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OTOPATHOLOGY REPORT

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Meniere's disease: Structural considerations in early cochlea hydrops

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Abstract

Objective: Structural features of the human cochlea may control early lesion formation in endolymphatic hydrops. This process may hinge on three structural features: the flattened spiral shape of the human cochlea, the toroidal configuration of the distended cochlea duct, and the distensibility characteristics of Reissner's membrane. An analytical method is presented to assess the variation in hydropic distention that may occur in the several turns of the cochlea due to these structural features.

Methods: A normal human cochlea is used to illustrate the method of analysis. Structural dimensions were taken from a mid-modiolar section. Reissner's membrane was projected to assume a spiral toroid shape as it distends. Peak membrane stress proclivities in each cochlea turn were calculated analytically. Membrane strain was assessed from a collagen model of Reissner's membrane. Sagittal membrane displacements were quantified geometrically.

Results: Stress levels in Reissner's membrane were projected to be the lowest in the lower basal turn and to increase progressively to a peak value in the apex. Strain in Reissner's membrane in the apical turn was projected to be substantially higher than in the lower turns. Sagittal displacement of Reissner's membrane was projected to be most pronounced in the apical turn in all the stages of early cochlea hydrops.

Conclusion: Structural features appear to underlie a differential susceptibility to hydrops in the human cochlea. The flattened spiral shape of the human cochlea coupled with the anticlastic configuration and the distensile characteristics of Reissner's membrane are projected to result in distinct histological stages as hydropic disease in the cochlea progresses.

KEYWORDS
apical hydrops, low frequency hearing loss, Meniere's disease

1 | INTRODUCTION

Meniere's disease (MD) has been described as first causing a hearing loss, later followed by attacks of vestibular symptoms.[1] Endolymphatic hydrops has been identified as the pathology underlying MD.[2] Such hydrops affects the cochlea first, extends to the saccule, and then involves the utricle, ampullae, and semicircular canals in that order.[3] This distribution has been ascribed to generally higher membrane stress

levels in the cochlea, overall with progressively lower membrane stress across the labyrinth following an anatomic sequence from cochlea to canals.[4] Although the progression of disease across the labyrinth from cochlea to canals has been correlated with parallel increases in membrane stress levels, the mechanics of disease progression within the cochlea has not been elucidated. A recent imaging study has found that the pattern of hydrops progression in vivo is from the apex to base.[5] This raises the question as to how structural features in the cochlea might be responsible for this pattern.

A stress variation may exist within the cochlea that affects Reissner's membrane (RM) differentially in the several turns. This process may hinge on three structural features: the flattened spiral shape of the human cochlea, the toroidal configuration assumed by a dilated RM within the cochlea, and the nonlinear distensibility characteristics of RM. The flattened spiral shape of the human cochlea stems from its increasing coil radius from the apex to base, as shown in Figure 1. And given the toroidal shape assumed by RM in each coil as it distends, this radial variation from the base to apex increases the degree of anticlastic shape of RM along the innermost portion of each coil. In turn, the degree of anticlastic shape controls the level of associated membrane stress[4] and consequent differential distention of RM. Such differential distention implies a variable degree of membrane hydropic displacement in each coil. This study seeks to quantify these factors and their potential hydropic effects on RM in the several coils of the human cochlea.

2 | METHODS

A normal human cochlea was selected to illustrate this structural analysis. This mid-modiolus cochlea section was selected at random for the sole purpose of illustrating the methodology illustrated in this study. Its shape appears consistent with the normally flattened cochlea structure typical of humans.[6] Analysis of morphological variation in normal and hydropic human cochleae is beyond the scope of the current study. The mid-modiolus external radius 'R' of each cochlea duct coil was measured from the modiolus center line to the point on the osseous spiral lamina where RM is attached, as shown in Figure 1. The scale bar permitted determination of actual physical values in these measurements. RM was assumed to have a hemi-cylindrical configuration which can be modeled as a toroid as depicted in Figure 2. In such a configuration, the internal radius 'r' of the distended RM assumes a value of one half of RM's normal width in each turn which was measured from the mid-modiolus cochlea section shown in Figure 1.

The evaluation of peak tensile stress in the medial wall of the distended RM in the several coils of the cochlea is based on an analytical formulation of stress in a membrane of toroid shape[4] shown in Equation 1. This equation shows that for constant values of (r/w) and (P),

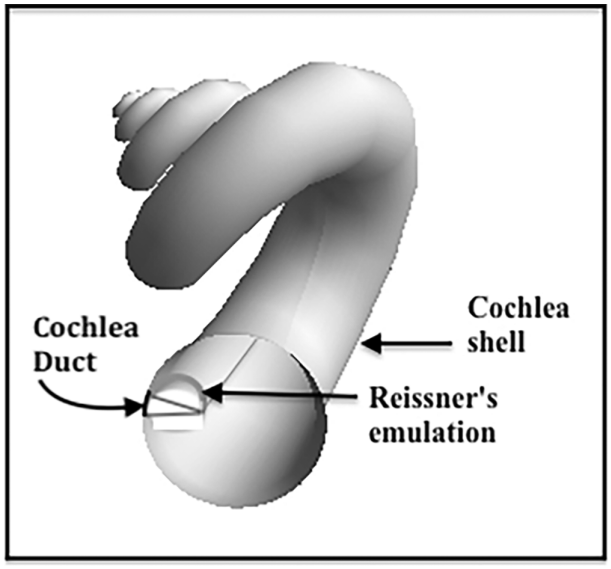

FIGURE 2 Cochlea duct with a hemi-cylindrical Reissner's membrane distended medially toward the cochlea modiolus.

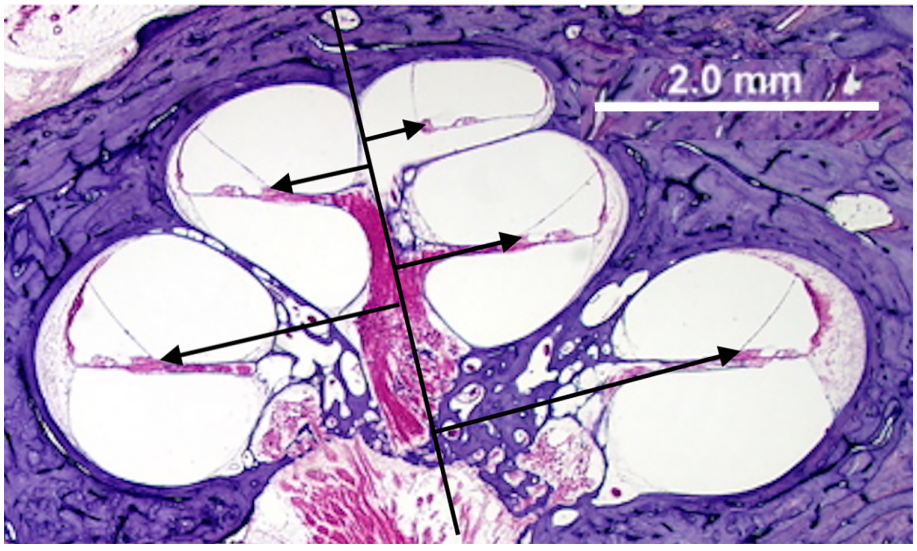

FIGURE 1 The human cochlea exhibits a flattened spiral shape with an increasing cochlea duct radius in each turn from the apex to base. The arrows indicate the radial distance of the medial boundary of Reissner's membrane from the modiolus center line.

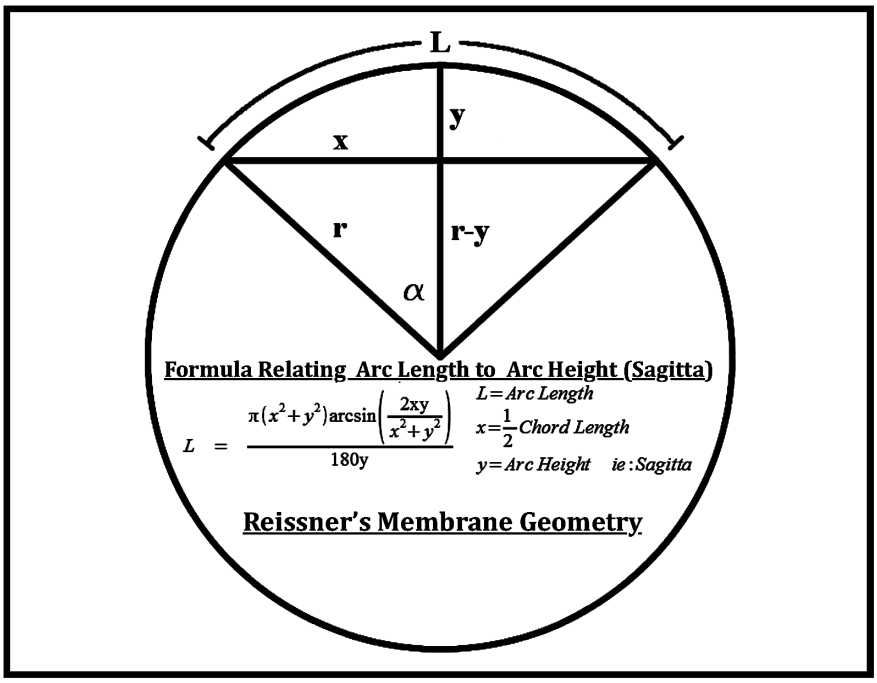

FIGURE 3 Figure and formulation for assessing the distention and displacement of Reissner's membrane based on circle sector analysis.

the relative magnitude of hoop stress among the several coils is dependent on the geometric shape factor (GSF) in curly brackets. Evaluation of this GSF for each turn provides a measure of the peak stress that occurs along the innermost margin of each toroid coil due to its maximal anticlastic shape at this location.

$$t_{\text{hoop max}} = \{½(2 - r/R)/(1 - r/R)\}(r/w)(p) = GSF^{*}(r/w)(P) \quad (1)$$

where 't'$_{\text{hoop max}}$ represents peak hoop stress in the inner wall of the toroid.

'r' denotes the internal radius of RM.
'R' denotes the external radius of RM.
'w' indicates wall thickness of RM.
'P' represents transmural pressure.
'GSF' represents a geometric stress factor {½ (2 – r/ R) / (1 – r/ R)}.

whose value depends on the relative dimensions of the structure.

To determine RM strain, the distensibility characteristics of a previously reported collagen model of RM were utilized[7] were used to emulate the nonlinear distensile characteristics of human RM. Graded stress levels are assigned to each turn based on calculated GSF values. The resultant strain values in the model membrane will be found to fall into one of the three distinct zones: an initial viscoelastic zone, a transitional elastoplastic zone, and terminal plastic zone. Strains in the viscoelastic zone are potentially reversible, strains in the plastic zone are irreversible, whereas strains in the elastoplastic zone may be fully or partially reversible.

Sagittal displacement values corresponding to the various degrees of RM distention in all turns were then evaluated geometrically. This was based on circle sector analysis as illustrated in Figure 3. This figure gives the analytical function that relates arc length 'L' (the distended length of RM) to arc height 'y' (the sagittal displacement of RM from its normal position). Because this formula cannot be readily solved for 'y', an online calculator can be used to quantify the relationship between RM arc distention 'L' and arc displacement 'y' relative to a nondisplaced unit value of RM width 'x'.[8]

3 | RESULTS

Table 1 presents a composite of all radial measurements, computed radial ratios, and calculated GSF values in the sample cochlea, corresponding values for stress and strain taken from the collagen model of RM, and values for sagittal displacement of RM derived from circle sector analysis.

The external radial dimension 'R' of each turn in the model human cochlea was found to be fivefold higher in the base than in the apex. The tight winding of the apical turn around the modiolus indicated by its minimal external radial value ('R' = 0.44), coupled with the greater breadth of RM in the apical turn indicated by the higher internal radius ('r' = 0.40) accounts for the clear disparity in GSF in the apical turn (GSF 6.05) compared with the lower turns (GSF 1.09–1.46). This indicates that tensile stress in the apical turn is projected to be several times higher than the stresses in all the lower turns.

The corresponding RM strain values were obtained graphically as shown in Figure 4. Stress levels were utilized that correspond to the computed GSF values. Stress in the apical turn (6.1) has a corresponding strain of 1.55 which is in the plastic zone and irreversible. Stresses and strains in middle and lower turns all clustered at the low end of the curve in the elastic, potentially reversible zone.

Figure 5 shows that computed sagittal displacement of RM is most pronounced in the cochlea apex (0.50), with lesser displacements in the

TABLE 1 Structural determinants of hydrops in a model human cochlea.

Model cochlea turn	Int radius 'r' in mm	Ext Radius 'R' in mm	Ratio 'r/R' mm/mm	Shape factor 'GSF'	Applied RM stress 'KPa'	Associated RM strain Re: L_o	Resultant RM sagitta Re:RM_o
Apical	0.40	0.44	0.91	6.05	6.1	1.57	0.50
Upper Middle	0.34	0.72	0.48	1.46	1.5	1.22	0.30
Lower Middle	0.35	0.93	0.37	1.29	1.3	1.21	0.29
Upper Basal	0.35	1.74	0.20	1.13	1.2	1.20	0.28
Lower Basal	0.33	2.23	0.15	1.09	1.1	1.19	0.27

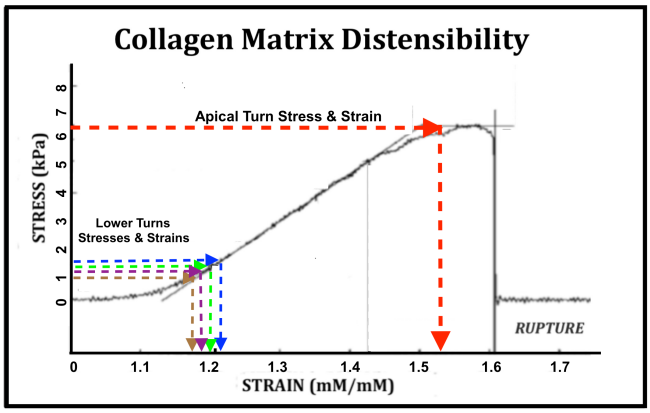

FIGURE 4 Relative stress and strain values in a collagen model of Reissner's membrane.

middle turns (0.30 and 0.29), and with lowest displacements in the basal turns (0.28 and 0.27). These smaller displacements in the middle and lower turns correspond to elastic RM distensions that may be reversible in premortem and thus may only be radiographically detectable in vivo.

4 | DISCUSSION

4.1 | Summary of results

The external radius of the cochlea duct in each of the several turns of the illustrative cochlea model progressively increases from the apex to base, with the measured basal turn radius fivefold that of the apex. This results in tensile stress in RM projected to be the greatest in the apical turn of the cochlea and least in the lower basal turn based on an analytical formulation. The associated strain values for RM progressively decline from the apex to base. The sagittal displacement of RM in the apical turn was projected to be always greater than that in the lower turns in all stages of early cochlea hydrops.

4.2 | Analysis of results

Sagittal displacement of RM in the apical turn of the cochlea is projected to be an early and prominent finding in endolymphatic hydrops. This is attributed to high membrane stress and strain related to the tight coiling at the cochlea apex. Such tight coiling in the human cochlea apex is exceeded only by that in the cow and the elephant, whereas multiple other mammalian species have looser coiling.[9] This feature might offer some insight into the particularly human susceptibility to MD. It is not known whether cows and elephants suffer from a similar affliction due to their cochlea anatomy.

Heightened susceptibility to tensile stress in the cochlea apex appears to be due to the maximal anticlastic shape of RM at the location. This can be understood from an examination of Equation 1 that describes the toroidal model used to emulate a distended RM. In this equation, when the external radius of the coil 'R' becomes smaller and approaches the limiting value of the internal radius 'r', the torus is more tightly wound, and the value of the curly bracket term rises without limit, and stress mounts in parallel. In contrast, as the value for external radius 'R' increases toward the lower basal turn, the torus effectively becomes more cylindrical and the curly bracket term approaches a limiting value of 1.0, the value associated with a cylinder.

In this structural assessment, a gradual endolymph volume increase will be associated with a slowly rising quasi-static pressure in the cochlea duct. This transmural pressure will be applied to the entire undersurface of RM. Lowly stressed, loosely coiled areas at the cochlea base will distend less, whereas more highly stressed tightly coiled areas at the apex will distend more until the total volume increment has been accommodated. The initial volume increment will be preferentially accommodated in the apical turn until the increasingly stiff portion of the RM load/deformation curve (shown in Figure 4) forces the next volume increment to be accommodated by the next most stressed area. Because the cochlea duct is continuous from the apex to base, this means that initial distention in the apex will eventually spread downward to the immediately adjacent area of RM. This volume displacement of RM will gradually move down the cochlea duct from the apex to base as each dilated turn stiffens. This process is analogous to the way a cylindrical balloon progressively inflates: most of the initial inflation taking place in the most susceptible region, which upon reaching its distensibility limit, shifts inflation to the more distensible region that is immediately adjacent.

Depending on the degree of endolymph volume increase and the attendant transmural pressure in the cochlea duct, a continuous gradation of hydrops may occur. Mild hydropic displacements would be limited to elastic distention in all turns in the early stages of MD. Such reversible displacements of RM in vivo would not be in evident in the postmortem histology. Additional incremental hydropic displacement

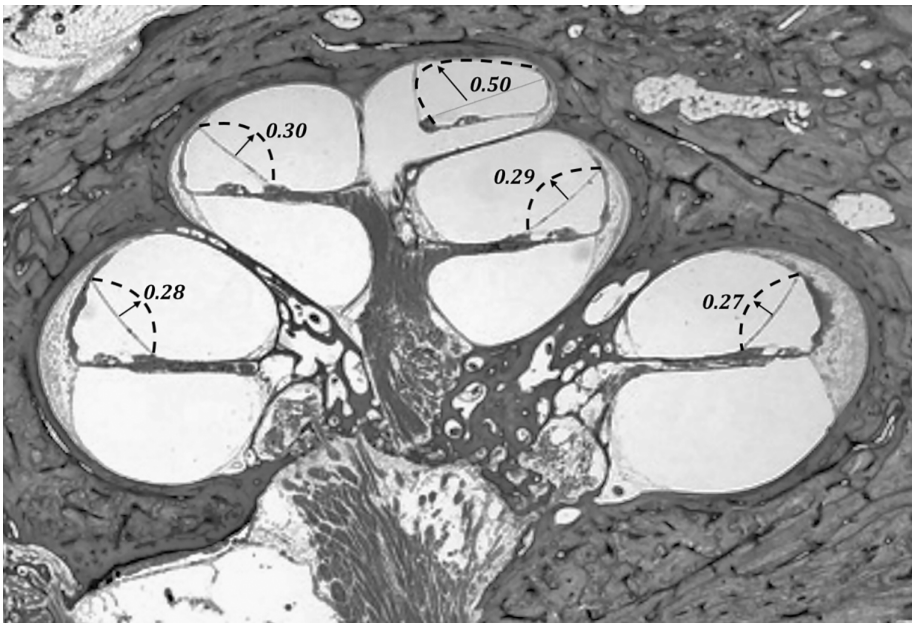

FIGURE 5 Same model cochlea as shown in Figure 1 with projected relative degrees of endolymphatic hydrops in vivo. The low hydropic displacements of RM in the middle and lower turns are potentially elastic and reversible in vivo and would not be evident in the postmortem histology, whereas the plastic distention in the apical turn would persist in the histology as isolated apical hydrops. The numerical values illustrated for peak RM displacement are calculated values relative to the length of RM in its non-displaced position and are not to scale.

would involve a larger plastic distention in the apical turn that would be identifiable in the histology accompanied by elastic distention in the middle and lower turns that are reversible in vivo and therefore not evident in the histology. Further hydropic displacements would involve larger plastic deformations of RM that involve more than the apical turn, extending at least to the middle turn and possibly the basal turn. These lesions would be permanent and evident in the final histology.

4.3 | Limitations of results

In this projection of early cochlea hydrops, disease progression is assumed to be slow, gradual, and continuous. This implies that there is no abrupt membrane rupture in any turn and that elastic distention progresses to plastic distention of RM as seen in Guinea pigs.[10] All dimensions used for computation are based on a typical normal human cochlea used for the purpose of illustrating the analytical methodology. Given that the histological plane of section can vary somewhat from specimen to specimen, the measured values in the model are thought to be typical but should be considered approximate. This model study also assumes a constant value for the cochlea duct internal radius 'r' in the toroidal model. However, this radial value clearly changes as RM distends. Its value is indeterminate at the extremes and thus for heuristic purposes has been set at its nadir value of one half the initial length of RM [0.5 RM_O]. This nadir value is associated with a hemi-circular shape for RM as shown in Figure 2.

This analysis also assumes a uniform isotropic distensibility for RM basement membrane. However, anisotropic distensibility could arise from a number of factors. First, were there a deficiency in any critical component such as nidogen, perlecan, or other unidentified structural molecules, there might be a loss of normal mechanical strength.[11] Second, gene alterations, as seen in Alport's syndrome, might cause structural malformation in the basement membrane itself in the form of Type IV collagen mutations and collagen isomer substitutions.[12] Third, antibodies might target the structures within the basement membrane, as seen in Goodpasture's syndrome.[13] Fourth, the basement membrane itself might also be the target of immune processes such as those occurs in pemphigoid.[14] Any of these aberrations could potentially weaken RM nonuniformly and result in a hydropic pattern that departs from this study's projections.

This static analysis does not attempt to address the impact of dynamic effects due to high strain rates, as might be induced with abrupt changes in transmural pressure. Rather, it uses data available from a collagen model of RM strained at a steady rate that exemplifies the sigmoid viscoelastic deformation behavior typical of collagen polymers.[15]

In consequence of the assumptions in this analysis, the projected findings must be considered approximate and tentative. They may be refined further when more detailed information is available on the actual stress–strain characteristics of human RM. However, these projections do provide preliminary insight into how the structural features of the human cochlea spiral can contribute to its differential susceptibility to early endolymphatic hydrops.

4.4 | Comparison with published data

Considering RM as cone shaped has been previously suggested.[16] This is reasonable when RM has a normal flat configuration. However, as soon as the hydropic process starts, RM takes on a convex displacement for which a cone shape no longer applies. Rather, such convex displacement of RM would result in a curvature toward the apex that is more consistent with the toroidal shape utilized herein.

Results of human studies of hydrops are generally supportive of the current findings. An analytical study affirmed a progressive spread

of hydropic lesions across the entire human labyrinth based on membrane stress proclivities.[17] A histological study found that long established cochlea hydrops in humans most frequently involved the cochlea apex, with less frequent involvement in the lower turns.[18] Any exceptions to the apex to base pattern may have been due to focal membrane irregularities in RM strength. An imaging study in human cases of MD reported that hydrops was found to start in the upper turns of the cochlea, only later involving the lower turns.[5]

Results in Guinea pig studies of hydrops provide additional but qualified support for the model findings. This is because the Guinea pig cochlea with 4.5 turns is taller and more cylindrical in profile. However, its apical turn is closer to the modiolus than the remaining 4 turns where the differential increase in modiolus radius is far less pronounced than that found in the human cochlea. It should be pointed out that other laboratory animals share this cochlea dissimilarity. Gray points out that carnivora and rodents have a pointed type of cochlea, whereas primates have a cochlea of the flat type.[6] This means that Guinea pigs as well as mice, rats, chinchilla, and cats all have pointed cochleae that are dissimilar to the flattened structure of the human cochlea. The cochlea coiling in such laboratory animals is not as tight as that of the human.[9] Such animal cochleae would therefore be suboptimal as models of human cochlea structure.

Nevertheless, acute hydrops in Guinea pigs, induced by scala media injection of artificial endolymph, was found to induce rupture of RM, most often in the apical turn, consistent with the structural considerations posited herein.[19] In another study on Guinea pigs, cochlea hydrops in the experimental animals subjected to vestibular aqueduct ablation is reported to develop as early as the first postoperative day, later spreading to other chambers over the course of weeks and months.[20] This report does not address the question of hydropic progression within the guinea pig cochlea during its very earliest stages. However, a more recent study on Guinea pigs based on waveform analysis suggests that early hydrops does first appear in the cochlea apex and is accompanied by a low-frequency hearing impairment.[21]

Additionally, it should be noted that the apical terminus of RM may have a somewhat bulbous quality that gives it 'pseudo-hydropic' appearance on routine TB histology, thus contributing to the hydropic apex to base pattern proposed herein.[22] It has also been reported that RM may be thinner in the cochlea apex, making it even more stress prone, and further exaggerating the apex to base stress pattern cited in this report.[23]

Modeling of hydrops in RM as a toroid is supported by studies of RM deformational behavior. Bekesy reported that under constant transmural pressure in the cochlea duct, the medial edge of RM, attached to the osseous spiral lamina, undergoes the maximum displacement.[24] This would be expected because this sector of the model toroid would be the most anticlastic and therefore experience the greatest tensile stress.

The assumption that RM is elastic during low amplitude distention is consistent with its physiological behavior during sound processing where it undergoes stretching as it passively follows the movements of the basilar membrane. The typical low-frequency hearing loss seen in MD has been previously ascribed to the hydropic distention of the cochlea duct.[25] Although the analysis here does not examine the exact mechanism at the root of the hearing loss in MD, there would appear to be an association between the degree of hydrops in each turn and the degree of hearing loss associated with each turn.

4.5 | Clinical significance and future research directions

The most pronounced distention of RM is projected to occur in the apical turn of the cochlea, the area associated with low-frequency hearing loss as seen in early MD. This would imply that the increased sensitivity to low-frequency sound that is normally mediated by the tight apical winding[9] carries with it a potential overlap with low-frequency hearing loss due to endolymphatic hydrops. If the hydropic process underlying MD originates in the cochlea apex as some evidence suggests,[5] such an association would raise suspicions about the role of low-frequency noise exposure in the etiology of MD. Future research might clarify such a correspondence by correlating inner ear MRI with low-frequency hearing loss in real time.

5 | CONCLUSIONS

Structural features appear to underlie a differential susceptibility to hydrops in the several turns of the human cochlea. The flattened spiral shape of the cochlea, the anticlastic configuration of distended RM, and the nonlinear distensibility of RM result in a hydropic proclivity that is the greatest in the apex and progressively less in the lower turns. This implies a continuum of hydropic effects in the cochlea wherein RM displacement in the apical turn is projected to be always greater than that in the lower turns in all the stages of early disease. In the earliest stage, RM may undergo mild distention in all turns and yet remain fully elastic and reversible in vivo and therefore appear normal in the histology. In a subsequent stage, RM may undergo plastic distention limited to the apical turn and yet remain elastic in the lower turns, resulting in hydrops limited to the apical turn in the histology. In the final stage, marked plastic deformation of RM spreads to the middle and eventually to the lower turns and is evident in the histology.

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