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## **Hearing Loss at High Frequencies and Oxidative Stress: A New Paradigm for Different Etiologies**

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### **Abstract**

The clinical assessment of hearing loss has been transformed and revised in terms of interpreting the characteristics of patterns found in relation to the relative frequency of certain diseases. However, increasing the threshold to 4 kHz as a starting point for hearing loss has shown to be common to different diseases such as noise-induced hearing loss. In noise-induced hearing loss, for example, six mechanisms can be considered: conversion of sound pressure level into hearing level, vascular failure in the cochlear region responsible for hearing at 4 kHz, sound wave propagation velocity is very high and causes the displacement amplitude in the cochlear duct, the structure anatomy of the cochlea causes a collision of fluids in the first curve of the cochlea, characteristics of auricular pavilion resonance and external auditory canal, and sound attenuation of the acoustic reflex. It is hoped that this new paradigm for the different hearing losses will result in a different approach to the physiological changes that affect the auditory system in the form of high-frequency hearing loss. As such, preventing, treating, and avoiding exacerbations are possibilities to be investigated in order to guarantee efficient communication and quality of life for individuals.

**Keywords:** hearing loss, noise-induced hearing loss, oxidative stress, presbycusis, chronic kidney disease

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## 1. Introduction

Hearing is one of the primary means of human contact with the world, from the perception of acoustic signals that indicate danger through an alert system to the development of language and intellect. In the evolutionary process, the human auditory system underwent transformations that enabled it to capture, amplify (magnify), perceive, and discriminate sound, the last two achieved from the inner ear (cochlea) to the auditory cortex.

Human hearing perceives sounds ranging from 20 Hz to 16 kHz, and exhibits tonotopy from the cochlea to the auditory cortex, such that hearing frequencies are recognized in an organized manner along the auditory pathway. Under certain conditions that lead to hearing loss, initial and selective damage may occur at certain sound frequencies. This pattern of selective damage can be observed in a number of pathological conditions whose physiopathological foundation may be based on an oxidative stress model. Among these conditions are noise-induced hearing loss (NIHL), age-related hearing loss (presbycusis), ototoxic hearing loss, and hearing loss associated with chronic kidney disease (CKD).

## 2. Oxidative stress

Free radicals are species (molecules, ions) that contain free electrons (unpaired) in their structure and, as such, are usually highly reactive with other molecules [1]. Due to this reactivity, radicals can damage membranes and other cellular structures under oxidative stress conditions.

Oxidation reactions cause the formation of a variety of unstable reactive species that can trigger chain reactions in milliseconds, leading to disease and programmed cell death (apoptosis) [2]. Among the reactive species formed are reactive oxygen species (ROS), which participate in several physiological and pathological processes in the organism.

With the evolution of the cell and the use of molecular oxygen in energy metabolism, ROS began to play increasingly studied and significant roles in a number of diseases [3]. The main ROS are the superoxide anion radical ( $O_2^-$ ), hydrogen peroxide ( $H_2O_2$ ), and the hydroxyl radical (OH), the last being the most reactive and harmful [1].

Given that free radical production occurs naturally in the organism, an elaborate endogenous antioxidant system evolved to control the harmful effect of reactive species. This system includes antioxidant scavenger enzymes such as superoxide-dismutase (SOD) 1 and 2, catalase, glutathione (GSH), and related enzymes, including glutathione peroxidase (GPx), glutathione S-transferase (GST), and glutathione reductase (GSH-Red), which converts ROS into neutral, non-reactive molecules.

Thus, hearing losses with different etiologies have been studied at the cellular and molecular level, and there is a convergent tendency with respect to the association between them and oxidative stress.

### 3. Hearing losses

Over the centuries, man has advanced in a number of ways, but this progress has also introduced lifestyle habits that sometimes cause new risk factors for hearing loss.

Exposure to high levels of sound pressure (noise), both professionally and at leisure, can cause irreversible hearing loss, which is often progressive when an individual remains in contact with a daily sound source [4, 5].

Increased life expectancy means age-related hearing loss (presbycusis) has become more common and is one of the most prevalent chronic diseases worldwide.

The emergence of new drugs has led to the cure of numerous hitherto lethal diseases; however, the ototoxic effect of certain medications causes hearing loss and leaves sequelae in children and adults alike [6, 7].

Chronic kidney disease (CKD), which has multiple etiologies, can evolve with progressive hearing loss, representing yet another disability for kidney patients and compromising their quality of life. Moreover, the use of certain drugs for patients with CKD may worsen auditory function and be an aggravating factor for hearing loss [8].

These hearing disorders exhibit a sensorineural pattern due to the sites affected, which vary from the cochlea to the auditory cortical regions, with a preference for high sound frequencies. However, high-frequency damage is a starting point, and 4 kHz is seen as the border between frequencies that often remain preserved and those affected.

Assessment of the physiopathological model of these hearing losses shows that oxidative stress occurs under all the aforementioned conditions and emerges as a new paradigm that more deeply connects characteristic acoustic aspects common to all of them. The real reason for which hearing loss arises, preferentially and usually around 4 kHz, is not fully understood, but there may be a common point in molecular and physiopathological terms that leads to this spectral selectivity.

Starting with a model that considers oxidative stress, we will discuss each of the hearing loss conditions influenced by excess free radicals and expressed by an increase in high-frequency hearing thresholds.

#### 3.1. Noise-induced hearing loss

Excessive exposure to noise induces sensorineural hearing loss resulting from damage to cochlear and neural structures in the inner ear, denominated NIHL. NIHL can be temporally classified into two types: hearing loss induced by chronic noise and acute acoustic trauma. Chronic NIHL is a hearing deficiency caused by continuous exposure to high levels of sound pressure that exert an average of 90 dBA, for eight hours a day, over several years or more [4], whereas acute acoustic trauma is hearing loss caused by short exposure to excessively loud sounds (100–150 dBA, decibel weighting curve A) [9].

Exposure to different sound levels leads to metabolic and mechanical damage. Metabolic damage could occur after exposure to noise between 85 and 115 dBA, whereas mechanical damage can emerge after exposure to sound levels above 115 dBA. Noise-induced hearing loss is due primarily to neural degeneration, which starts immediately after exposure to noise and progresses for several years after exposure [10].

Susceptibility to the harmful effects of noise differs significantly among individuals, that is, after identical exposure to noise, not all people suffer hearing loss, and when they do, the degree can vary. Thus, NIHL was classified as a disease resulting from external (environmental) causes, in addition to genetic predisposition [11].

Ciliated cells, particularly the more vulnerable external variety, are compromised in NIHL. There are around 12,000 external ciliated cells arranged in three rows in the basal region of the cochlea and in four or five rows in the apical region [12]. Thus, there are fewer ciliated cells at the cochlear base than the apex. With a sharp loss of ciliated cells, secondary neural degeneration is reflected in the auditory nerve and brainstem auditory nuclei [13].

The cochlea is a metabolically active organ and oxidative stress plays an important role in the pathogenic mechanisms of NIHL. The mitochondria generate energy to maintain cochlear metabolism; however, they are also the primary ROS generator. The fact that ciliated cells are highly energy-demanding during and after exposure to noise leads to a prolonged local release of free radicals, which may damage the cochlear epithelium, particularly if the antioxidant defense system is not efficient enough to neutralize them [11]. However, due to this exposure to ROS, as well as harmful environmental influences (noise), mitochondrial DNA (mtDNA) run the risk of maintaining mutations that may hinder the function of different organelles and lead to chronic diseases such as NIHL [14, 15].

Organ of Corti lesions occur primarily at the basal turn (Rosenthal's canal), in the area responsible for sounds between 3 and 6 kHz, regardless of the frequency range of aggressor noise, caused by six possible mechanisms [5]:

1. Conversion of dBA for sound intensity under the international guidelines to protect the auditory system into dBHL for hearing level;
2. Vascular failure in the cochlear region responsible for hearing at 4 kHz;
3. Sound wave propagation velocity is very high and causes the displacement amplitude in the cochlear duct to begin to grow in the 4 kHz region;
4. The structure anatomy of the cochlea causes a collision of fluids in the first curve of the cochlea;
5. Characteristics of auricular pavilion resonance and external auditory canal cause injury in the 4 kHz region.
6. Sound attenuation of the acoustic reflex occurs only for low frequencies.

The first mechanism raises the most speculation due to the dynamics of noise that exhibits the same intensity in dBA (decibel weighting curve A). This occurs because sound measures in dBA are the result of a weighted average of the amplitudes of each frequency that makes up

the sound measured [16, 17]. **Table 1** illustrates an example of the necessary correction in dB in order to calculate sound intensity in dBA.

**Table 1** shows that for a pure tone of 500 Hz to emit 100 dBA, it must exhibit 108.6 dB SPL. If the frequency were 4 kHz, sound should produce 101 dB SPL. As can be observed, for a complex sound to emit 100 dBA, different possible combinations of amplitudes by frequency exist.

The guidelines that protect workers in most of the countries that have such legislation include dB and weighting curve A as intensity measures. However, auditory assessments are conducted at dB hearing levels and depend on the specific earphones used in the assessment in order to match the dB hearing level and dB SPL. **Table 2** contains the reference values corresponding to 0 dBHL, by frequency, using Telephonics TDH-39 earphones, the most commonly found in audiometers.

Thus, for a person to have the sensation of hearing 0 dBHL, the sound must emit 7 dB SPL, if its frequency is 1 kHz. As such, for them to hear at 30 dBHL, at this frequency, the sound must produce 37 dB SPL [18].

Finally, **Figure 1** exhibits the correspondence curves, by frequency, for a sound in dBA, listened to through TDH-39 earphones and the matching result from one unit to another.

**Figure 1** shows that the weighting differences and adjustments to dBHL result in greater weight for sound frequencies between 0.5 and 4 kHz. Thus, a sound that has different frequencies could exhibit higher physical intensities in the dB SPL band particularly, and more energy

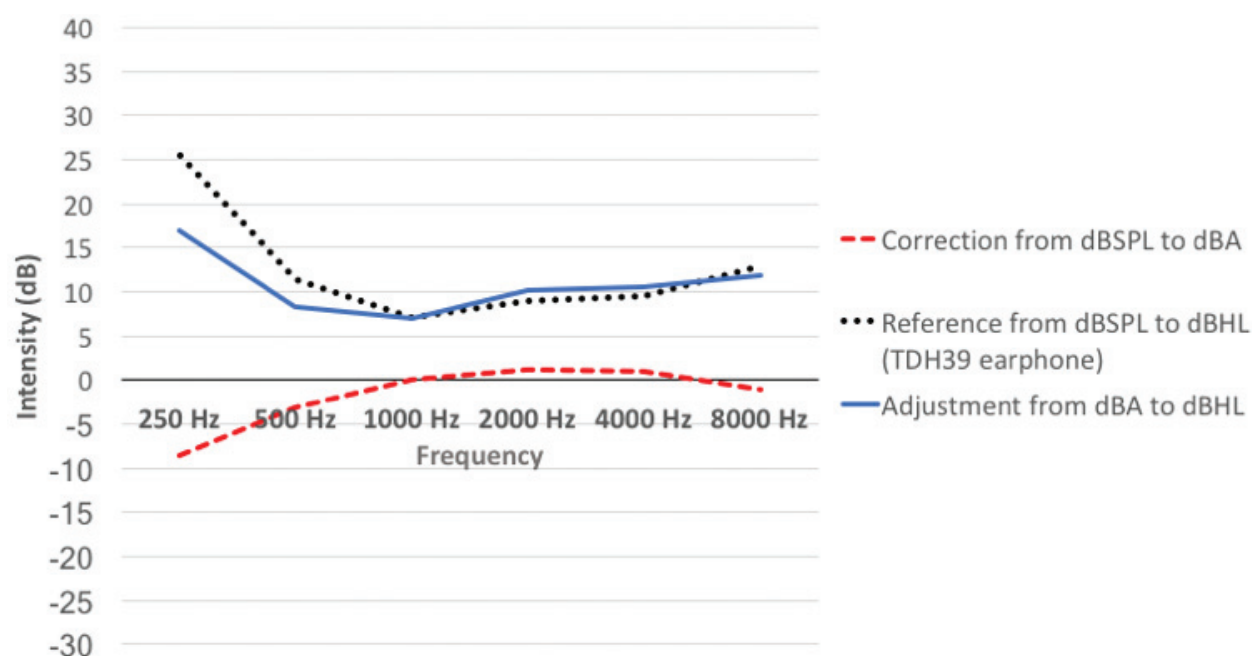
Frequency (Hz)	dB SPL correction for dBA
250	−8.6
500	−3.2
1000	0
2000	1.2
4000	1
8000	−1.1

**Table 1.** dB correction to calculate intensity in dBA, by frequency.

Frequency (Hz)	Reference (dB SPL)
250	25.5
500	11.5
1000	7
2000	9
4000	9.5
8000	13

**Table 2.** Reference levels (dB SPL) for an intensity of 0 dBNA, by frequency.





**Figure 1.** Adjustment from dBA to dBHL (TDH39 earphone).

could cause greater damage. However, it is necessary to know the other mechanisms in order to have a clearer understanding of the implications in the present topic.

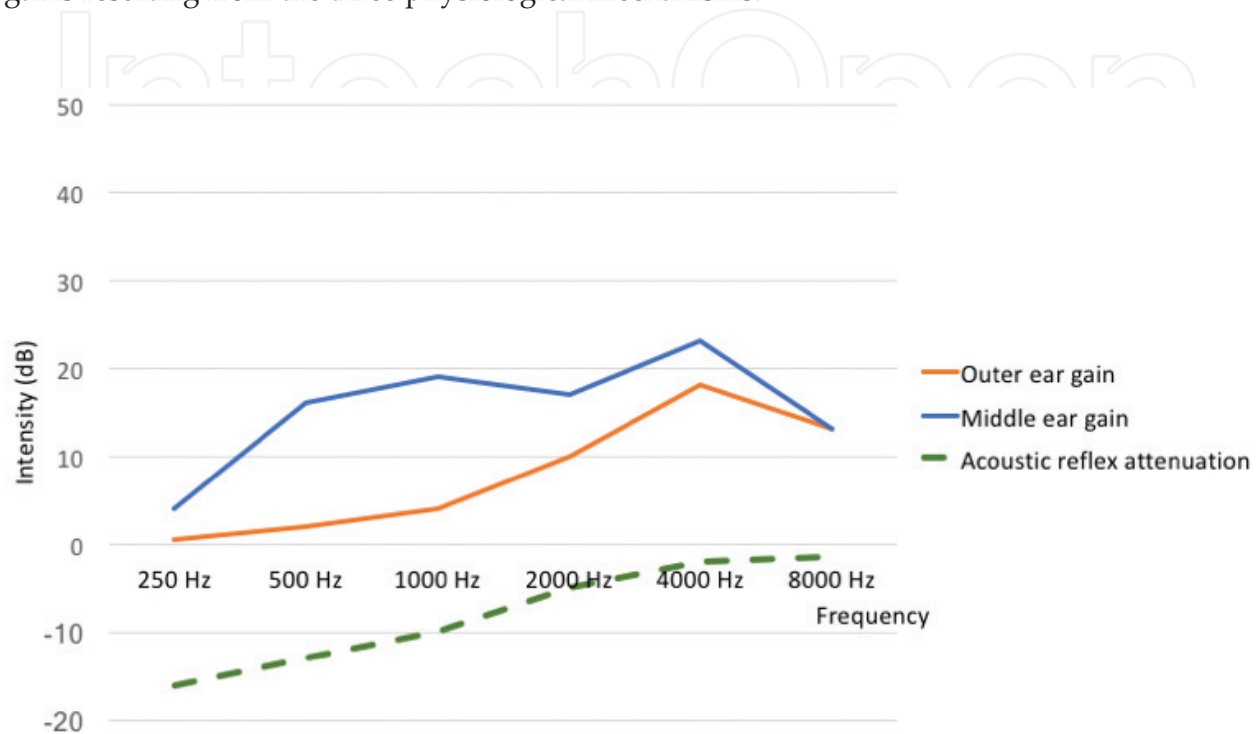
The second, third, and fourth mechanisms described earlier explain why a frequency of 4 kHz is the first and most affected in terms of the degree of hearing loss [4, 5]. Furthermore, ciliated cells from the basal turn, the area responsible for high frequencies, are more susceptible to oxidative stress than those from the cochlear apex [19].

Even at a low oxidative stress levels, external ciliated cells from the basal turn are more vulnerable to damage, while internal and external ciliated cells from the middle and apical turns are more preserved [20]. The difference in antioxidant levels in basal turn to apical turn cells explains this greater susceptibility to lesions caused by ciliated cells from the base of the cochlea [19]. At the enzyme level, exposure to noise increases oxidase NADPHA (NOX) levels in the cochlea and a decline in SOD increases susceptibility to acoustic lesions. The accumulation of ROS subsequently triggers a complex cascade of biochemical processes including activation of c-Jun N-terminal kinase (JNK) and p38MAPK, the release of cytochrome and mitochondria and proca spase activation [3, 8, 9] (intrinsic apoptotic pathway) [21, 22].

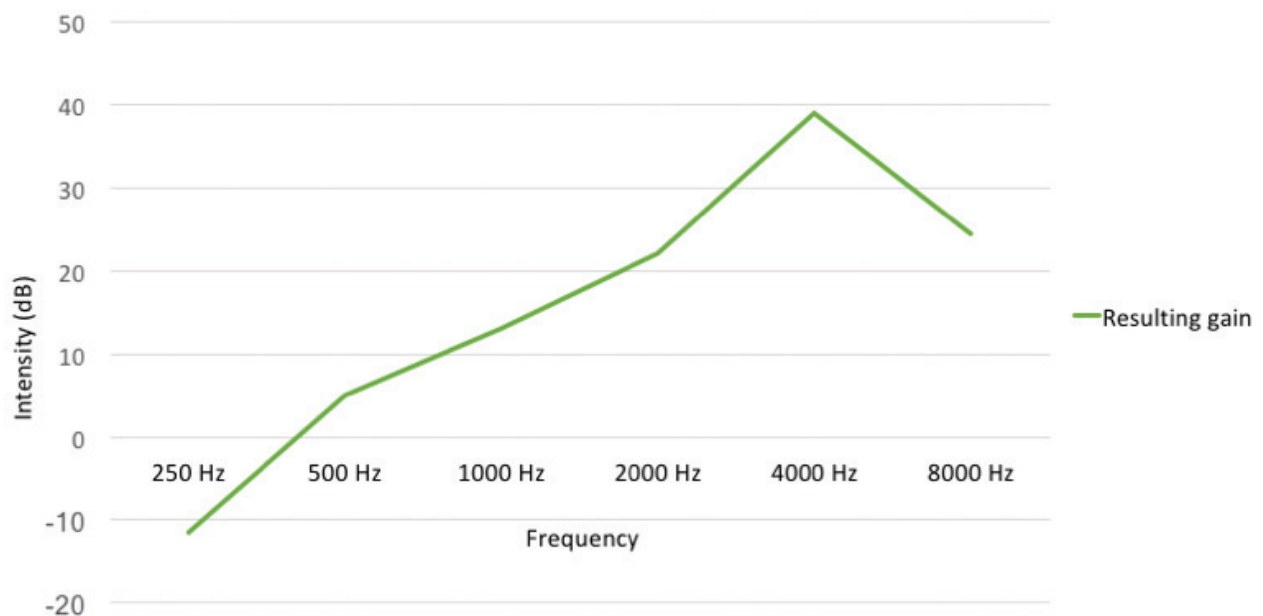
Furthermore, the physiological mechanisms of resonance in the auditory system, primarily the concha and external auditory canal, are highly relevant in the audiometric configuration process of noise-induced hearing loss, especially at strong intensities [10]. The physiology of hearing studies the resonance in tubes in order to understand sound reception.

Resonance is closely related to the formation of stationary waves, which originate from a combination of two physical phenomena: reflection and interference [23]. Resonance in the external auditory canal, calculated by the expression  $V_{\text{sound}}/4L$  ( $L$  = length of the canal), is around 3800 Hz, which can vary with temperature and be slightly higher or lower, due to the mobility of the tympanic membrane and the anatomic differences between subjects. As such, it

can be concluded that, of the different sound frequencies that reach the ears, those around 3800 Hz are extraordinarily amplified. Since 3.8 kHz is not assessed in audiometry, these reflexes can be found at 4 and 3 kHz. **Figure 2** presents the results of pavilion (concha), external auditory canal (outer ear), and middle ear resonance studies, as well as attenuation caused by the stapedius reflex, which only has an effect at low frequencies [24–26]. **Figure 3** shows the gains resulting from the three physiological mechanisms.



**Figure 2.** Outer/middle ear gain and acoustic reflex attenuation.

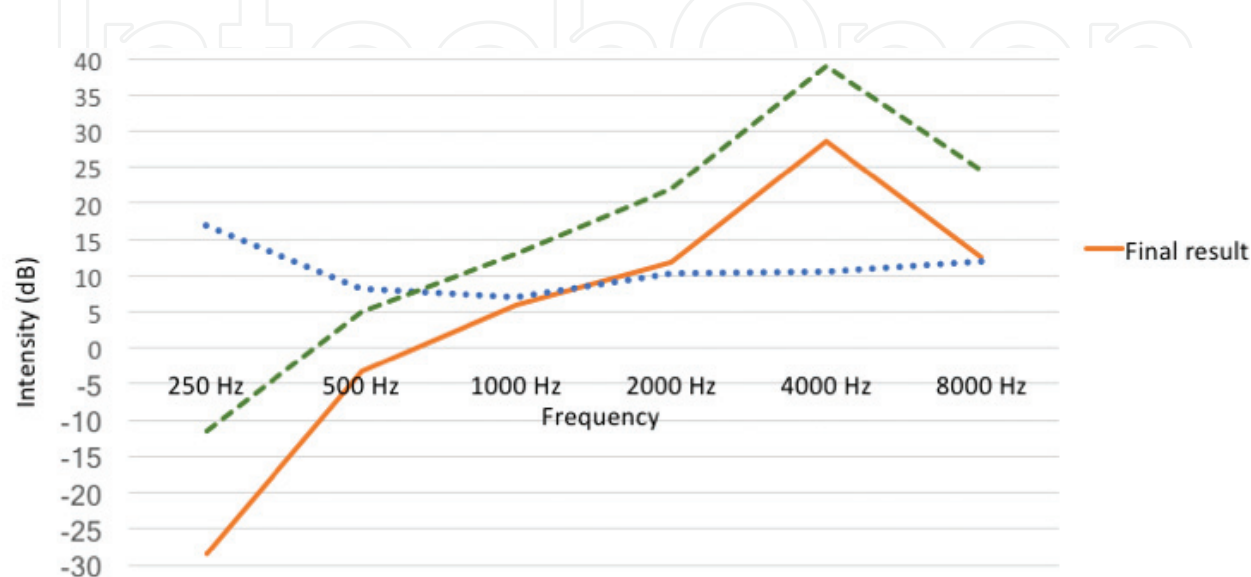


**Figure 3.** Resulting gain caused by the three physiological mechanisms.

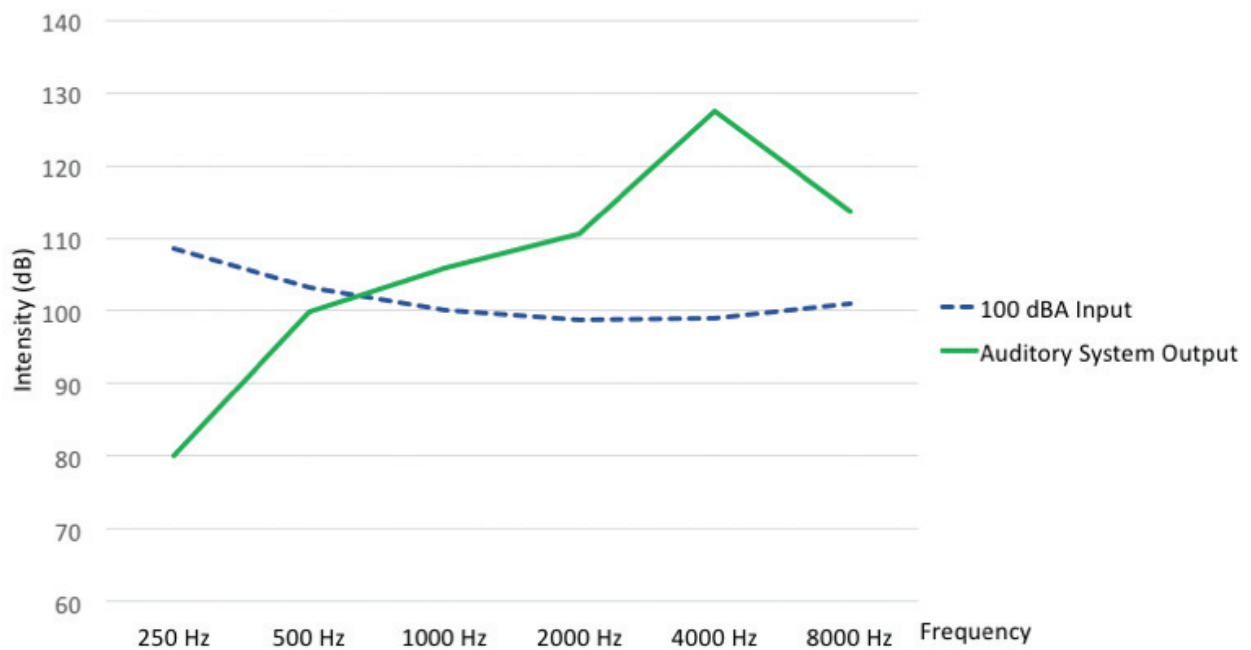


Finally, relating the final physiological gain and the differences in adjustment between dBA and dBHL, despite knowing that there may be overlapping effects, and attempting to minimize errors and approach reality, **Figure 4**, which exhibits the result of the three physiological mechanisms, the dBA to dBHL adjustment, and the final result (orange line).

Finally, a sound input of 100 dBA illustrates how sound interacts with the auditory system and the spectrum resulting from this interaction (green line), as shown in **Figure 5**.



**Figure 4.** Final outcome, adjustment from dBA to dBHL, and physiological mechanisms.



**Figure 5.** Final outcome: example of a 100 dBA input stimulus.

An input sound level of 100 dBA, resulting from weighting of 108.6, 103.2, 100, 98.8, 98, and 101.1 dB for 250, 500, 1, 2, 4, and 8 kHz, respectively, has an output of 80.2, 99.9, 106, 110.6, 127.5, and 113.7 dB, respectively. In other words, 4 kHz receives around 30 dB more than the original input, while at a frequency of 250 Hz, the intensity is approximately 28 dB lower.

Thus, considering the six aforementioned mechanisms, in addition to the lower number of external ciliated cells at the base of the cochlea and their increased susceptibility to oxidative stress, the audiometric profile of NIHL is defined as being at high frequencies, with the greatest effect at 4 kHz.

### 3.2. Presbycusis

Presbycusis is a highly complex multifactorial process involving hearing loss at high frequencies concomitantly with physical signs of aging [27].

It is the most common sensory disorder in the elderly, occurring in 25–40% of individuals aged 65 years or older and the prevalence tends to increase with age, ranging from 40 to 66% of people over 75 years old and more than 80% in those over the age of 85. The number of people with this disorder is expected to grow substantially due to the increase in life expectancy [28, 29].

Individuals with presbycusis exhibit reduced sensitivity and hearing comprehension in noisy environments, slow central processing of acoustic information and compromised sound source localization. As such, the limitations that emerge are proportional to the degree of auditory deficiency, affecting dialogue, musical appreciation, identification of warning signs, and, finally, participation in social activities [28] (**Table 3**).

The pathogenesis of presbycusis is not well understood. There is an association with extrinsic (noise, exposure to environmental ototoxic agents, traumatism, vascular injury, and diet), and intrinsic risk factors (metabolic changes, genetic factors, and physiological aging process) [31]. Furthermore, other changes have been proposed, such as altered vascular characteristics, a decrease in oxygen and nutrient supply and residue elimination, genetic mutations, and a significant increase in ROS production [28].

As stated earlier, mitochondria play a crucial role in maintaining cochlear energy homeostasis. Over the course of aging, a number of changes occur in the mitochondria and mitochondrial DNA (mtDNA), including (1) an increase in mitochondrial structural disorganization, (2)

Sensory	Atrophy occurs with loss of ciliated cells and supporting cells of the organ of Corti, starting in the basal turn of the cochlea and progressing slowly toward the apex
Neural	Neuronal atrophy occurs in the cochlea and central neural pathways. It is estimated that 2100 neurons are lost each decade
Metabolic/ strial	Atrophy occurs in the stria vascularis, which normally maintains chemical, bioelectrical and metabolic equilibrium of the cochlea
Mechanical	Thickening of the basilar membrane occurs, more severely in the basal turn of the cochlea, where the basilar membrane is narrow

**Table 3.** Histologically, there are four types of presbycusis [23].

decline in their oxidative phosphorylation, (3) accumulation of mutations in the mtDNA, (4) rise in mitochondrial ROS production, and (5) increase in oxidative DNA, protein, and lipid damage [14].

Thus, the cellular environment in oxidative stress due to noise exposure is one of the main determinants of NIHL, since there may be multiple conditions causing this stress, all contributing to presbycusis in a same individual. The sensory and metabolic forms display a history of exposure to noise and the degree of impairment is greater at high frequencies [32]. In addition, the two forms exhibit an intrinsic cause and effect relationship with oxidative stress, while the mechanical and neural forms display different physiopathological mechanisms but are not exempt from the influence of excessive free radicals.

3.3. Ototoxic hearing loss

Ototoxic hearing loss is caused by the cochleotoxic effect of certain substances widely used in clinical practice. However, other substances present in professional activities also have harmful effects on the cochlea [33]. In addition to the cochleotoxic capacity of the drug, hearing loss is determined by other factors, including exposure to noise, genetic predisposition, malnutrition, advanced age, overall poor health, hypoacusis, and ringing in the ears [33, 34]. Genetic predisposition involves mitochondrial inheritance and oxidative stress [33] (Table 4).

The following drugs exhibit a cochleotoxic effect [33, 35–37].

Once inside the cell, aminoglycosides induce ROS production. They are considered “redox-inactive compounds” and, as such, need to be converted into the redox-active form to induce ROS formation. ROS generation involves the formation of an aminoglycoside-iron complex that catalyzes the oxidation of unsaturated fatty acids located in the internal layer of the plasma membrane [27].

The increase in ROS may be due to the depletion of thiol and antioxidant enzyme-reducing buffers and/or direct activation of ROS-producing systems. Cisplatin administration leads to reduced glutathione concentration in the cochlea and a significant decline in SOD activities, catalase, cochlear glutathione peroxidase, and glutathione reductase [27].

Aminoglycosides	Dihydrostreptomycin, neomycin, amikacin, and kanamycins A and B
Beta blocker	Propranolol
Diuretics	Etacrynic acid and furosemide cause reversible hearing loss and can exacerbate hearing loss caused by aminoglycosides
Non-steroidal anti-inflammatories	Salicylates and acetylsalicylic acid. Hearing loss is normally reversible
Cisplatin	Used in chemotherapy against cancer in both children and adults. In children, it can lead to delayed language development

Table 4. The following drugs exhibit a cochleotoxic effect [26, 28–30].

Under certain conditions, base disease in itself causes a condition of permanent oxidative stress in patients. Type 1 diabetes, pancreatitis, different metabolic syndromes, cardiovascular diseases, and chronic kidney failure are frequent examples of pathological conditions with permanent oxidative stress in which patients are more susceptible to hearing loss, and can be aggravated by the use of ototoxic drugs [38]. Hearing loss is normally bilateral, symmetrical, and greater at high frequencies.

### **3.4. Hearing loss associated with chronic kidney disease**

Chronic kidney disease (CKD) is a metabolic syndrome caused by the progressive, irreversible and generally slow loss of renal excretory capacity [39]. In 2013, it was estimated that 2.5 million patients were in dialysis worldwide, a number that is expected to reach 6.5 million by 2030 [40].

The prevalence of hearing loss in patients with CKD, even children [41–45], is higher than in the general population [41]. The best-known association between CKD and hearing loss is Alport syndrome, which has a genetic origin [46]. However, in most cases, hearing loss in patients with CKD has no genetic origin but is due to anatomical, physiological, and pathological similarities between the nephron and stria vascularis of the cochlea [47]. Of CKD cases, 35% are caused by systemic hypertension (SHT) and 29% by diabetes mellitus (DM) [48].

Several factors lead to permanent oxidative stress in CKD, such as the base disease (hypertension, diabetes) that caused CKD, namely uremia. This state of oxidative stress can be aggravated in the inner ear when drugs with a potential ototoxic effect are used [38].

The primary lesion site of hearing loss in CKD is the cochlea [49]; however, some studies also report the involvement of retrocochlear pathways and the central nervous system [41, 50]. Hearing loss normally occurs symmetrically at high frequencies [8, 43, 51].

## **4. Oxidative stress as a new paradigm in hearing loss at high frequencies in different etiologies**

The hearing losses under study are examples of pathological conditions in the inner ear that are clinically distinct, and often accumulate over a lifetime. Final expression is determined by molecular mechanisms based on oxidative stress. Assessing the different aspects such as etiology, clinical picture and treatment of these hearing disorders should not be restricted to pre-established immutable models that treat each of them separately without including the intrinsic and extrinsic factors that significantly influence auditory damage.

Prevention possibilities and rehabilitation perspectives for these hearing disorders have been discussed for decades. It is important to prevent NIHL by non-exposure to damaging sound levels, but this is not enough, since factors such as genetic predisposition to hearing loss and the use of ototoxic drugs may exacerbate the final audiological clinical condition. Presbycusis

is the final product of different factors that are harmful to hearing during an individual's lifetime, such that its prevention is hindered by the limits in controlling these factors from childhood onward. Avoiding hearing loss caused by the use of ototoxic drugs is a challenge, since they cannot always be substituted by non-cochleotoxic medication due to the greater efficacy of the former in treating serious diseases, such as cancer. Maintaining good auditory acuity in chronic kidney patients is essential, since hearing loss becomes one more disorder for patients who depend on care and need good communication. Hearing loss related to CKD leads to restricted participation, as well as social and emotional impacts; however, the pathophysiology of CKD causes progressive and irreversible cochlear damage.

Some cell factors characterize the basal turn of the cochlea as a risk zone, justifying selective hearing loss at high frequencies in NIHL, presbycusis, ototoxic hearing loss, and CKD. The lower number of ciliated cells and their greater susceptibility in the basal turn make it a risk zone under aggressor conditions (noise, aging, ototoxic, CKD).

Furthermore, the acoustic reflex is efficient in protecting at frequencies below 2 kHz, leaving high frequencies under unfavorable conditions [52]. This reflex is defined as the contraction of middle ear muscles induced by intense acoustic stimulation. The tensor tympani muscle pulls the malleus (hammer) away from the eardrum and the stapedius muscle exerts force behind the stirrup, causing greater stiffness in the system and reducing sound transmission, primarily at low frequencies, that is, below 1 kHz. Thus, changes in middle-ear impedance, due to the aforementioned contractions, have little or no effect on frequencies above 2 kHz [53].

Studying hearing loss using a new model based on oxidative stress leads to new perspectives on how to prevent this disorder. Several factors display important limitations with respect to preventing auditory damage. However, when oxidative stress is present, understanding how it occurs and devising therapies to minimize it is a new prevention strategy that could be applied to workers exposed to intense noise, individuals with a family history of presbycusis, patients using ototoxic drugs and chronic kidney patients. Adjuvant antioxidant therapies represent a new method to help prevent hearing loss. This model serves as a potential alternative to treat the forms of hearing loss under study, and should be assessed more thoroughly for these and other hearing disorders.

## 5. Conclusions

NIHL, presbycusis, ototoxic hearing loss, and hearing loss associated with CKD may seem disconnected and quite different from one another, but oxidative stress emerges as a paradigm that helps reassess the reasoning behind these losses and better understand the environment of the cochlea when exposed to harmful intrinsic and extrinsic factors.

It is hoped that this new paradigm for the different hearing losses will result in a different approach to the physiological changes that affect the auditory system in the form of high-frequency hearing

loss. As such, preventing, treating, and avoiding exacerbations are possibilities to be investigated in order to guarantee efficient communication and quality of life for individuals.

## Conflict of interest

There is no conflict of interest.

## List of the technical terms

CKD	chronic kidney disease
dBA	decibel weighting curve A
dBHL	decibel hearing level
DM	diabetes mellitus
GPx	glutathione peroxidase
GSH	glutathione
GSH-Red	glutathione reductase
GST	glutathione S-transferase
JNK	c-Jun N-terminal kinase
Hz	hertz
kHz	kilo hertz
L	length of the ear canal
NIHL	noise-induced hearing loss
NOX	noise increases oxidase
mtDNA	mitochondrial DNA
p38MAPK	the release of cytochrome and mitochondria and procaspase activation
ROS	reactive oxygen species
SHT	systemic hypertension



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