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SHORT REVIEW

# Kidney Disease and Inner Ear Sufferance of Non-Familial Origin: A Review of the Literature and a Proposal of Explanation

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Hearing loss and chronic kidney disease (CKD) are frequently associated; in addition to possible dysfunctions of genetic origin, clinical studies about the frequent incidence of hearing disorders in patients with CKD were reported. We aimed to find out a satisfactory explanation for the mechanisms underlying this association.

We present a review of the literature, particularly dealing with the association of hearing loss with haemodialysis and CKD of non-familial origin.

The recorded studies seem to indicate that a link between labyrinthine and kidney disorders is reliably supposed to exist, but a clear explanation is lacking. A possible explanation, that hemodynamic changes could play a role, is proposed.

As a clear statement is lacking, we suggest that a functional interaction based on the consequences of a hemodynamic imbalance can play a role and substantiate a reliable explanation for the frequent association of non-syndromic CKD and hearing loss.

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## Introduction

Hearing loss and chronic kidney disease (CKD) are frequently associated, and this association has been known since 1927 when Alport described a case of familial kidney disease with concomitant hearing loss [1]. Over the years, a series of observations concerning infrequent affections or syndromes with a close relationship between hearing impairment and CKD was reported [2]: even if the ever more detailed specific knowledge evidenced a shared basis for possible dysfunctions derived from genetic anomalies [3,4], a number of clinical studies about the frequent incidence of hearing impairment in patients with CKD was reported independently of hereditary ascertained disorders. An interesting aspect is represented by the cochlear involvement documented by the alteration of evoked otoacoustic emissions [5-8]: this is not surprising, as the physiologic, ultrastructural and antigenic analogies between the kidney and the cochlea [2] permit to infer that the link between inner ear damage and kidney failure is likely to be much more than a coincidental finding. Actually, it is well known that the function of both organs is characterized by complex processes of water and ion regulation, that are maintained by the work of different proton pump systems and aim at a homeostasis of ions and pH. The similarities of labyrinthine and renal function are well exemplified by the shared essential importance of aquaporins [9], specific cellular water channels, and by the presence of an ion transport system that to date has been demonstrated only in the rat and in the human endolymphatic sac beside the kidney [10]. From this point of view, the possible explanation for the association between inner ear and kidney affections by an alteration of the mechanisms involving fluid and

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electrolyte balance both in the kidney and in the cochlear stria vascularis [11] seems logical.

In more general terms, a number of risk factors can reasonably be considered as a potential threaten to the homeostasis of both kidney and inner ear: age, diabetes, hypertension, electrolyte disorders and haemodialysis itself are reported [2]. Nevertheless, a precise and documented cause for this association seems to be still lacking. For this reason, a review of the literature on this topics seems of some interest, in order to find out some reliable mechanisms able to explain an association that cannot be labelled as casual even in non syndromic patients.

*Review of the literature*

Despite the frequent finding of the association of hearing loss and kidney diseases in non-syndromic patients, the matter still presents confusing aspects. Firstly, it must be outlined that haemodialysis per se rather than CKD is frequently reported in association with hearing loss: however, the causative role of the former is uncertain, and the affection and its related therapeutic procedure are often taken together. The possible influence of haemodialysis on hearing function can reasonably be explained as this procedure causes considerable metabolic and electrolyte disturbances within a few hours in human organism [12]; however, the majority of the reported studies cannot individuate a direct effect on cochlear homeostasis. In the early '90s, a long term follow-up investigation stated that although the possible various insults deriving from haemodialysis, this procedure per se does not harm to the cochlea [13]. The same conclusions were reached by more recent investigations [7,14,15], whereas other studies report the possibility of an adverse effect by this method of management of renal insufficiency [14,16-19]. Consequently, an exam of more or less recent reports does not permit to date to draw precise conclusions about the influence of haemodialysis on hearing function [12,20,21], even if a periodic audiological assessment incorporated in the care of patients with chronic renal failure is recommended [22,23].

As concerns the association between hearing loss and CKD per se, it must be outlined that most of the investigations are represented by small observational studies, whereas the first cross-sectional population-based study has been only recently presented [2]: this study confirmed the existence of a link between the affections in older adults but was not able to indicate precise causal factors and to draw definitive conclusions. A smaller comparison of the hearing loss in older patients with CKD with an age-matched control population was made by Antonelli et al [24], who also found a difference between the study and the control groups; they attributed the hearing loss to a subclinical uremic axonal neuropathy shown by the alteration of ABR response [24]. Changes in ABR pattern were also reported in other studies [7,8,12], and their coincidence with alterations in otoacoustic emissions [7,8] backs up the inference that repeated biochemical and electrolytic disturbances can act on the cochlea, the acoustic nerve and the brainstem [8]. The association between inner ear and kidney affections was also described in a paediatric age group, in which the alterations were more commonly observed in transient otoacoustic emissions than in audiogram [5], thus witnessing an early cochlear involvement. Actually, the involvement of young people is even reported by other authors [6,14], and otoacoustic emissions are considered a more sensitive tool to detect incipient cochlear damage than behaviour thresholds [6].

Taken together, all these observations induce to conclude that a link between labyrinthine and kidney disorders is reliably supposed to exist, independently from age, but a clear explanation is lacking.

*Hemodynamic imbalance: a similar role for inner ear and kidney?*

In our opinion, it is possible that a simpler pathogenic analogy can be found between kidney disease and inner ear impairment [25], based on the role of hemodynamic changes.

Starting from an attempt to explain the origin of "idiopathic" sudden sensorineural hearing loss in young subjects without vascular risk factors [26,27] some observations were reported over the years by our group about the possibility that a hemodynamic imbalance can represent a causal factor: according to our first hypothesis, that was subsequently confirmed by a series of studies [27,33], some unexplained inner ear

disorders or sufferance can depend on a sharp reduction of blood pressure values followed by an abnormal peripheral sympathetic vasomotor response; the inner ear circulation, due to its terminal type, can thus be jeopardized by a more or less transient condition able to generate an acute local ischemia and subsequent hypoxia. This mechanism is likely to act both under physiological conditions that must deal with a generic exaggerated sympathetic reactivity [26-31] and under pathological conditions as treated hypertension [32] and/or chronic heart failure [33]. According to this statement, our observations led us to hypothesize and to support a common origin for different inner ear disorders that have never found a completely satisfactory explanation, including Meniere's Disease [34,35].

In strict analogy with our observations regarding the inner ear [33], the renal hypoperfusion originating from a decreased cardiac output is known to be a fundamental factor per se in the reduction of the glomerular filtration rate in patients with chronic heart failure [36].

As stated above, a complicate structure that accomplishes a complicate function is common to kidney and labyrinth; moreover, their blood supply may be conditioned by particular factors that can yield additional difficulties in maintaining a stable perfusion: namely, the pressure of inner ear fluids [37] and the post-glomerular vasomotor tone [36] respectively. From a more systematic point of view, as the labyrinthine vascularisation is of terminal type, the kidney, despite its more "central" anatomic location and its much greater volume of circulation, can to some extent at least share this character. The highly energy-requiring metabolism of both organs can justify a more marked vulnerability to the consequences of brusque hemodynamic variations, especially in subjects with an exaggerated sympathetic drive acting on the physiological vasomotor response to hypoperfusion. The documentation of this possibility as concerns the inner ear is in agreement with previous experimental models [38,39]; reasonably, it can be able to help explain the known susceptibility of the kidney to ischemia-reperfusion derived injuries.

A final analogy is represented by the possible activation of vasopressin receptors, that are present in both organs, thus witnessing their common capability to yield a neurohormonal response to hemodynamic variations.

These remarks could substantiate a possible explanation for the frequent association of non-syndromic CKD and hearing loss, through a simpler and more direct interpretation based on the similarities between inner ear and kidney as concerns their pathophysiology [25]: the difficulty of maintaining a stable perfusion linked to stable pressure values could play a central role in a certain number of cases of both labyrinthine and renal disorders. On the other hand, the architectural and functional analogies and some crucial common mechanisms can easily lead to postulate a certain degree of functional interaction between kidney and labyrinth, that could account for the frequency of associate disorders: accordingly, the most reliable link is reasonably to be individuated in blood pressure.

In our opinion, a greater attention to the possible systemic warning derived from an initial sufferance of the inner ear [40] and a more thorough evaluation of renal conditions in patients with hearing loss of uncertain origin should be recommended: as an audiological monitoring in patients with CKD has been suggested [2], a reciprocal procedure may result in a better understanding of some not well explained audiological affections.

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