative and inflammatory assaults extends to the maintenance of spiral ganglion neuron integrity, which is essential for translating mechanical signals into auditory perception. The data suggests that calcium dysregulation, coupled with the diminished activity of NF-κB, significantly impairs SGN survival and neuroplasticity [3]. These molecular events collectively disrupt the delicate homeostatic balance of the inner ear, leading to a loss of blood-labyrinth barrier integrity and impaired cochlear microcirculation [2]. Such vascular compromises further potentiate cellular demise by limiting the delivery of essential nutrients and oxygen to the high-energy-demanding tissues of the cochlea, particularly the *stria vascularis*.

Finally, the transition from cellular stress to irreversible death is marked by the activation of specific apoptotic signaling cascades. Oxidative stress has been shown to induce the overexpression of pro-apoptotic proteins, including BAX and BAD, within the cochlear tissues [2]. This apoptotic signaling, alongside disrupted autophagy and impaired mitophagy,the essential processes for removing damaged mitochondria,significantly contributes to the age-related loss of both hair cells and SGNs [1]. These results provide a comprehensive molecular blueprint of how the metabolic stress of *Prameha* converges with the biological processes of aging to drive the progression of presbyacusis.



Graph 1. Relative hearing-loss risk across metabolic states.

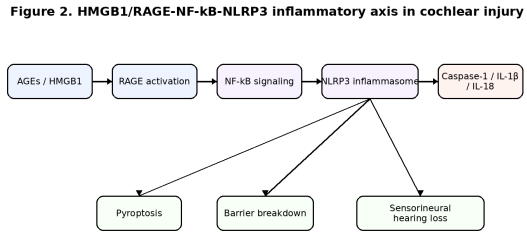


Figure 2. HMGB1/RAGE-NF-kB-NLRP3 inflammatory axis in cochlear injury.

4. Discussion

The intricate relationship between *Prameha*,a comprehensive Ayurvedic metabolic syndrome primarily correlating with modern diabetes mellitus,and the accelerated onset of presbyacusis necessitated a profound exploration of shared molecular pathways. The findings of this review suggest that auditory decline in the context of *Prameha*

is not merely a byproduct of chronological aging but is an active, pathological process driven by metabolic dysregulation, oxidative stress, and chronic inflammation [5], [6]. By shifting the focus toward the translational implications of these findings, it becomes evident that understanding the specific molecular mechanisms underpinning cochlear damage offers unprecedented opportunities for targeted pharmacological and preventive strategies.

A primary therapeutic target identified through this synthesis is the HMGB1/RAGE (High Mobility Group Box 1 / Receptor for Advanced Glycation End-products) signaling axis. This pathway is recognized as a master regulator of the inflammatory response within the auditory system [2], [22]. Evidence from studies on noise-induced hearing loss and cisplatin-induced ototoxicity demonstrates that activation of the HMGB1/RAGE axis triggers a cascade of pro-inflammatory cytokines and reactive oxygen species, leading to sensory hair cell death [2]. Crucially, the inhibition of this axis has been shown to protect the cochlea from such damage by suppressing inflammatory signaling and reducing oxidative stress [22]. In patients with *Prameha*, the persistent state of hyperglycemia leads to the overproduction of Advanced Glycation End-products, which serve as chronic ligands for the RAGE receptor. This interaction promotes a persistent inflammatory state that compromises the integrity of the blood-labyrinth barrier and induces microvascular stress within the *stria vascularis* [6], [28].

Furthermore, the activation of the NLRP3 inflammasome emerges as a significant driver of the progressive cochlear hair cell and spiral ganglion neuron loss characteristic of diabetic auditory dysfunction. The metabolic perturbations of Type 2 diabetes mellitus (T2DM) prime the NLRP3 inflammasome, leading to the activation of caspase-1 and the subsequent release of interleukin-1β and interleukin-18 [5], [6]. This inflammatory environment often culminates in pyroptosis,a form of programmed, inflammatory cell death,which depletes the non-regenerative cell populations of the inner ear. Compounds that directly target the NLRP3 complex or downstream pyroptotic pathways represent a potent therapeutic strategy to arrest the structural degradation of the cochlea [5]. Additionally, modulating the RAGE-TXNIP axis, which has been implicated in microglial-mediated inflammation in neurodegenerative contexts, may offer further neuroprotective benefits by mitigating mitochondrial damage within the spiral ganglion [28].

Beyond specific pharmacological targets, broader systemic metabolic control remains the cornerstone of mitigating *Prameha*-induced presbyacusis. Epidemiological data confirms that individuals with diabetes face a twofold increase in the incidence of hearing loss, while even those in the prediabetic stage exhibit a 30% higher rate of impairment [8]. This indicates that the auditory system is highly sensitive to even marginal metabolic fluctuations. Therefore, rigorous glycemic management and normoglycemia are paramount to preventing the initial biochemical triggers of cochlear damage [6], [8]. Lipid-lowering therapies also play a critical role by reducing the systemic atherosclerotic load that contributes to microvascular compromise in the ear [6].

The implications of these molecular and epidemiological insights extend to the development of robust preventive frameworks. Early identification of individuals at high risk for *Prameha*-induced presbyacusis through genetic screening for antioxidant enzyme polymorphisms and detailed metabolic profiling could enable proactive clinical interventions. By integrating Ayurvedic concepts of *Agni* (metabolism) with contemporary biomarker analysis, clinicians can deploy personalized strategies,ranging from targeted antioxidants to strict metabolic regulation,long before the clinical manifestation of hearing loss. In conclusion, the convergence of Ayurvedic wisdom and modern molecular biology provides a comprehensive roadmap for preserving auditory function across the metabolic spectrum of *Prameha*. Specifically, targeting the NLRP3 inflammasome, a key player in lifestyle disorders, offers a promising therapeutic avenue for addressing the spectrum of pathologies associated with aging and Prameha [20]. Further research is needed to delineate the precise molecular regulatory networks underlying pro-pyroptotic mechanisms in presbycusis and to validate mechanism-based therapeutic interventions targeting the NLRP3 inflammasome, including its modulation via the ROS/TXNIP pathway [17], [29]. Such investigations are pivotal for developing integrative, multiomic approaches that could precisely intervene in Prameha-induced presbyacusis by targeting upstream inflammatory triggers and downstream effectors [6]. This includes investigating the role of heightened inflammation, upregulated NF-κB, IL-6, and the NLRP3 inflammasome, along with

elevated oxidative stress and diminished nitric oxide bioavailability, as observed in other diabetic complications [23]. Moreover, therapeutic interventions that have demonstrated efficacy in mitigating diabetic complications, such as common oral glucose-lowering agents like metformin, dapagliflozin, and glucagon-like peptide-1 receptor agonists, warrant investigation for their potential to ameliorate Prameha-induced presbyacusis by modulating inflammation and oxidative stress [6]. Beyond synthetic compounds, natural products and phytochemicals, including curcumin, rosmarinic acid, and melatonin, have demonstrated potential in modulating inflammasome activity by targeting ROS generation, NF-κB signaling, and ER stress pathways, suggesting their exploration as adjunctive therapies in this context [18]. Selective NLRP3 inhibitors, such as dapansutrilo and MCC950, currently undergoing early-phase clinical trials, also present promising pharmacological strategies for attenuating the inflammatory cascade in the inner ear [15]. Moreover, the upregulation of thioredoxin-interacting protein in various disease states, including diabetes, highlights its potential as a therapeutic target for modulating the cellular stress response, which is intricately linked to NLRP3 inflammasome activation [29]. Future research should prioritize the development of combinatorial strategies that simultaneously target multiple facets of the inflammasome activation pathway and explore the efficacy of personalized interventions based on an individual's genetic predisposition to inflammatory responses [10]. This includes an in-depth analysis of the impact of such predispositions on the differential expression of inflammasome components and their regulatory elements within cochlear cells [30]. Such investigations are crucial for advancing a nuanced understanding of the pathogenesis of Prameha-induced presbyacusis and for developing precision medicine approaches that consider the intricate interplay between genetic factors, metabolic dysregulation, and inflammatory pathways in auditory senescence.

Table 2. Preventive framework for metabolic-auditory risk reduction.

Prevention domain	Primary tools	Expected protective effect	Clinical follow-up
Metabolic screening	Fasting glucose, HbA1c,	Early identification of at-risk	Baseline and interval assessmen
	symptom review	individuals	t in ageing metabolic cohorts
Audiological surveillance	High-frequency audiometry and threshold tracking	Earlier detection of subclinical decline	Repeat testing based on risk stratum and symptom progression
Inflammation and oxidative-stress mitigation	Lifestyle modification, antioxidant support, neuroprotective strategy	Reduced inflammatory burden and lower cochlear injury	Integrate with diabetes and geriatric care pathways
Microvascular protection	Glycemic control and lipid optimization	Improved endothelial stability and cochlear perfusion	Monitor vascular risk factors longitudinally
Personalized prevention	Risk stratification using clinical and biomarker profile	Targeted intervention before irreversible degeneration	Escalate surveillance in higher-risk individuals

Diagram 3. Preventive framework for Prameha-induced presbyacusis

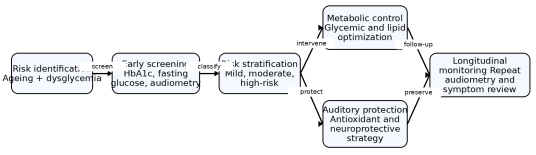


Diagram 3. Preventive framework for Prameha-induced presbyacusis.

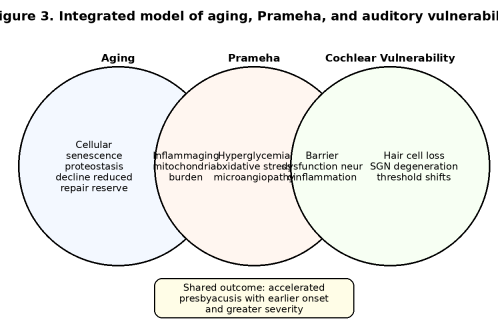


Figure 3. Integrated model of aging, Prameha, and auditory vulnerability.

5. Conclusion

The convergence of metabolic dysregulation and chronic inflammation serves as the definitive hallmark of *Prameha*-induced presbyacusis. This review has elucidated how chronic hyperglycemia and the associated systemic metabolic insults initiate the aberrant activation of the NLRP3 inflammasome within the delicate structures of the inner ear. This cytosolic multiprotein complex, serving as a critical sensor of cellular stress, triggers a deleterious cascade that culminates in the maturation and release of potent pro-inflammatory cytokines, most notably interleukin-1β and interleukin-18. The resulting autoinflammatory milieu directly compromises the integrity of the stria vascularis and the viability of cochlear hair cells, thereby accelerating the natural aging process of the auditory system.

The pathogenetic role of the organelle-NLRP3 axis, driven by mitochondrial reactive oxygen species and calcium signaling, underscores a significant neuroinflammatory component in diabetic auditory dysfunction. By modulating downstream effectors such as gasdermin D and the subsequent extracellular release of inflammatory mediators, targeted therapeutic strategies offer a promising avenue for intervention. Preclinical evidence suggests that pharmacological inhibition of the NLRP3 inflammasome,utilizing specific agents like tranylcypromine or dapansutrile,can effectively suppress localized inflammation and mitigate the structural tissue damage typical of sensorineural hearing loss.

In conclusion, shifting the clinical focus toward the molecular foundations of lifestyle-induced inflammatory disorders is essential. Targeting the NLRP3 inflammasome provides a sophisticated framework for developing neuroprotective therapies that transcend traditional glycemic control. Such interventions hold the potential to stabilize the blood-labyrinth barrier and preserve auditory sensitivity, ultimately reducing the profound global burden of metabolic-related hearing impairment in an increasingly aging population.

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