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The Metabolic Matrix Hypothesis of Recurrent BPPV: Otoconia–Otolithic Membrane–Endolymph Fragility

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Abstract

Background: Benign paroxysmal positional vertigo (BPPV) is treated as a purely mechanical disorder of displaced otoconia, yet this model alone does not readily account for spontaneous otoconia detachment, bilateral or multicanal disease, high recurrence rates, or the clustering of BPPV with systemic metabolic conditions in a subset of patients. **Objective:** To propose and structure a unifying mechanistic model — the Metabolic Matrix Hypothesis — linking systemic metabolic states to otoconial fragility, and to derive testable predictions. **Methods:** Hypothesis-generating narrative and theoretical synthesis – not a systematic review or meta-analysis – of otoconial matrix biology, otolithic membrane anchoring, endolymph chemistry, and the dispersed clinical literature on metabolic risk factors for BPPV. Evidence supporting each proposed pathway is graded narratively as established clinical association, experimental or animal evidence, mechanistic inference, or speculative extension. **Conclusions:** In a biologically distinct subset of patients, recurrent idiopathic BPPV may represent the mechanical expression of a systemic metabolic fragility of the otoconia–otolithic membrane–endolymph unit. Vitamin D deficiency, estrogen withdrawal, osteoporosis, insulin resistance, oxidative stress, thyroid autoimmunity, and microvascular insufficiency may act as convergent entry points into impaired matrix resilience rather than independent risks. The model generates testable predictions and a clinically accessible metabolic evaluation for recurrent, bilateral, or multicanal disease, complementing repositioning maneuvers.

Keywords: benign paroxysmal positional vertigo; otoconia; otolithic membrane; vitamin D; otolin-1; recurrence

1. Introduction

Benign paroxysmal positional vertigo (BPPV) is the most common cause of vestibular vertigo, and its core mechanism is not in dispute: otoconia — biomineralized calcium carbonate particles that normally rest on the utricular macula — become displaced into one or more semicircular canals, where they generate aberrant endolymph flow or ampullary deflection during head movement and produce the characteristic positional nystagmus and vertigo [1,2], a presentation now codified in the Bárány Society's international diagnostic criteria [3].

Canalith repositioning resolves the great majority of individual episodes [2], yet the mechanical account does not by itself account for several everyday observations. Reported recurrence ranges from roughly 15% to more than 50% at one year, and reaches 50–80% over longer follow-up in some series [4]. Many cases are idiopathic, arising without any identifiable precipitant. Incidence and recurrence both rise with age and concentrate in women, in the postmenopausal years, and in patients with osteoporosis, vitamin D deficiency, diabetes mellitus or thyroid autoimmunity — none of which has an obvious mechanical link to a loose crystal [4–6]. Bilateral and multicanal disease, which imply diffuse utricular instability rather than a single focal event, likewise cluster in patients with systemic metabolic disease [5].

These questions are sharpened by clinical observation. Published cohorts report that recurrence is common and that a substantial minority of patients have multicanal involvement, with recurrence rising through middle age rather than in simple proportion to it [3,4,5]. What the published cohorts share is an omission rather than a finding: none characterizes patients metabolically at the index episode, which is precisely the gap this hypothesis sets out to address.

The unifying question is therefore not how otoconia move once dislodged, but why they dislodge at all, and why some patients dislodge them again and again. We argue that, in a definable subset, part of the answer is biological rather than purely accidental: a systemic metabolic vulnerability of the otoconia–otolithic membrane–endolymph unit.

A clutch of very recent studies has independently reinforced this metabolic reading. A large otolith-function study using vestibular-evoked myogenic potentials (VEMPs) identified age, free thyroxine, glycemic control, and HDL cholesterol as correlates of saccular and utricular integrity [7], and an epidemiological analysis tied primary hyperparathyroidism—a disorder of systemic calcium handling—to an elevated prevalence of BPPV [8]. Both converge on the same metabolic suspects, yet each examines them singly and stops at the threshold of mechanism, explicitly leaving undefined the path from a systemic exposure to a fragile otoconial complex. The present work takes that next step: rather than cataloguing associations one at a time, it integrates them into a single mechanistic chain centered on the otoconia–otolithic membrane–endolymph unit, and recasts that chain as a set of falsifiable predictions and a research agenda.

2. Scope, Article Type, and Methods

This article is a narrative and theoretical review written to generate a hypothesis. It is not a systematic review or a meta-analysis: no protocol was registered, no effect estimates were pooled, and the literature was not appraised against a formal grading instrument. Its purpose is to assemble dispersed evidence into a single mechanistic proposition and to state that proposition in a form that can be tested and refuted.

Literature was identified by searching PubMed/MEDLINE, Europe PMC, and Google Scholar from database inception to June 2026, combining the terms benign paroxysmal positional vertigo, BPPV, recurrence, otoconia, otoconin-90, otolin-1, otolithic membrane, endolymph, calcium, vitamin D, estrogen, menopause, osteoporosis, bone mineral density, insulin resistance, diabetes, oxidative stress, thyroid, autoimmunity, hypertension, and microvascular. Reference lists of retrieved articles were then searched iteratively (citation snowballing) until no further relevant primary sources emerged. Searches were restricted to English-language publications.

Selection was purposive rather than exhaustive. Priority was given, in order, to human clinical studies (randomized trials, meta-analyses and systematic reviews first), to human histopathological and temporal-bone material, and to mechanistic animal or in vitro work where no human equivalent exists. A study was included when it bore on otoconial or otolithic-membrane integrity, on endolymph composition, or on a systemic metabolic exposure plausibly connected to either. Case reports and non-peer-reviewed sources were not used to support the model, and studies confined to post-traumatic, post-surgical or post-neuritis BPPV were excluded from it.

Conflicting evidence is reported rather than resolved: where meta-analyses disagree, both results are given and the discrepancy is discussed (Sections 4.1 and 4.9). Throughout the text, each claim is labelled by the kind of evidence that supports it – an established clinical association, experimental or animal evidence, a mechanistic inference, or a speculative extension – and Table 1 summarizes that grading for every pathway the model invokes.

Target phenotype. The model is proposed for a defined subset and not for BPPV in general: idiopathic disease with at least two discrete, separately treated episodes within twelve months. Bilateral or

multicanal involvement is regarded as supportive of the phenotype but is not required for it. Post-traumatic, post-surgical, post-neuritis and vestibular migraine-associated positional vertigo are excluded, as is any case with an identifiable structural, inflammatory or ototoxic precipitant. Because the model concerns the fragility of the otoconia–otolithic membrane–endolymph unit rather than the behaviour of a crystal once free, it is agnostic as to whether the resulting disease presents as canalithiasis or as cupulolithiasis; both are compatible with it.

3. Biology of the Otoconial Complex

3.1 Otoconia as biomineralized matrix structures

Otoconia are not inert crystals. Each is a composite biomineral — a calcite (CaCO_3) core built upon and held together by an organic protein matrix [9]. That matrix depends on a set of structural proteins — otoconin-90 (OC90), otolin-1, otogelin and otogelin-like, α - and β -tectorin, otoancorin, otolith matrix protein-1 (OMP-1), cochlin, otopetrin 1 and 2 (OTOP1/2) and plasma-membrane calcium ATPase 2 (PMCA2) — which govern calcium carbonate nucleation, crystal morphology and the fidelity of mineralization, and which sustain the otoconium long after development [9]. OC90 is the principal soluble matrix protein and the essential organizer of the matrix: its loss yields grossly abnormal otoconia [10], and OC90 is also required to recruit otolin into the matrix [11]. In vitro, recombinant OC90 facilitates calcite nucleation, restrains growth kinetics and shapes crystal morphology toward the form typical of otoconia [12]. Otolin-1 — a collagen-like glycoprotein unique to the inner ear — assembles into higher-order oligomers that scaffold mineralization [13], while the matrix as a whole recruits component proteins and sequesters calcium in a spatially specific manner during development [14]. That calcium-sequestering role is itself dual: the matrix provides a local reservoir of calcium for otoconial formation and maintenance, while buffering the peri-cellular calcium that, left high, would impair hair-cell function [14]. Both otolin-1 and OC90 modulate calcite crystal morphology in vitro, with otolin-1 acting as an active nucleator rather than passive glue [15,16]. Mineralization fidelity therefore depends closely on matrix integrity: if the expression or function of these proteins is impaired — congenitally or through later metabolic insult — the structural quality of the otoconium in adult life could be compromised, yielding crystals more prone to dissolution and fragmentation.

3.2 Otolithic membrane anchoring and its failure

The otoconia do not lie free. They are embedded in the otolithic membrane — a layered viscoelastic structure overlying the macula, in which the otoconia sit in a loose superficial filament network above a gelatinous layer and a deeper subcupular meshwork that couples to the hair-cell processes — and are held by a protein-mediated anchoring system in which otolin-1 plays a dual role: it forms the fine fibrils that interconnect adjacent otoconia and it builds the subsurface layer that anchors them to the gel [11,17,18]. These fibrils grow out of the rhombohedral faces of the otoconia into a flexible, interconnected network [17], and the matrix proteins OMP-1 and otolin-1 are required for normal otolith growth and for correct anchoring onto the sensory maculae [19]. Channels that traverse the otoconial cortex permit exchange of material between the endolymph and the mineral interior [11], offering a route by which the systemic ionic and metabolic environment can reach the crystal itself.

This anchoring system is where age and biology appear to fail. Immunogold studies show that, by mid-life, the otoconial subsurface layer demineralizes, weakening or abolishing the anchoring of the interconnecting fibrils; otoconia then lose their attachment to one another and to the gel and may be released into the endolymph by minor mechanical disturbance, from where they translocate into the semicircular canals [11]. Degeneration of this kind has been documented directly in human utricular otoconia [20,21], and material recovered surgically from the posterior canal in BPPV contains not isolated crystals alone but fragments of the utricular otolithic membrane with attached and detached

otoconia [1] — consistent with failure of the membrane–otoconia complex as a unit rather than of single crystals breaking from an intact bed.

Two further lines of evidence indicate that the otoconial mineral is subject to ongoing but limited maintenance rather than being inert, and is therefore exposed to systemic influence. The insoluble organic matrix normally shields the calcite from dissolution and confers long-term mineral stability [22]. Moreover, under altered gravity, otoconia visibly remodel: longer-duration spaceflight is associated with apparent mass addition to the outer shell, whereas hypergravity produces destructive thinning of the shell and cavitation of the core [23]; and tracer studies show calcium exchange at the crystal surfaces of adult otoconia, indicating a turnover that is real but slow and surface-restricted rather than the brisk remodeling of bone [24]. Together these observations shift the explanatory weight from the wandering crystal to the matrix that should have held it — and to the metabolic determinants of that matrix.

A genetic dimension reinforces that otoconial integrity is biologically determined rather than a matter of mechanical chance. Familial clustering of recurrent BPPV is well recognized, and a frameshift variant in the clustered protocadherin gene *PCDHGA10* has been identified as a strong candidate in familial recurrent disease; because the cells that carry it normally produce otoconial proteins, the variant is predicted to compromise otoconia formation and maintenance, is associated with earlier onset, and may help explain the poor durability of repositioning in some patients [25]. Such heritable contributors lie outside the present model, which concerns acquired, modifiable fragility, but they make the same essential point from another direction: a less resilient otoconial apparatus, however it arises, is what lowers the threshold for the disease.

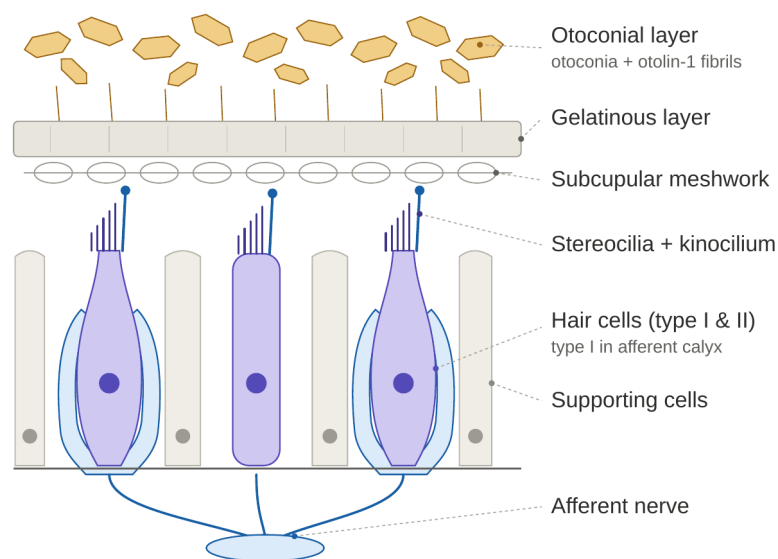


Figure 1. Original schematic of the otolithic membrane and the underlying macular sensory epithelium. Otoconia form the otoconial layer above a gelatinous layer and a subcupular meshwork, interconnected and anchored by otolin-1 fibrils. Type I hair cells (enclosed by an afferent nerve calyx) and type II hair cells, flanked by supporting cells, project stereocilia and a single kinocilium into the membrane, with afferent fibers converging below. Age- and metabolism-related demineralization of the subsurface anchoring layer is proposed to loosen the otoconia–membrane complex and release otoconia into the semicircular canals. Drawn by the author; the layered organization and hair-cell morphology follow classical descriptions of the vestibular maculae [18].

3.3 Endolymph chemistry and otoconia dissolution

Endolymph in the canals is low in calcium, and that low level is not incidental but actively maintained: the plasma-membrane calcium pump PMCA2 in the hair-cell stereocilia extrudes calcium into the

endolymph [26], while the endolymphatic sac behaves as a 'calciostatic' organ that senses and handles calcium through the calcium-sensing receptor and TRP channels — machinery whose disturbance is implicated in inner-ear fluid disorders [27]. More precisely, this low calcium is held down by active reabsorption out of the lumen through the apical epithelial calcium channels transient receptor potential vanilloid type 5 and type 6 (TRPV5 and TRPV6) of the canal, utricular and saccular epithelia, with basolateral extrusion by calcium-ATPases and sodium–calcium exchange [28]; this absorptive system is responsive to active vitamin D (at the transcript level) and is inhibited by luminal acidification, so that a fall in endolymph pH itself raises endolymph calcium [29]. Against that actively regulated background, classic experiments showed that displaced otoconia gradually dissolve in this milieu — a plausible basis for spontaneous recovery — and that raising endolymph calcium slows that dissolution, so calcium balance helps set the natural history of an episode [30]. The mineral stays intact only while the surrounding endolymph remains saturated with respect to its constituent ions: the solubility product of calcium carbonate sets the calcium and carbonate concentrations required for stability, and a shift in either — through pH change, ionic dilution, or complexation — begins dissolution [22]. More recent modeling extends this to carbonate/bicarbonate balance and pH — the latter set partly by carbonic anhydrase, whose activity in the inner ear has been demonstrated in the cochlea [31] and by systemic acid–base status — quantities that a systemic metabolic disturbance could shift [32], and in vitro work confirms that pH and ionic changes alter how human and artificial otoconia dissolve and fragment [22]. Endolymph chemistry is thus a credible mediator between the body's metabolic state and the fate of a displaced crystal.

4. Metabolic Associations with BPPV: Converging Evidence

4.1 Vitamin D deficiency and calcium metabolism

The firmest metabolic link is to vitamin D, proposed as a contributor to BPPV more than a decade ago [33]. A randomized trial showed that supplementing vitamin D (with calcium) cut recurrence in patients whose serum levels were subnormal [34], and later systematic reviews and meta-analyses have upheld both the association and the case for supplementing deficient patients with recurrent disease [35]. The evidence is not unanimous: one meta-analysis failed to establish a link with the occurrence of BPPV, yet still found low vitamin D significantly more common among patients with recurrent episodes [36] — a pattern that fits a model in which vitamin D matters specifically for recurrence rather than for the first event. A local action is plausible: the vitamin D receptor is expressed in vestibular epithelium, and mice lacking either the receptor or its activating enzyme 1 α -hydroxylase develop vestibular dysfunction with disorganized otoconial mineralization [37]. Vitamin D status is in turn bound up with osteoporosis and bone turnover, themselves independently tied to BPPV [38].

4.2 Estrogen deficiency, osteoporosis, and anchoring protein expression

Osteoporosis and the postmenopausal state recur throughout the observational and meta-analytic literature as risk factors, including in older women specifically [38,39,40,41], and meta-analysis links reduced bone mineral density to BPPV [42]. Bone turnover is also relevant at the biochemical level: idiopathic BPPV patients tend to show higher markers of bone turnover, and these track vitamin D status [43].

The more direct and mechanistically informative link is hormonal. Estrogen acts on the vestibular maculae through nuclear estrogen receptors — the β subtype (estrogen receptor β , ESR2) appearing to be the critical mediator — to sustain the expression of otoconial matrix and anchoring proteins such as otoconin-90 and otolin-1. When estrogen is withdrawn experimentally by ovariectomy, this regulation fails: expression of these component and anchoring proteins falls, otoconia are less well maintained and less firmly anchored to the membrane, and aberrant matrix-protein expression even generates ectopic debris within the ampulla [44]. Estrogen is also antioxidant, so its loss raises

oxidative markers in the utricle and disorganizes the otoconial layer — changes reversed by estrogen supplementation (estradiol) or by treatment with the selective estrogen-receptor modulator raloxifene [45], linking estrogen withdrawal to the oxidative-stress mechanism discussed below. Progesterone declines alongside estrogen at menopause and its receptors are present in vestibular tissue, but its specific role in otoconial maintenance is far less well defined; estrogen is the characterized actor. Menopausal women with BPPV show markedly greater falls in plasma estrogen and progesterone than those without it [46].

This is the most direct evidence available that a systemic hormonal state can degrade the biology of otoconial maintenance and anchoring — through reduced matrix-protein synthesis and increased oxidative damage — rather than merely shifting serum calcium. In postmenopausal women the convergence of vitamin D deficiency, estrogen withdrawal and accelerated bone turnover may therefore define a particularly fragile otoconial phenotype, consistent with the demographic in which BPPV and its recurrence are concentrated [39,46,47].

4.3 Otolin-1 as a biomarker of matrix degeneration

If the otoconial matrix really degrades, it might leave a measurable trace. Otolin-1 is an inner-ear matrix glycoprotein that exits the endolymph across the labyrinth–blood barrier into the systemic circulation, which makes it measurable in serum [48]. Its blood level rises with age, in parallel with the age-related demineralization of otoconia [49], and is related to vitamin D status [50]. Against that baseline, serum otolin-1 is raised in BPPV relative to controls across several studies and in meta-analysis [51], higher levels predict recurrence [52], and a head-to-head comparison found otolin-1 more clearly associated with BPPV than OC90, with serum otolin-1 within patients varying inversely with vitamin D status — tying the degradation marker directly to the metabolic axis [53]. Otolin-1 is not yet a validated routine assay, but its behavior is consistent with matrix degeneration — rather than simple mechanical bad luck — driving a share of cases.

4.4 Glucose-insulin dysregulation and inflammation

Metabolic dysregulation enters by a second door. Hyperinsulinemia and hyperglycemia have been linked to recurrence of idiopathic BPPV [54], combined analyses connect diabetes and hypothyroidism to the disease [55], and a transcriptomic study identified genes and pathways shared between recurrent BPPV and type 2 diabetes, pointing to immune-mediated inflammation as a common thread [56]. The plausible intermediaries are labyrinthine microangiopathy, low-grade inflammation, oxidative stress and disturbed calcium handling. The status of this strand should be stated plainly: the clinical link between glycemic dysregulation and recurrent BPPV is observational and, as set out in Section 4.9, substantially confounded by age and adiposity. The intermediaries proposed above are mechanistic inference rather than demonstrated pathway, and none has yet been shown to act upon otoconial matrix or endolymph in a diabetic patient.

4.5 Oxidative stress

Oxidative status is also altered in BPPV, with reported changes in trace elements and oxidative markers [57,58] and reduced circulating antioxidants — uric acid, bilirubin, albumin and creatinine — suggesting a thinner antioxidant reserve [59]. Combining vitamin D with antioxidants has been proposed as recurrence prophylaxis [47]. Against a background of metabolic syndrome, aging, vascular disease or diabetes, oxidative stress is a biologically reasonable cofactor. This remains the weakest of the clinical strands. The human studies are small, largely single-centre and cross-sectional; they measure systemic surrogate markers rather than inner-ear oxidative damage; and reverse causation cannot be excluded, since an acute vertiginous illness may itself perturb antioxidant status. Oxidative stress is best regarded here as a biologically plausible cofactor rather than an established contributor.

4.6 Thyroid autoimmunity

Finally, the thyroid, where two distinct routes are plausible rather than a simple mechanical deposit. Hypothyroidism and Hashimoto thyroiditis have repeatedly been associated with BPPV and its recurrence [60,55]. Hormonally, thyroid hormone helps regulate calcium metabolism and the maintenance of neurosensory tissue, and the vestibular microenvironment is sensitive to its fluctuation, so hypothyroidism could predispose to otoconial degeneration [55]. Immunologically, the inner ear is itself an immunocompetent organ — in human temporal bones the endolymphatic sac carries resident macrophages and innate-immune machinery and processes antigens reaching the labyrinth from nearby structures [61] — so a systemic autoimmune diathesis could in principle act there. An early and narrow version of this idea invoked immune-complex deposition with mechanical irritation of labyrinthine receptors [62]; the more telling observation is that the association with autoimmune thyroiditis holds even in euthyroid patients, independent of thyroid function — implicating the autoimmune process itself, with the anti-thyroid-peroxidase and anti-thyroglobulin antibodies serving as its marker rather than hormone deficiency [63]. What is actually attacked in the inner ear is not settled: in immune-mediated inner-ear disease, circulating antibodies have been described against inner-ear proteins such as cochlin, β -tectorin and heat-shock protein 70, and against antigens expressed in the saccular and utricular walls, none of them thyroid-specific [64]. No thyroid autoantibody has been shown to bind a defined otoconial or macular target, so the realistic mechanism is either molecular mimicry between thyroid and inner-ear antigens or, more probably, bystander immune-mediated inflammation of an immunocompetent labyrinth rather than a specific antibody attack. The thyroid therefore plausibly acts through two separate doors, hormonal and autoimmune, both converging on the inner-ear environment rather than on a single deposit damaging the macula. Two qualifications are essential. First, the epidemiological association is observational and vulnerable to detection bias, since patients already under endocrine follow-up are more likely to have both conditions recorded. Second, the immunological route is inference rather than demonstration: no thyroid autoantibody has been shown to bind an otoconial or macular target, and the human temporal-bone work establishes only that the endolymphatic sac is immunologically competent, not that it is attacked in thyroid autoimmunity. Of the two doors, the hormonal one is the better supported; the autoimmune one remains a hypothesis.

4.7 Vascular and microvascular insufficiency

The inner ear is an end-organ: its entire blood supply derives from the labyrinthine (internal auditory) artery, a terminal vessel with minimal collateral circulation, so the utricular macula and the endolymph-maintaining dark cells depend on continuous, stable perfusion and tolerate vascular compromise poorly. The labyrinth is therefore vulnerable at both ends of the blood-pressure spectrum. Sustained hypertension drives microangiopathy — arteriolar thickening, luminal narrowing and atherosclerosis of the labyrinthine territory — that chronically lowers perfusion and erodes autoregulatory reserve; conversely, hypotension and orthostatic hypotension reduce perfusion pressure in a vessel that has no collateral supply to compensate, producing transient ischemia. Either way, the macula receives inadequate or unstable delivery of oxygen, calcium and vitamin D metabolites, and dark-cell regulation of endolymph ionic balance is impaired. Consistent with this, vascular risk factors recur across the literature — hypertension, hypotension, hyperlipidemia, diabetes and cardiovascular disease associate with BPPV and, more consistently, with its recurrence, although occurrence-level evidence is mixed [4,5,65]. Vascular insufficiency is therefore not a separate pathway but another route into the same shared vulnerability, degrading both otoconial maintenance and the endolymph chemistry on which crystal stability depends (Section 3.3). The evidence here is associative and among the most confounded in this review: hypertension, hyperlipidemia and dysglycemia cluster with age, with adiposity and with one another, and few of the available studies adjust adequately for that clustering (Section 4.9). The end-artery argument is anatomically sound but has not been demonstrated to operate in BPPV, and is offered as mechanistic inference rather than as established pathway.

4.8 Vitamin K2, magnesium, and the calcium-handling axis

This section is a hypothesis-level extension, not a recommendation for practice: neither vitamin K2 nor magnesium has been studied in BPPV, and nothing in it should be read as an evidence-based intervention for recurrence. Because vitamin D sits at the center of the calcium argument (Section 4.1), it bears noting that vitamin D does not act alone: it operates within a cofactor network whose other members are mechanistically pertinent and clinically modifiable. Vitamin K2 (menaquinone) is the cofactor for γ -carboxylation of vitamin K-dependent Gla proteins: carboxylated osteocalcin, an osteoblast product whose synthesis is itself induced by vitamin D, binds calcium into the bone matrix, whereas carboxylated matrix Gla protein restrains calcium deposition in soft tissue and vessel walls. When vitamin K2 is insufficient these proteins remain undercarboxylated, so vitamin D-driven calcium is less efficiently directed into bone and more available for ectopic deposition [66]. Magnesium, in turn, is required to activate vitamin D itself — the hydroxylating enzymes in liver and kidney are magnesium-dependent, so magnesium deficiency blunts the response to vitamin D and is corrected by repletion — and is independently necessary for bone mineralization while acting as a physiological calcium antagonist and membrane stabilizer that restrains calcium-driven depolarization [67]. The otoconial matrix proteins (otoconin-90, otolin-1) are not themselves vitamin K-dependent Gla proteins, so any role for these cofactors in otoconia would be indirect — exerted through systemic calcium partitioning, bone turnover (Section 4.2), vascular integrity (Section 4.7) and the endolymph calcium balance that governs crystal stability (Section 3.3) — and remains untested in BPPV. The practical implication is nonetheless concrete: correcting vitamin D for recurrence prevention is likely to be most rational when magnesium sufficiency and vitamin K2 status are weighed alongside it, so that mobilized calcium is steered toward bone rather than toward the vasculature or other soft tissue. This is a hypothesis-level extension, offered to be tested rather than assumed.

4.9 Confounding, contradictory evidence, and interpretation

The associations assembled above share a structural weakness that must be stated before they are integrated. Almost all are cross-sectional or retrospective, and almost all concern exposures that rise with age and gather in the same people. Age, female sex, menopausal status, adiposity and multimorbidity are common causes both of BPPV and of vitamin D deficiency, osteoporosis, hypertension, dyslipidemia, dysglycemia and thyroid disease, so an unadjusted association between any one of them and BPPV is weak evidence of a specific link. Few of the studies cited here adjust beyond age and sex, and several do not adjust at all.

Two further biases run in the same direction. Detection bias inflates associations with conditions that bring patients into regular medical contact — thyroid disease and diabetes especially — because both the exposure and a positional vertigo are more likely to be recorded in someone already under follow-up. Publication bias, considered again in Section 9, favours positive reports in a field where negative metabolic findings are unlikely to be written up. The true effect sizes are therefore probably smaller, and less consistent, than the assembled literature suggests.

The contradictions deserve their weight rather than smoothing. For vitamin D, a widely cited meta-analysis found no association with the occurrence of BPPV even while confirming one with recurrence [36]. For thyroid disease, the association with hypothyroidism is not reproduced in every series, and its persistence in euthyroid autoimmune patients [63], while supporting an immune route, correspondingly weakens the simpler hormonal explanation offered in Section 4.6. Vascular risk factors associate more consistently with recurrence than with occurrence [4,5,65], which fits the present model but fits residual confounding by age equally well. Reported oxidative markers differ between studies in both direction and analyte. No single strand would carry the hypothesis; the argument rests on their convergence, and convergence among confounded associations is a weaker form of evidence than convergence among independent ones.

The model should accordingly be read as a proposal about a subgroup rather than as a demonstrated mechanism. Its value lies in the specific and refutable predictions set out in Section 6, not in the strength of any individual association reviewed here.

Table 1. Strength of evidence for each pathway invoked by the Metabolic Matrix Hypothesis. Evidence type refers to the best available study design; status distinguishes pathways supported by human clinical data from those that remain mechanistic inference or speculative extension.

Metabolic factor	Best available evidence	Proposed mechanism	Strength	Clinical relevance	Status
Vitamin D deficiency	Randomized trial; meta-analyses (human)	Reduced calcium availability; vitamin D receptor expressed in vestibular epithelium	Moderate for recurrence; inconsistent for occurrence	Repletion reasonable in deficient recurrent patients	Established association; mechanism partly experimental
Estrogen withdrawal / menopause	Human observational; ovariectomy models (animal)	Reduced otoconin-90 and otolin-1 expression; impaired anchoring; oxidative damage	Moderate	Explains demographic concentration; no BPPV-specific hormonal indication	Association established; mechanism animal-experimental
Osteoporosis / low bone mineral density	Meta-analyses (human)	Shared calcium and bone-turnover pathway	Moderate	Densitometry where otherwise indicated	Association established; mechanism inferred
Serum otolin-1	Case-control studies; meta-analysis (human)	Leakage of degraded matrix protein into the circulation	Moderate; no validated threshold	Research use only	Association established; clinical use hypothetical
Glucose-insulin dysregulation	Observational; transcriptomic (human)	Microangiopathy; low-grade inflammation; disturbed calcium handling	Weak to moderate; confounded by age and adiposity	Standard metabolic care only	Association probable; mechanism inferred
Oxidative stress	Small case-control studies (human)	Reduced antioxidant reserve; matrix damage	Weak	Research	Mechanistic inference
Thyroid autoimmunity	Observational, including euthyroid patients (human)	Bystander inflammation in an immunocompetent labyrinth; no defined otoconial autoantigen	Weak to moderate; detection bias likely	Test where clinically indicated	Association probable; immune mechanism speculative
Vascular / microvascular insufficiency	Observational, mixed results (human)	End-artery vulnerability; impaired dark-cell regulation	Weak to moderate; heavily confounded	Standard cardiovascular care only	Mechanistic inference
Vitamin K2 and magnesium	Indirect only (bone and vascular literature); none in BPPV	Systemic calcium partitioning; vitamin D activation	Very weak; untested in BPPV	None; not a BPPV recommendation	Speculative extension
Genetic susceptibility (PCDHGA10)	Single family-based study (human)	Impaired otoconial protein production	Weak; familial rather than acquired	Research	Hypothetical; outside the acquired model

Grading criteria. Strength of evidence was rated on an ordinal scheme applied consistently across rows rather than by a formal instrument. Moderate denotes human evidence including at least one randomized trial or meta-analysis and reasonably consistent across studies; weak to moderate denotes replicated human observational evidence that is inconsistent or substantially confounded; weak denotes few or small human studies, or surrogate outcomes only; very weak denotes an exposure that has not been measured in BPPV at all. Ratings took account, in order, of the best available study design, the species and system studied, consistency between studies, whether the exposure has been examined in BPPV, and vulnerability to confounding (Section 4.9). This is not a GRADE assessment: risk of bias, heterogeneity and funnel-plot asymmetry were not evaluated at study level, and the ratings are relative to one another within this table rather than calibrated against an external standard.

5. The Hypothesis

We propose that recurrent idiopathic BPPV — especially when bilateral, multicanal, postmenopausal, or accompanied by metabolic disease — represents, in a distinct subgroup, the mechanical expression of a systemic metabolic fragility of the otoconia–otolithic membrane–endolymph unit.

Vitamin D deficiency, estrogen deficiency, osteoporosis, insulin resistance, oxidative stress, low-grade inflammation, thyroid autoimmunity, and microvascular dysfunction may converge on a shared biological vulnerability: impaired structural integrity of otoconial matrix anchoring proteins, defective calcium carbonate biomineralization, weakening of the otolithic membrane, and altered endolymph ion chemistry. This systemic fragility lowers the threshold for otoconia detachment, promotes membrane–otoconia complex fragmentation, impairs endolymph-mediated dissolution, and may in that way drive recurrence.

This does not displace the mechanical model; it sits beneath it. The displacement event still occurs — but it occurs more readily, more often, and in more canals at once when the otoconial complex is biologically weakened. Recurrent idiopathic BPPV is thereby reframed not as an accident of anatomy but as a phenotype of metabolic vulnerability. Nor does it claim to account for every recurrent case. Some idiopathic BPPV will remain stochastic, or the ordinary consequence of age-related otoconial degeneration, with no identifiable systemic contribution; the model asserts only that a definable subgroup exists in which such a contribution is present and measurable.

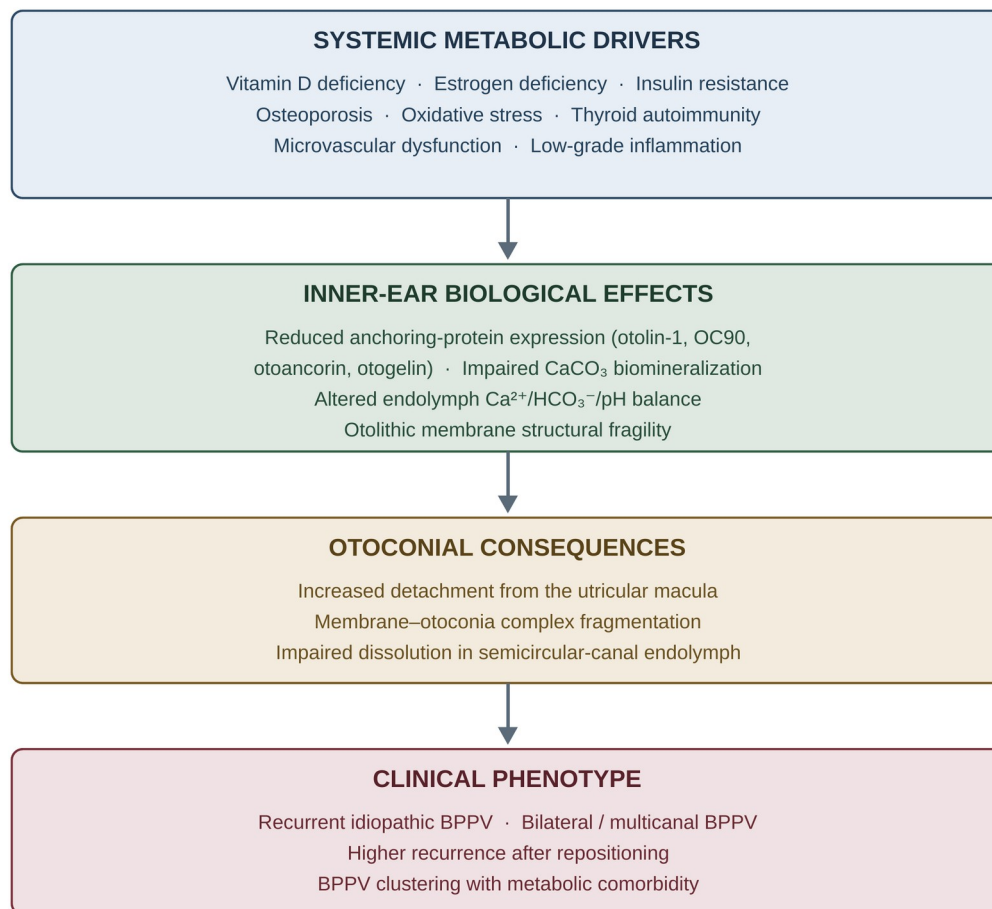


Figure 2. Proposed convergent pathways in the Metabolic Matrix Hypothesis of recurrent BPPV. Diverse systemic metabolic states are proposed to converge on a shared reduction in the structural and biochemical resilience of the otoconia–otolithic membrane–endolymph unit, lowering the threshold for otoconia detachment, fragmentation and recurrence. The model complements, rather than replaces, the established mechanical (canalithiasis/cupulolithiasis) explanation.

6. Predictions and Testable Hypotheses

1. Patients with recurrent idiopathic BPPV will show higher rates of vitamin D deficiency, osteopenia/osteoporosis, insulin resistance, and thyroid autoimmunity than single-episode patients or controls, independent of age and sex.
2. Patients with bilateral or multicanal BPPV will carry a greater metabolic risk burden than those with unilateral, single-canal disease.
3. Serum otolin-1 will be higher in recurrent than in single-episode BPPV and will track recurrence frequency or a composite metabolic burden score.
4. Vestibular evoked myogenic potentials (VEMPs) will reveal greater utricular and saccular dysfunction in patients with the proposed metabolic phenotype.
5. Correcting modifiable metabolic factors — vitamin D repletion in deficient patients being the most immediate target — will reduce recurrence beyond what repositioning achieves alone.
6. Conversely, factors plausible on general vascular or oxidative grounds but peripheral to matrix integrity and calcium handling — homocysteine, vitamin B12, and folate — should show no consistent association with BPPV; the studies that have measured them report none [68], distinguishing this model from the claim that metabolic disturbance of any kind raises risk.

7. Proposed Research Framework

The hypothesis is testable with a three-group prospective design: (A) recurrent idiopathic BPPV meeting the phenotype defined in Section 2 (at least two discrete episodes within twelve months); (B) single-episode idiopathic BPPV; and (C) age- and sex-matched controls without BPPV.

Clinically accessible metabolic panel: 25-hydroxyvitamin D (25-OH vitamin D), calcium, phosphate, magnesium, parathyroid hormone (PTH), creatinine with estimated glomerular filtration rate (eGFR); glycated hemoglobin (HbA1c), fasting glucose, fasting insulin with the homeostatic model assessment of insulin resistance (HOMA-IR); lipid profile including the triglyceride to high-density lipoprotein cholesterol (TG/HDL) ratio; thyroid-stimulating hormone (TSH), free thyroxine (free T4), free triiodothyronine (free T3), anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin antibodies; C-reactive protein (CRP), uric acid, albumin; body mass index (BMI), waist circumference, blood pressure; dual-energy X-ray absorptiometry (DXA) when clinically indicated.

Functional assessment: cervical and ocular VEMP; Dix-Hallpike, supine roll, and straight head-hanging tests for full canal-involvement mapping (posterior, lateral and anterior canals).

The rationale for including vestibular evoked myogenic potentials (VEMPs) needs stating, since their relationship to BPPV is indirect. They are proposed here as markers of otolith-organ vulnerability: cervical and ocular VEMPs index saccular and utricular pathway function and can disclose subclinical macular dysfunction in patients who are asymptomatic between episodes. They are not offered as diagnostic tests for BPPV, which remains a diagnosis made from positional nystagmus, nor as validated predictors of recurrence, for which no such marker yet exists. Their purpose in this framework is narrower and falsifiable: to establish whether the proposed metabolic phenotype is accompanied by measurable otolith-organ impairment between attacks. If the model is correct, recurrent patients carrying the metabolic burden should show poorer interictal otolith function than recurrent patients without it.

Research biomarkers (where available): serum otolin-1 and OC90.

Characterizing patients metabolically at the index episode and again at recurrence is the logical next step. Published cohorts describe recurrence rates and multicanal involvement in detail, but none

reports systematic metabolic phenotyping at the index episode [4,5,65]; it is that omission, rather than any positive finding, which defines the opportunity.

8. Clinical Implications

Canalith repositioning remains the first-line treatment for benign paroxysmal positional vertigo, and nothing proposed here alters that. Metabolic assessment is an adjunctive strategy directed at recurrence, appropriate only where clinically indicated — that is, in patients meeting the phenotype defined in Section 2: recurrent idiopathic disease, particularly when bilateral or multicanal, in postmenopausal women, older patients, or those with established metabolic disease. A broad metabolic panel is not indicated for BPPV in general, and still less after a single episode.

Within that group the available tests fall into three tiers, which should not be conflated. First, supported by direct evidence in BPPV: serum 25-hydroxyvitamin D, with repletion where deficient, this being the only metabolic intervention so far tested in a randomized trial and upheld in meta-analysis [34,35]. Second, justified by general medical comorbidity assessment rather than by BPPV-specific evidence: bone-metabolism assessment and densitometry where otherwise indicated [38], fasting glucose and glycated hemoglobin [54,55], thyroid function and autoimmunity in the appropriate clinical context [55,60], and cardiovascular risk profiling [56]. These are worth doing because they constitute good general medicine in the patients concerned, not because correcting them has been shown to prevent BPPV. Third, proposed for research only: serum otolin-1 and otoconin-90, vestibular evoked myogenic potentials, and magnesium and vitamin K2 status (Section 4.8), none of which has established clinical utility in this disease.

Repositioning maneuvers remain the primary, evidence-based treatment for the episode itself. Metabolic correction is proposed only as an adjunct aimed at long-term recurrence — not as a substitute for resolving acute vertigo.

9. Limitations

Most metabolic associations with BPPV are observational, and causality is unproven for the majority of the proposed pathways. They are, moreover, mutually confounded: age, sex, menopausal status and adiposity are common causes both of the disease and of most of the exposures, and few studies adjust adequately for them (Section 4.9). Publication bias is likely to have inflated some of the associations on which this synthesis draws, since negative metabolic findings in BPPV are unlikely to reach print.

Several links in the mechanistic chain rest on animal or in vitro work with no human equivalent — the estrogen-withdrawal, endolymph-calcium and vitamin D receptor data in particular — and their extrapolation to human disease is an assumption rather than a finding. The integrity of the human utricular gel and the in vivo expression of otoconial matrix proteins cannot currently be measured outside research settings, and endolymph composition cannot be sampled directly in living patients under ordinary clinical conditions, so the central claim of the model is not at present directly testable in humans. Otolin-1 remains without a validated assay or an established clinical threshold, and its specificity for matrix degeneration is unproven.

The proposed phenotype is expressly a subset of idiopathic recurrent disease: the model does not apply to post-traumatic, post-surgical, post-neuritis or migraine-associated positional vertigo, and it does not hold that every recurrent idiopathic case is metabolically driven. Many will remain stochastic, or simply age-related, with no identifiable systemic contribution.

Finally, there is a risk in the proposal itself. To frame a common, treatable and mechanically resolvable condition as a marker of systemic metabolic fragility invites over-investigation and over-medicalization — further tests, incidental findings and avoidable anxiety — in patients whose vertigo would be

resolved by a repositioning maneuver. Until the predictions set out in Section 6 have been tested prospectively, the evaluation proposed here should remain narrow, confined to the defined phenotype, and secondary to treating the episode.

10. Conclusions

The mechanical model of BPPV is correct and clinically indispensable; it simply does not, by itself, explain why otoconia come loose in some patients, why recurrence is so common, or why the disease keeps company with systemic metabolic disorders. We propose that, in a biologically distinct subgroup, recurrent idiopathic BPPV is the mechanical expression of a systemic metabolic fragility of the otoconia–otolithic membrane–endolymph unit, and that the familiar associations — vitamin D deficiency, estrogen withdrawal, insulin resistance, oxidative stress, thyroid autoimmunity — are not so many independent risks but convergent routes into one shared vulnerability: a less resilient otoconial matrix and otolithic membrane. The model invokes no new biology; it asks only that established metabolic pathways, known otoconial biology, and existing clinical associations be read together rather than apart. The next step is prospective validation through accessible metabolic phenotyping in well-characterized cohorts. The claim is deliberately bounded: it concerns a subgroup, not the disease as a whole, and it complements the mechanical account rather than competing with it. Whether that subgroup is real, and how large it is, are empirical questions that the predictions above are designed to settle.

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Author Contributions

P.S.-G.: conceptualization, literature search and synthesis, writing — original draft, writing — review and editing.

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References

1. Kao WTK, Parnes LS, Chole RA. Otoconia and otolithic membrane fragments within the posterior semicircular canal in benign paroxysmal positional vertigo. *Laryngoscope*. 2017;127(3):709–714.

2. Hornibrook J. Benign paroxysmal positional vertigo (BPPV): history, pathophysiology, office treatment and future directions. *Int J Otolaryngol.* 2011;2011:835671.
3. von Brevern M, Bertholon P, Brandt T, Fife T, Imai T, Nuti D, et al. Benign paroxysmal positional vertigo: diagnostic criteria. *J Vestib Res.* 2015;25(3-4):105–117.
4. Sfakianaki I, Binos P, Karkos P, Dimas GG, Psillas G. Risk factors for recurrence of benign paroxysmal positional vertigo. A clinical review. *J Clin Med.* 2021;10(19):4372.
5. Alolayet H, Murdin L. Benign paroxysmal positional vertigo a systematic review of the effects of comorbidities. *Front Neurol.* 2025;16:1595693.
6. Liu J, Liu J, Dai Y, He F, Zhai H. Research progress on risk factors of recurrence of benign paroxysmal positional vertigo. *Front Neurol.* 2026;16:1735898.
7. Choi EH, Park JH, Kwon H, Jung I, Kim HJ, Choi JY, et al. Otolith deterioration: factors affecting microvascular and structural integrity. *J Clin Neurol.* 2026;22(1):89–101.
8. Mirza M, McClure HM, Parham K. Hyperparathyroidism and dizziness: an epidemiological assessment. *OTO Open.* 2026;10(1):e70209.
9. Lundberg YW, Xu Y, Thiessen KD, Kramer KL. Mechanisms of otoconia and otolith development. *Dev Dyn.* 2015;244(3):239–253.
10. Zhao X, Yang H, Yamoah EN, Lundberg YW. Gene targeting reveals the role of Oc90 as the essential organizer of the otoconial organic matrix. *Dev Biol.* 2007;304(2):508–524.
11. Andrade LR, Lins U, Farina M, Kachar B, Thalmann R. Immunogold TEM of otoconin 90 and otolin — relevance to mineralization of otoconia, and pathogenesis of benign positional vertigo. *Hear Res.* 2012;292(1-2):14–25.
12. Lu W, Zhou D, Freeman JJ, Thalmann I, Ornitz DM, Thalmann R. In vitro effects of recombinant otoconin 90 upon calcite crystal growth: significance of tertiary structure. *Hear Res.* 2010;268(1-2):172–183.
13. Deans MR, Peterson JM, Wong GW. Mammalian otolin: a multimeric glycoprotein specific to the inner ear that interacts with otoconial matrix protein otoconin-90 and cerebellin-1. *PLoS One.* 2010;5(9):e12765.
14. Yang H, Zhao X, Xu Y, Wang L, He Q, Lundberg YW. Matrix recruitment and calcium sequestration for spatial specific otoconia development. *PLoS One.* 2011;6(5):e20498.
15. Moreland KT, Hong M, Lu W, Rowley CW, Ornitz DM, De Yoreo JJ, et al. In vitro calcite crystal morphology is modulated by otoconial proteins otolin-1 and otoconin-90. *PLoS One.* 2014;9(4):e95333.
16. Bielak K, Benkowska-Biernacka D, Ptak M, Stolarski J, Kalka M, Ozyhar A, et al. Otolin-1, an otolith- and otoconia-related protein, controls calcium carbonate bioinspired mineralization. *Biochim Biophys Acta Gen Subj.* 2023;1867(5):130327.
17. Kniep R, Zahn D, Wulfes J, Walther LE. The sense of balance in humans: structural features of otoconia and their response to linear acceleration. *PLoS One.* 2017;12(4):e0175769.
18. Lindeman HH. Studies on the morphology of the sensory regions of the vestibular apparatus. *Ergeb Anat Entwicklunsgesch.* 1969;42(1):1–113.
19. Murayama E, Herbomel P, Kawakami A, Takeda H, Nagasawa H. Otolith matrix proteins OMP-1 and Otolin-1 are necessary for normal otolith growth and their correct anchoring onto the sensory maculae. *Mech Dev.* 2005;122(6):791–803.
20. Walther LE, Wenzel A, Buder J, Bloching MB, Kniep R, Blödown A. Detection of human utricular otoconia degeneration in vital specimen and implications for benign paroxysmal positional vertigo. *Eur Arch Otorhinolaryngol.* 2014;271(12):3133–3138.
21. Ross MD, Peacor D, Johnsson LG, Allard LF. Observations on normal and degenerating human otoconia. *Ann Otol Rhinol Laryngol.* 1976;85(3):310–326.
22. Walther LE, Blödown A, Buder J, Kniep R. Principles of calcite dissolution in human and artificial otoconia. *PLoS One.* 2014;9(7):e102516.
23. Boyle R, Varelas J. Otoconia structure after short- and long-duration exposure to altered gravity. *J Assoc Res Otolaryngol.* 2021;22(5):509–525.
24. Thalmann R, Ignatova E, Kachar B, Ornitz DM, Thalmann I. Development and maintenance of otoconia: biochemical considerations. *Ann N Y Acad Sci.* 2001;942(1):162–178.
25. Xu Y, Zhang Y, Lopez IA, Hilbers J, Griswold AJ, Ishiyama A, et al. Identification of a genetic variant underlying familial cases of recurrent benign paroxysmal positional vertigo. *PLoS One.* 2021;16(5):e0251386.
26. Wood JD, Muchinsky SJ, Filoteo AG, Penniston JT, Tempel BL. Low endolymph calcium concentrations in deafwaddler2J mice suggest that PMCA2 contributes to endolymph calcium maintenance. *J Assoc Res Otolaryngol.* 2004;5(2):99–110.

27. Bächinger D, Egli H, Goosmann MM, Monge Naldi A, Eckhard AH. Immunolocalization of calcium sensing and transport proteins in the murine endolymphatic sac indicates calciostatic functions within the inner ear. *Cell Tissue Res.* 2019;378(2):163–173.
28. Yamauchi D, Nakaya K, Raveendran NN, Harbidge DG, Singh R, Wangemann P, et al. Expression of epithelial calcium transport system in rat cochlea and vestibular labyrinth. *BMC Physiol.* 2010;10:1.
29. Nakaya K, Harbidge DG, Wangemann P, Schultz BD, Green ED, Wall SM, et al. Lack of pendrin HCO_3^- transport elevates vestibular endolymphatic $[\text{Ca}^{2+}]$ by inhibition of acid-sensitive TRPV5 and TRPV6 channels. *Am J Physiol Renal Physiol.* 2007;292(5):F1314–F1321.
30. Zucca G, Valli S, Valli P, Perin P, Mira E. Why do benign paroxysmal positional vertigo episodes recover spontaneously? *J Vestib Res.* 1998;8(4):325–329.
31. Ikeda K, Kusakari J, Takasaka T, Saito Y. Early effects of acetazolamide on anionic activities of the guinea pig endolymph: evidence for active function of carbonic anhydrase in the cochlea. *Hear Res.* 1987;31(3):211–216.
32. Han DG. A minimal ion–chemistry model for predicting benign paroxysmal positional vertigo risk based on endolymphatic calcium and pH. *Front Neurol.* 2025;16:1690931.
33. Büki B, Ecker M, Jünger H, Lundberg YW. Vitamin D deficiency and benign paroxysmal positioning vertigo. *Med Hypotheses.* 2013;80(2):201–204.
34. Jeong SH, Kim JS, Kim HJ, Choi JY, Koo JW, Choi KD, et al. Prevention of benign paroxysmal positional vertigo with vitamin D supplementation: a randomized trial. *Neurology.* 2020;95(9):e1117–e1125.
35. Li Y, Gao P, Ding R, Xu Y, Wang Z, Pei X, et al. Association between vitamin D, vitamin D supplementation and benign paroxysmal positional vertigo: a systematic review and meta-analysis. *Front Neurol.* 2025;16:1560616.
36. AlGarni MA, Mirza AA, Althobaiti AA, Al-Nemari HH, Bakhsh LS. Association of benign paroxysmal positional vertigo with vitamin D deficiency: a systematic review and meta-analysis. *Eur Arch Otorhinolaryngol.* 2018;275(11):2705–2711.
37. Minasyan A, Keisala T, Zou J, Zhang Y, Toppila E, Syväla H, et al. Vestibular dysfunction in vitamin D receptor mutant mice. *J Steroid Biochem Mol Biol.* 2009;114(3-5):161–166.
38. Kim CH, Kim K, Choi Y. Do patients with benign paroxysmal positional vertigo have a higher prevalence of osteoporosis? A systematic review and meta-analysis. *J Pers Med.* 2024;14(3):303.
39. Ogun OA, Büki B, Cohn ES, Janky KL, Lundberg YW. Menopause and benign paroxysmal positional vertigo. *Menopause.* 2014;21(8):886–889.
40. Vibert D, Kompis M, Häusler R. Benign paroxysmal positional vertigo in older women may be related to osteoporosis and osteopenia. *Ann Otol Rhinol Laryngol.* 2003;112(10):885–889.
41. Jeong SH, Choi SH, Kim JY, Koo JW, Kim HJ, Kim JS. Osteopenia and osteoporosis in idiopathic benign positional vertigo. *Neurology.* 2009;72(12):1069–1076.
42. He LL, Li XY, Hou MM, Li XQ. Association between bone mineral density and benign paroxysmal positional vertigo: a meta-analysis. *Eur Arch Otorhinolaryngol.* 2019;276(6):1561–1571.
43. Parham K. Benign paroxysmal positional vertigo: an integrated perspective. *Adv Otolaryngol.* 2014;2014:792635.
44. Yang L, Xu Y, Zhang Y, Vijayakumar S, Jones SM, Lundberg YW. Mechanism underlying the effects of estrogen deficiency on otoconia. *J Assoc Res Otolaryngol.* 2018;19(4):353–362.
45. Nakata T, Okada M, Nishihara E, Ikeda A, Asoh S, Takagi T, et al. Effect of hormonal therapy on the otoconial changes caused by estrogen deficiency. *Sci Rep.* 2022;12:22596.
46. Guerra J, Devesa J. Causes and treatment of idiopathic benign paroxysmal positional vertigo based on endocrinological and other metabolic factors. *J Otol.* 2020;15(4):155–160.
47. Libonati GA, Leone A, Martellucci S, Gallo A, Albera R, Lucisano S, et al. Prevention of recurrent benign paroxysmal positional vertigo: the role of combined supplementation with vitamin D and antioxidants. *Audiol Res.* 2022;12(4):445–456.
48. Parham K, Sacks D, Bixby C, Fall P. Inner ear protein as a biomarker in circulation? *Otolaryngol Head Neck Surg.* 2014;151(6):1038–1040.
49. Tabtabai R, Haynes L, Kuchel GA, Parham K. Age-related increase in blood levels of otolin-1 in humans. *Otol Neurotol.* 2017;38(6):865–869.
50. Parham K, Kuchel GA, McElhaney JE, Haynes L. A relationship between blood levels of otolin-1 and vitamin D. *Otol Neurotol.* 2018;39(4):e269–e273.
51. Liu X, Han K, Zhou M, Wu Y. Association between otolin-1 and benign paroxysmal positional vertigo: a meta-analysis. *Front Neurol.* 2022;13:950023.
52. Fan Z, Hu Z, Han W, Lu X, Liu X, Zhou M, et al. High serum levels of otolin-1 in patients with benign paroxysmal positional vertigo predict recurrence. *Front Neurol.* 2022;13:841677.

53. Aygün D, Dumur S, Elgörmüş MN, Alpaslan MS, Uzun H. Serum otoconin-90 and otolin-1 concentrations in benign paroxysmal positional vertigo. *Biomolecules*. 2024;14(10):1279.
54. Webster G, Sens PM, Salmito MC, Cavalcante JDR, dos Santos PRB, da Silva AL, et al. Hyperinsulinemia and hyperglycemia: risk factors for recurrence of benign paroxysmal positional vertigo. *Braz J Otorhinolaryngol*. 2015;81(4):347–351.
55. Arabian R, Vintimilla A. Exploring the association between BPPV, hypothyroidism, and metabolic comorbidities: a retrospective case-control study. *J Multimorb Comorb*. 2025;15:26335565251371254.
56. Hui J, Zi D, Liang L, Ren X. Transcriptomic analysis reveals cross-talk genes between type 2 diabetes and recurrent benign paroxysmal positional vertigo. *Heliyon*. 2024;10(15):e35209.
57. Günizi H, Savaş HB. An evaluation of trace elements and oxidative stress in patients with benign paroxysmal positional vertigo. *PLoS One*. 2023;18(2):e0277960.
58. Ozdemir O, Aral H, Ruzgar H, Arslan HF, Yigit O. Investigating the role of oxidative stress in benign paroxysmal positional vertigo with spot urine. *Med Bull Sisli Etfal Hosp*. 2023;57(1):54–60.
59. Xie KH, Liu LL, Su CY, Huang XF, Wu BX, Liu RN, et al. Low antioxidant status of serum uric acid, bilirubin, albumin, and creatinine in patients with benign paroxysmal positional vertigo. *Front Neurol*. 2020;11:601695.
60. Tricarico L, Di Cesare T, Galli J, Fetoni AR, Paludetti G, Picciotti PM. Benign paroxysmal positional vertigo: is hypothyroidism a risk factor for recurrence? *Acta Otorhinolaryngol Ital*. 2022;42(5):465–470.
61. Kämpfe Nordström C, Danckwardt-Lillieström N, Laurell G, Liu W, Rask-Andersen H. The human endolymphatic sac and inner ear immunity: macrophage interaction and molecular expression. *Front Immunol*. 2019;9:3181.
62. Modugno GC, Pirodda A, Ferri GG, Montana T, Rasciti L, Ceroni AR. A relationship between autoimmune thyroiditis and benign paroxysmal positional vertigo? *Med Hypotheses*. 2000;54(4):614–615.
63. Papi G, Guidetti G, Corsello SM, Di Donato C, Pontecorvi A. The association between benign paroxysmal positional vertigo and autoimmune chronic thyroiditis is not related to thyroid status. *Thyroid*. 2010;20(2):237–238.
64. Mijovic T, Zeitouni A, Colmegna I. Autoimmune sensorineural hearing loss: the otology–rheumatology interface. *Rheumatology (Oxford)*. 2013;52(5):780–789.
65. Teggi R, Guidetti R, Gatti O, et al. Recurrence of benign paroxysmal positional vertigo: our experience in 3042 patients. *Acta Otorhinolaryngol Ital*. 2021;41(6):461–466.
66. Maresz K. Proper calcium use: vitamin K2 as a promoter of bone and cardiovascular health. *Integr Med (Encinitas)*. 2015;14(1):34–39.
67. Uwitonze AM, Razzaque MS. Role of magnesium in vitamin D activation and function. *J Am Osteopath Assoc*. 2018;118(3):181–189.
68. Aydın E, Babakurban ST, Ozgirgin ON, Özlüoğlu LN. The relationship of homocysteine, vitamin B12, folic acid levels with vertigo. *Kulak Burun Bogaz Ihtis Derg*. 2012;22(4):214–218.