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Effect of Hyperinsulinism on Sensorineural Hearing Impairment in Ménière's Disease: A Cohort Study

*†Joel Lavinsky, †‡Michelle Lavinsky Wolff, §Andrea Ruschel Trasel, §Marcel Machado Valerio, and *†§Luiz Lavinsky

**Graduate Program in Medicine, Surgical Sciences, Universidade Federal do Rio Grande do Sul; †Otolaryngology Service, Hospital de Clínicas de Porto Alegre; ‡Graduate Program in Epidemiology, Universidade Federal do Rio Grande do Sul; and §School of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil*

Objective: To compare the degree of sensorineural hearing loss in patients with Ménière's disease (MD) with and without hyperinsulinism by different methods of assessment.
Study Design: Historical cohort study.
Setting: Ménière's Disease Care and Research Clinics of Hospital de Clinicas de Porto Alegre, a tertiary care university hospital in Southern Brazil.
Patients: Patients with a definite diagnosis of MD based on the American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) guidelines.
Intervention: Patients were assessed by glucose overload tests (5-h glucose and insulin curves) and under baseline physiological conditions (Homeostasis Model Assessment/Insulin Resistance [HOMA-IR], Quantitative Insulin Sensitivity Check Index [QUICKI], and glucose/insulin ratio). These patients underwent annual pure-tone audiometry and were analyzed using 4-tone average (FTA), that is, arithmetic mean of 500, 1,000, 2,000, and 3,000 Hz, during the third, fourth, and fifth years of disease progression.
Main Outcome Measure: Hearing loss assessed by FTA and classified in Stages I to IV (AAO-HNS).
Results: Forty-nine (76.6%) patients were defined as hyperinsulinemic and 15 (23.4%) as normoinsulinemic. Impairment on FTA was higher in the hyperinsulinemic group (52.04 ± 17.5 versus 39.75 ± 9.20, $p = 0.027$) when assessed by the 5-hour insulin curve. Hyperinsulinemic subjects were 3.5 times more likely to develop hearing damage greater than 40 dB (i.e., Stages III and IV) than normoinsulinemic subjects (OR = 3.52; 95% CI, 1.05–11.76). A moderate correlation between the insulin curve and the HOMA-IR was found ($r = 0.524$, $p = 0.001$).
Conclusion: Hyperinsulinism in MD is associated with greater clinical hearing damage. **Key Words:** Deafness—Diagnosis—Glucose overload test—Hyperinsulinism—Ménière disease.
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Ménière's disease (MD) was first described over 150 years ago (1), but its pathogenesis, diagnosis, and treatment remain controversial. Metabolic disorders are known to be involved in the pathogenesis of MD, especially glucose-insulin homeostasis disorders (2).

Metabolic disorders, such as insulin resistance (IR) and the resulting hyperinsulinism, even at early stages, might already reflect a functional and energetic impairment of the sodium/potassium ATPase in the inner ear. This enzyme is responsible for maintaining potassium at a high and sodium at a low concentration in the endolymph, similar to what happens in the intracellular space. The ionic balance is maintained at the expense of energy expenditure. Hyperinsulinemic patients have functional impairment of the sodium/potassium ATPase and consequent increased sodium and decreased potassium concentration within the endolymph. These ionic changes increase osmotic pressure, resulting in endolymphatic hydrops.

Angeli et al. (3) reported changes in evoked auditory potentials using electrocochleography (ECochG) during acute induction of hyperinsulinism in sheep. There was a progressive suppression of the action potential amplitude compared with controls, without induced hyperinsulinism ($p = 0.001$). Maia et al. (4) monitored otoacoustic emissions in a study with a similar design and reported statistically significant decrease in distortion product thresholds in the intervention group. Both studies are part of the same line of research.

Address correspondence and reprint requests to Joel Lavinsky, M.D., Rua Quintino Bocaiúva 673, 4° andar, CEP 90440-003, Porto Alegre, RS, Brazil; E-mail: jlavinskybr@yahoo.com

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Hyperinsulinism is a result of a metabolic disorder as IR, in which the biological response of insulin is reduced at the cellular level. Hyperinsulinism represents the first step in a process that leads to hyperglycemia and Type 2 diabetes mellitus (T2DM) (5). In the early stages of hyperinsulinism alone (with euglycemia), cochleovestibular manifestations may already exist (6). Therefore, early detection of this disorder is of paramount importance to prevent T2DM and in the management of the cochleovestibular diseases with metabolic substract.

Although there is consensus on the laboratory diagnosis of T2DM, the best method to establish the diagnosis of IR is still controversial. Several diagnostic tests are available, but the gold standard (euglycemic hyperinsulinemic clamp) is a highly complex method and impractical in population-based studies (7). In clinical practice, IR may be diagnosed by an oral glucose tolerance test, in which glycemic and insulinemic responses are evaluated. Baseline fasting glucose and insulin values are also used but have low sensitivity (8). Population-based studies tend to use mathematical models, such as the homeostasis model assessment (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI), which use fasting values in the formula to translate insulin sensitivity and secretory capacity of pancreatic beta cells.

Studies of patients with MD have shown a prevalence of 67.7% of abnormalities in insulin curves (9). In a sample of patients with various cochleovestibular diseases, 86% showed abnormalities (10). A study conducted by D'Avila and Lavinsky (11) identified that 72% of patients with MD have some degree of hyperinsulinism.

There is experimental evidence in animal model that systemic changes in insulin homeostasis affect the endocochlear potential. Furthermore, it is known that most patients with MD exhibit hyperinsulinism. However, there are no comparative studies assessing the clinical effects of hyperinsulinism on MD. This study aimed to compare the degree of sensorineural hearing loss in patients with MD with and without hyperinsulinism by different methods of assessment.

MATERIALS AND METHODS

The medical records of 457 patients referred to Ménière's Disease Care and Research Clinics of Hospital de Clinicas de Porto Alegre (HCPA), Brazil, were reviewed. Sixty-four patients met the eligibility criteria for the study. The study was approved by HCPA institutional review board, protocol no. 12-0236, and was conducted in accordance with the provisions of the Declaration of Helsinki.

Patients were included in the study if they met all of the following criteria: a "definite" diagnosis of MD according to American Academy of Otolaryngology–Head and Neck Surgery (AAO-HNS) guidelines(12) (≥2 definitive spontaneous episodes of vertigo lasting for 20 min or longer, audiometrically documented hearing loss on at least 1 occasion, tinnitus, or aural fullness in the treated ear); MD of metabolic (Ménière's syndrome) or idiopathic etiology; 2-year clinical history of MD followed by at least 3 years of clinical follow-up; pure tone audiometry (PTA) performed in the third (24–36 mo), fourth (36–48 mo), and fifth year (48–60 mo) at the same institution; and full clinical treatment (13) (betahistine 48 mg/d, hydrochlorothiazide 25 mg/d, and low-sodium, low-glucose and high-protein diet) for at least 24 months after the onset of vertigo symptoms.

Exclusion criteria were as follows: "probable" (1 definitive episode of vertigo, audiometrically documented hearing loss on at least 1 occasion, and tinnitus or aural fullness in the treated ear) or "possible" diagnosis of MD (12) (spontaneous rotation vertigo lasting for ≥20 min, having no documented hearing loss or having sensorineural hearing loss, fluctuating or fixed, with disequilibrium but without definitive episodes), diagnosis of T2DM by fasting glucose 126 mg/dl or greater in more than 1 occasion (14), diseases with a clinical course similar to that of MD (Ménière-like conditions), history of hearing loss prior to the first episode of vertigo, and ear disease/surgery prior to or during follow-up.

All patients underwent a (15) full diagnostic evaluation including PTA with glycerol test and electrophysiologic and imaging tests (nuclear magnetic resonance) to rule out Ménière-like diseases. Likewise, an investigation (16) for cause was carried on to characterize the disease as idiopathic and/or metabolic. For that, a standard laboratory workup was used, including blood tests as well as glycemic, thyroid, lipid, renal, autoimmune, allergy, and infection profiles.

Based on baseline insulin curves, patients were defined as exposed (hyperinsulinemic) and unexposed (normoinsulinemic) and then followed annually by PTA (Fig. 1). Because all data have already been collected when this protocol study was designed, we defined this study as a historical cohort study. The recommendations proposed by the Strengthening the Reporting of Observational Studies in Epidemiology statement for cohort studies were followed.

Based on the protocol for metabolic investigation (Table 1), patients were classified as either hyperinsulinemic or normoinsulinemic according to the insulin curve. In a secondary analysis, the same patients were classified as either insulin-resistant or non–insulin-resistant based on fasting insulin sensitivity indices. The inclusion process and laboratory investigation were completed within the first 2 years of clinical symptoms of MD.

The glucose and insulin curves were performed through venous blood collection at baseline and 30, 60, 120, 180, 240, and 300 minutes after the oral administration of 100 g of glucose. Glucose and insulin levels were analyzed using chemiluminescence at the biochemistry laboratory of HCPA. In addition, insulin curves were graded based on the Kraft criteria (I, IIa, IIb, IIIa, IIIb, IV, and V) (6).

The insulin sensitivity indices for IR evaluation (HOMA, QUICKI, and glucose/insulin ratio) were calculated using the formulas presented at Table 1. Cutoff points were defined from the normal values reported in previous population-based studies (7). Lipid profile (total cholesterol, high-density lipoprotein [HDL], and triglycerides) and thyroid function were also analyzed.

During follow-up, annual PTA was performed. The 4-tone average (FTA) with the greatest impairment in the periods of 24 to 36, 36 to 48, and 48 to 60 months were used to define the outcome. The tests performed in the first 24 months were not considered. All examinations were performed in the same audiology facility, and the professionals involved in these tests were not aware of the glucose/insulin test results.

The hearing thresholds were manually collected using an AD27 audiometer (Interacoustics, Assens, Denmark), which was calibrated annually according to the American National Standards Institute (ANSI)-1969 standards. The booth had levels of noise reduction compliant with ANSI S 3.1-1991 specifications, below 30 dB SPL.

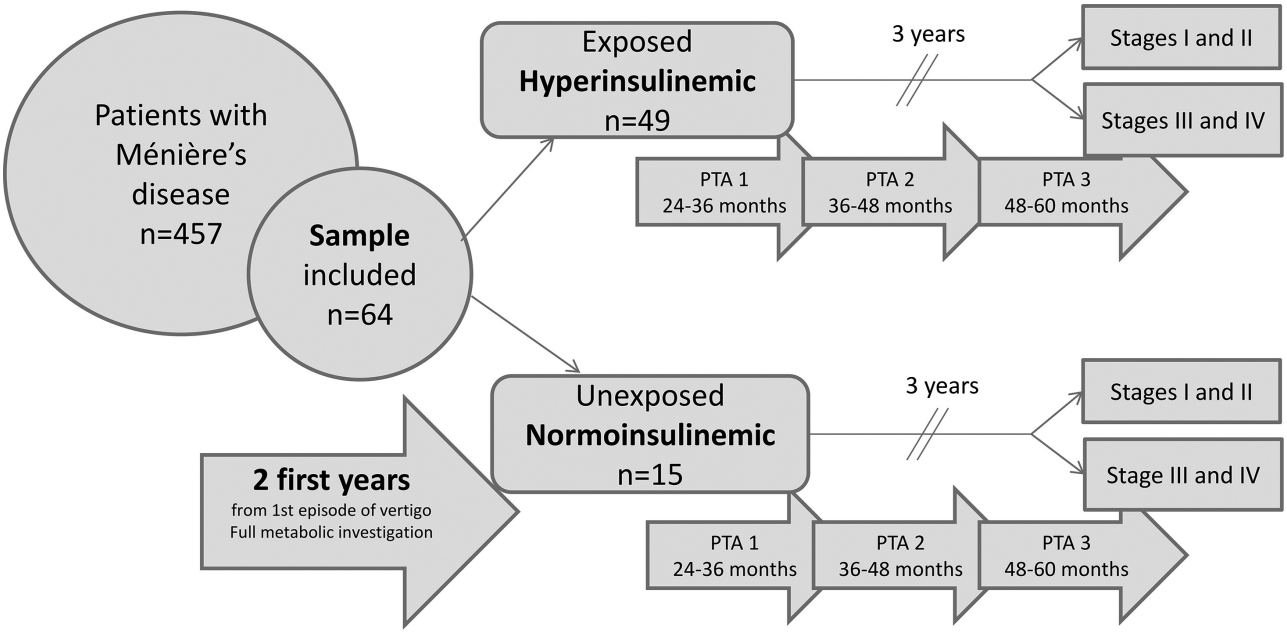

FIG. 1. Study design (PTA = pure-tone audiometry).

Hearing loss assessed by FTA was defined as the primary outcome. Following the AAO-HNS (12) recommendations for clinical studies on MD, we used the FTA (arithmetic mean) of thresholds at 500, 1,000, 2,000, and 3,000 Hz of the more severely impaired ear (in the case of bilateral MD). By the FTA, patients were stratified into 4 stages, according to the AAO-HNS (12), as follows: Stages I (<25 dB), II (26–40 dB), III (41–70 dB), and IV (>70 dB).

The sample size was calculated using the WinPepi program, version 11.24, to detect a difference of 15 dB between hyperinsulinemic and normoinsulinemic groups. The sample size required to detect this difference with 80% power and a 5% significance level would be 55 patients, 44 exposed and 11 unexposed.

The Statistical Package for the Social Sciences (SPSS), version 19.0, was used for data analysis. Continuous variables with normal distribution were expressed as mean ± standard deviation (SD). Categorical variables were described as percentages. Averages were compared using the Student's *t* test for independent samples (if normally distributed) or Mann-Whitney test (if not normally distributed). Comparisons between categorical variables were performed using the χ^2 test, the χ^2 test with Yates' correction, or Fisher's exact test. Analysis of covariance was used to adjust for the confounding variable "age." The Pearson correlation coefficient (*r*) was used to assess correlations among the diagnostic tests. A 2-tailed *p* value less than 0.05 indicated statistically significant differences.

RESULTS

Of the 457 medical records initially reviewed, a total of 393 patients were excluded. The late starting of follow-up (>2 yr after the diagnosis) was the more frequent reason for exclusion (n = 76). Other reasons were

TABLE 1. *Protocol for metabolic investigation used in patients with Ménière's disease and the diagnostic criteria for insulin resistance*

Protocol for metabolic investigation	Criteria for hyperinsulinemia/IR
Insulin curve (5 h with 100 g of glucose overload) (5)	1. Fasting insulin >25 μU/ml 2. Insulinemia at 120 min ≥50 μU/ml 3. Sum of insulin values at 120 and 180 min ≥60 μU/ml
Reactive hypoglycemia in the glucose curve (5 h with 100 g of glucose overload) (5)	1. Glucose ≤55 mg/dl at any point of the curve 2. Progression of fall in blood glucose > 1 mg/dl per minute (when glucose curve values ≥175 mg/dl)
Fasting glucose (mg/dl) (14)	G_0 ≥100 mg/dl and <126 mg/dl
Fasting insulin‡ (μIU/ml) (17)	I_0 >12 μIU/ml
HOMA-IR = G_0 (mg/dl) × I_0 (μIU/ml) /405 (7)	HOMA-IR >2.71
QUICKI = 1/ (log insulin (μIU/ml) + log glucose (mg/dl) (18)	QUICKI <0.333
G_0 (mg/dl) / **I_0** (μIU/ml) **ratio** (19)	G_0/I_0 ratio <6.4

G_0 indicates fasting glucose; HOMA-IR, Homeostasis Model Assessment of Insulin Resistance; I_0, fasting insulin; IR, insulin resistance; QUICKI, Quantitative Insulin Sensitivity Check Index.

"probable" or "possible" diagnosis of MD (n = 72), incomplete clinical treatment (n = 64), less than 3 years of audiometric follow-up (n = 62), Ménière-like conditions (n = 46), laboratory diagnosis of T2DM (n = 41), previous ear surgery/disease (n = 22), and nonidiopathic or metabolic etiology for MD (n = 10).

A total of 64 patients were included and divided into normoinsulinemic and hyperinsulinemic subjects according to their 5-hour insulin curve. The normoinsulinemic group comprised 15 patients (23.4%) and the hyperinsulinemic group, 49 patients (76.6%).

Patients were mostly female subjects (57.8%) in both groups with a mean age of 52.4 ± 2.1 years. Hyperinsulinemic patients were significantly older than normoinsulinemic subjects ($p = 0.031$) Dyslipidemia was highly prevalent (64.1%), as was hypothyroidism (26.6%). Bilateral MD was detected in 20.3% of the sample (Table 2).

In patients with hyperinsulinism, according to the Kraft classification (6), the most frequent type of insulin curve was IIIa (38.77%), followed by IIb (25.53%). Among dyslipidemic patients, the most common finding was low HDL (29.3%), followed by hypertriglyceridemia (17.5%) and hypercholesterolemia (10.3%) alone or in combination (6.9%).

The time interval between the beginning of disease progression (since the first vertigo) and the PTA with the greatest impairment was 3.92 ± 1.5 years, with no significant difference between groups ($p = 0.5$). The FTA was 49.16 ± 9.19 dB, and most patients (57.8%) were classified as stage III by the AAO-HNS criteria (12). All patients underwent PTA with the glycerol test (20), which was positive in 27 patients (42.2%), with no significant difference between groups ($p = 0.5$).

Figure 2 shows a comparison of the hearing thresholds of patients with and without hyperinsulinism as defined by the insulin curve after glucose overload. Impairment of the FTA was statistically higher in the hyperinsulinemic group ($p = 0.027$).

The FTA was classified into Stages I to IV (AAO-HNS). This stratification showed a statistically significant linear association in the χ^2 test ($p = 0.019$) (Fig. 3). Exposed subjects were 3.5 times more likely to progress to Stages III and IV than unexposed subjects (odds ratio [OR] = 3.52; 95% CI, 1.05–11.76) (Fig. 4).

TABLE 2. *Baseline characteristics according to the 5-hour insulin curve results*

Variables	Normoinsulinemic n = 15 (23.4%) n (%) or mean (SD)	Hyperinsulinemic n = 49 (76.6%) n (%) or mean (SD)	*p* value
Female sex	12 (80)	25 (51)	0.09[a]
Age (yr)	41.7 ± 12.4	50.6 ± 13.8	0.03[b]
Dyslipidemia	10 (66.7)	31 (63.3)	1.0[a]
Hypothyroidism	2 (13.3)	15 (30.6)	0.3[a]
Bilateral MD	3 (20)	10 (20.4)	1.0[a]

MD indicates Ménière's disease; SD, standard deviation.
[a]χ^2 test.
[b]Student's *t* test.

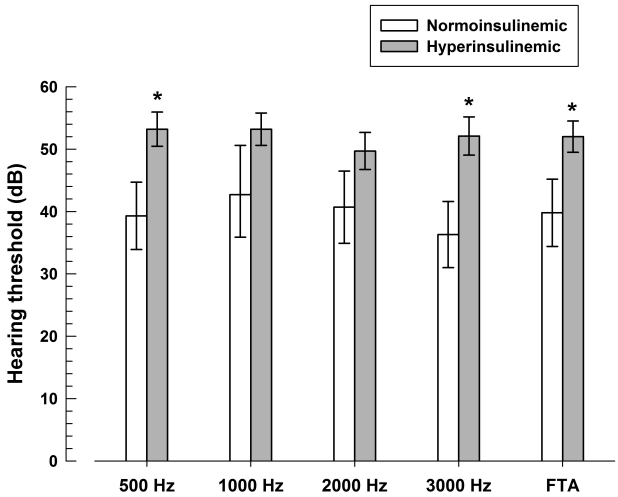

FIG. 2. Comparison of hearing thresholds for each frequency and the FTA between normoinsulinemic and hyperinsulinemic patients (FTA = 4-tone average). Student's *t* test for independent samples (*$p < 0.05$).

The same sample was analyzed using diagnostic tests for insulin resistance without glucose overload and in fasting samples (Fig. 5). Patients with altered fasting glucose levels had greater impairment of FTA than patients with normal levels ($p = 0.032$). All other tests showed worse FTA in insulin-resistant patients but without statistically significant difference ($p > 0.05$).

Reactive hypoglycemia (21) was assessed by 5-hour glucose curves. In the study sample, 28 patients (45.2%) had episodes of reactive hypoglycemia. A comparison of FTA between patients without reactive hypoglycemia (44.8 ± 18.8 dB) and with hypoglycemia (52.1 ± 17.2 dB) showed no statistical significance ($p = 0.12$).

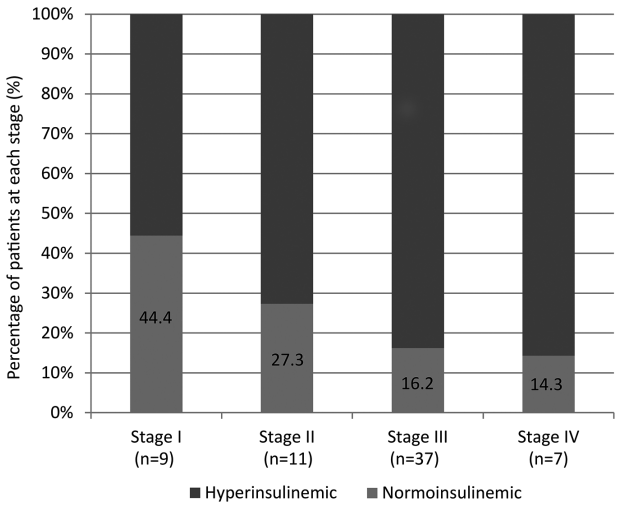

FIG. 3. Percentage of normoinsulinemic and hyperinsulinemic subjects at different stages (AAO-HNS criteria: I < 25 dB; II, 26–40 dB; III, 41–70 dB; and IV >70 dB). Linear and statistically significant distribution ($p = 0.019$).

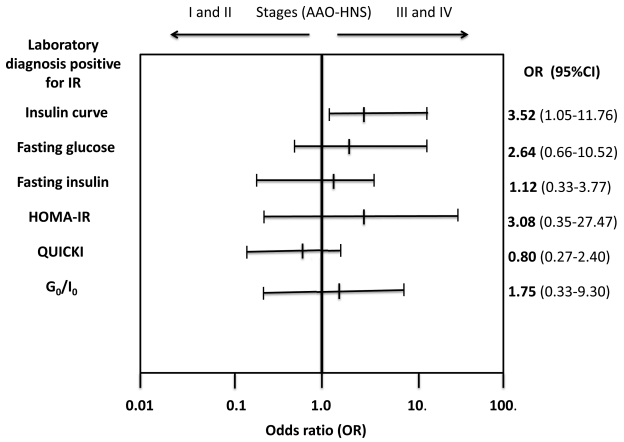

FIG. 4. Chance to progress to Stages III and IV (AAO-HNS) in the presence of insulin resistance (IR) by different methods of laboratory analysis (G_0 = fasting glucose; HOMA-IR = Homeostasis Model Assessment of Insulin Resistance; I_0 = fasting insulin; QUICKI = Quantitative Insulin Sensitivity Check Index).

There was a statistically significant correlation ($p < 0.05$) between insulin curves, as stratified into ascending grades of severity, according to the Kraft criteria (6), and absolute values of fasting tests (Table 3). Insulin curve types showed statistically significant correlation with the other tests, being moderate correlated ($r > 0.5$) with fasting insulin measurements and HOMA-IR. However, the degree of agreement in the differentiation of normal and abnormal patients between the insulin curve and the other tests was poor (Kappa index, <0.2).

DISCUSSION

Different studies have shown that hyperinsulinism is a common metabolic disorder in patients with MD. In our sample, the prevalence of hyperinsulinism using the insulin curve was 76.6%. This finding is in agreement with previous reports: Kirtane et al. (9), using the same diagnostic method in patients with MD, reported hyperinsulinism in 67.7% of the sample. In a study conducted by D'Avila and Lavinsky (11), the prevalence of alterations was 72%, and the most frequent types of insulin curves were IIb (39.06%) and IIIa (18.75%). Therefore, studies available are unanimous in showing that most patients with MD have varying degrees of hyperinsulinism when assessed by the insulin curve.

In samples of patients with cochleovestibular disorders (not only MD), the prevalence of hyperinsulinism was also high. In a study involving 100 patients, Mangabeira-Albernaz et al. (10) reported hyperinsulinism in 86% of patients who were evaluated by a 5-hour insulin curve. More recently, in a similar population, Serra et al. (22) identified hyperinsulinism in 55.5% using a 4-hour insulin curve.

Among the metabolic disorders assessed in this study, hyperinsulinism was the most prevalent (76.6%), followed by dyslipidemia (64.1%), reactive hypoglycemia (45.2%), and hypothyroidism (20.3%). To date, only 2 clinical studies (9,11) have assessed the prevalence of disorders of carbohydrate metabolism specifically in MD. Thus, the lack of evidence hinders comparisons with the literature.

A literature search (PubMed, Embase, and LILACS) returned no comparative studies evaluating the impact of metabolic disorders on clinical outcomes of MD. Likewise, the few clinical studies found in the literature have been limited to assess the prevalence of different metabolic disorders in patients with MD. Therefore, this is the first comparative, longitudinal study on the subject.

The AAO-HNS criteria (12) were strictly followed in patient selection, and the definition of the diagnosis was predominantly based on clinical factors. We only included patients with a "definite" diagnosis of MD and excluded those with "possible" or "probable" MD. Furthermore, based on a thorough (clinical, laboratory, electrophysiologic, and imaging) investigation, Ménière-like conditions were excluded.

As recommended in the AAO-HNS guidelines (12), staging of MD severity in clinical studies should be conducted objectively through the FTA. The number of episodes of vertigo and aural fullness/tinnitus intensity are extremely subjective and ambiguous. The use of other tests, such as ECochG, glycerol test, and vestibular-evoked myogenic potential (VEMP) testing, is encouraged in daily practice but not yet recommended by the AAO-HNS in clinical studies (12) because of the lack of standardization. Furthermore, there is evidence that cochlear damage is proportional to vestibular hypofunction (23) in

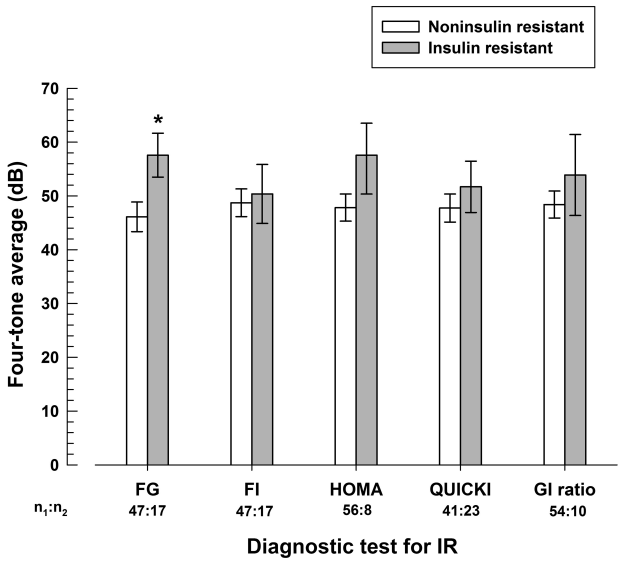

FIG. 5. Comparison of the FTA among patients with and without insulin resistance as diagnosed by different laboratory tests (FTA = 4-tone average; FG = fasting glucose; FI = fasting insulin; HOMA-IR = Homeostasis Model Assessment of Insulin Resistance; QUICKI = Quantitative Insulin Sensitivity Check Index; GI ratio = glucose-insulin ratio). Student's *t* test for independent samples (*$p < 0.05$).

TABLE 3. *Correlation between different degrees of hyperinsulinism (Kraft criteria) by the insulin curve and other diagnostic tests in homeostasis (Pearson coefficient)*

	Degrees of hyperinsulinism	Fasting insulin	Fasting glucose	HOMA-IR	QUICKI	G_0/I_0
Degrees of hyperinsulinism	1					
Fasting insulin	0.511[b]	1				
Fasting glucose	0.261[a]	0.326[b]	1			
HOMA-IR	0.524[b]	0.994[b]	0.370[b]	1		
QUICKI	−0.432[b]	−0.829[b]	−0.469[b]	−0.847[b]	1	
G_0/I_0	−0.323[b]	−0.677[b]	−0.104	−0.681[b]	0.898[b]	1

[a]Significant correlation at the 0.01 level (2-tailed).
[b]Significant correlation at the 0.05 level (2-tailed).

MD. Therefore, the FTA can be considered as a parameter to stage MD severity.

As recommended in the AAO-HNS guidelines (12), the FTA with the greatest damage during follow-up was chosen as the parameter for the characterization of hearing outcomes. PTA tests performed within the first 2 years of disease progression were excluded because it is a period of intense fluctuation of hearing thresholds (24).

Several retrospective studies on the natural history of disease progression (without clinical treatment) in MD have shown that in most patients, the hearing thresholds stabilize at 50 to 60 dB after 4 to 5 years (25). In our series, in which all patients received full clinical treatment, the overall FTA during this period was 49.16 ± 9.19 dB, and the greatest hearing damage was found after 3.92 years of disease progression. Therefore, the prescription of clinical treatment does not seem to prevent the progression of hearing loss in MD.

Despite no history of hearing loss, ear surgery or illness before the first episode of vertigo, there was no baseline PTA documentation (close to the first vertigo) showing hearing thresholds within normal limits. Moreover, a mean interval of 6 months elapsed between referral from the health facility and the first audiologic tests. This could be a potential confounding bias; however, rather than using the FTA difference (delta) in relation to baseline as an outcome, we used the absolute values of the greatest impairment during follow-up.

In this cohort study, the date of the first vertigo was considered the ''zero'' point for monitoring. The study was designed so that all patients included (exposed and unexposed) were in the same stage of disease progression, as this would increase the homogeneity of the sample. However, the disease may have started years before this ''zero'' point with oligosymptomatic cochleovestibular symptoms, and consequently, patients may have been at different stages within the course of the disease.

The mean age of the sample was 52.4 years. At this age, there is little influence of age on auditory degeneration. Nevertheless, when analyzing baseline characteristics, the hyperinsulinemic group showed significantly higher mean age ($p = 0.031$). This difference could be a confounding bias because patients at an older age could present worse hearing thresholds. Thus, this difference was adjusted by analysis of covariance to control for this potential bias, as the ''mean age'' could be an interaction variable.

The group of patients with hyperinsulinism, whether as a cause or aggravation of MD, exhibited greater hearing impairment. Patients exposed to hyperinsulinism were 3.5 times more likely to have hearing loss greater than 40 dB (Stage III or IV) than normoinsulinemic patients. This analysis indicates that patients exposed to hyperinsulinism are more likely to show more severe degrees of hearing damage.

The most striking difference was observed at 500 and 3,000 Hz, that is, in the apical and middle regions of the cochlea, respectively. These are classic frequencies of hearing impairment by metabolic disorders in the inner ear, characterizing the classic inverted U-shaped audiometric pattern. The inclusion of a third group of patients with hyperinsulinism and without MD might have allowed us to estimate the independent impact of hyperinsulinism on this pattern of sensorineural hearing loss.

Similar to the difference found by analyzing the insulin curve, ''altered'' fasting glucose levels (impaired glucose tolerance) were associated with greater hearing damage, compared with patients with normal levels. We excluded patients with diabetes (fasting glucose, >126 mg/dl) because there is evidence that diabetes may cause sensorineural damage by several mechanisms, such as microangiopathy and neuropathy.

Measurement of fasting glucose, similar to the findings in the insulin curve, showed that ''pre-diabetes'' stages may have clinical significance in MD. Moreover, it is an easy-to-use test, with broad and unrestricted acceptance in the literature. However, the proportion of abnormal patients (26.6%) was markedly lower compared with the results of the insulin curve (76.6%), that is, they have a poor correlation ($r = 0.261$) and agreement ($k < 0.2$).

In this study, measurement of fasting insulin and mathematical models (QUICKI, HOMA-IR, and G_0/I_0) were unanimous in demonstrating that insulin-resistant patients showed worse FTA. When comparing the FTA between resistant and nonresistant subjects, this difference was not statistically significant ($p > 0.05$). Thus, among tests without overload, only altered fasting glucose levels were able to differentiate the impact in the auditory sphere.

Although the degree of hyperinsulinism (by the insulin curve) showed a significant correlation with all tests performed, this correlation was only considered ''moderate'' ($r > 0.5$) with HOMA-IR and fasting insulin. That is, more advanced grades of hyperinsulinism show higher HOMA-IR and fasting insulin values.

However, the insulin curve considered "abnormal" had poor diagnostic agreement ($k < 0.2$) with the HOMA-IR considered "altered." Whereas the curve showed abnormalities in 76.6% of patients, the same occurred in only 12.5% with HOMA-IR in the same sample. Currently, HOMA is the index of choice for assessment of IR in clinical studies (8). Additionally, HOMA-IR shows strong correlation with the clamp, the gold standard for diagnosis of IR ($r = 0.88$). However, the cutoff point of this test for defining IR is still arguable. We used the value of 2.71, as there are population-based studies (7) that recommend this cutoff point for the general nondiabetic Brazilian population.

Therefore, the insulin curve was the method that demonstrated changes in a higher proportion of patients compared with fasting tests. Although the tests show correlation with each other, they differ in the ability to identify insulin-resistant subjects. The insulin curve probably shows higher sensitivity and lower specificity than HOMA-IR. However, to date, there are no studies on the sensitivity/specificity profile of the insulin curve in relation to the gold standard (clamp).

This study follows a line of research focused on the metabolic investigation of MD by the Research Group in Otology and Neurotology of our institution. Although previous studies have been conducted, they have been designed as experimental (3,4) or observational clinical trials, with a cross-sectional but not comparative design (11). This study is the first in the literature to evaluate the clinical impact of metabolic disorders in MD both comparatively and longitudinally.

In conclusion, patients with MD and hyperinsulinism/IR, as characterized by the insulin curve and altered fasting glucose levels, showed greater hearing impairment. Patients exposed to hyperinsulinism were 3.5 times more likely to have hearing loss greater than 40 dB (Stages III and IV) than normoinsulinemic patients. In patients with MD, there was a moderate correlation between the severity of hyperinsulinism, as defined by the 5-hour insulin curve, and other diagnostic methods used to assess IR in fasting samples.

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