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OTOLOGY

# Clinical observations and risk factors for tinnitus in a Sicilian cohort

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**Abstract** The aims of this study were to determine the distribution of risk factors associated with tinnitus analysing their role in the development of tinnitus and the effects of their interaction; to evidence the importance of a suitable and adequate clinical and audiologic assessment to avoid those modifiable risk factors responsible for cochlear dysfunction and tinnitus onset. 46 subjects with tinnitus and 74 controls were studied according to: age, sex, Body Mass Index (BMI), neck circumference, tobacco smoking, feeling fatigue or headache, self reporting snoring, hypertension, diabetes, coronary heart disease, and/or hyperlipidemia, and laboratory finding as lipid profile and levels of reactive oxygen metabolites (d-ROM). Audiological assessment was performed by multi-frequency audiometry ($PTA_{0.5–16\ kHz}$) and transient-evoked otoacoustic emissions (TEOAE diagnostic). Univariate analysis was performed to examine the association between determinants and occurrence of tinnitus; Mantel–Haenszel test (*G.or*) was used to investigate the joint effect of determinants on tinnitus. Tinnitus was more frequent among males with age >50 years; BMI >30 kg/m$^2$, neck circumference >40 cm, headache, hypertension, hypercholesterolemia resulted significant risk factors for tinnitus ($P < 0.0001$). Tinnitus group had more comorbidity ($P < 0.0001$) and worse audiometric thresholds (60.87 Vs 21.62 % hearing loss; $P < 0.0001$) with respect to control group. The interaction between hypertension–BMI $\geq$ 30 kg/m$^2$ ($G.or = 8.45$) and smoking–hypercholesterolemia ($G.or = 5.08$) increases the risk of tinnitus ($P < 0.0001$). Our results underline that several factors either individually or jointly contribute to tinnitus onset; a comprehensive knowledge about tinnitus risk factors and associated clinical conditions could contribute to minimizing this disorder.

**Keywords** Tinnitus · Hearing loss · Risk factors · Multi-frequency audiometry · TEOAE

## Introduction

Tinnitus is the perception of noise in the absence of an acoustic stimulus [1]. This common condition especially in Western societies [2–6] is usually subjective, perceived only by the patient, and therefore, diagnosis and monitoring rely on self-report.

About one-third of the population experiences tinnitus at least once in their life and about 1–5 % develops serious psychosocial complications; Quaranta et al. [7] evidenced a tinnitus prevalence of 14.5 % in Italian patients (8 % in normal hearing subjects, 30.5 % in presence of auditory dysfunctions) while Girard et al., studying 41631 Canadians subjects, found a lower prevalence (5.2 %) [8]; in

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Germany ~1.5 million people have problems with tinnitus and 800.000 suffer so severely that they are in continuous medical treatment [9].

The generation of an abnormal signal, which will in a cascade of events yield the tinnitus perception, can depend on different mechanisms [1]. In most cases the origin of tinnitus is unknown but a close association between tinnitus and hearing dysfunction is well documented. Six main pathways were recognized: (1) discordant damage of outer (OHC) and inner (IHC) hair cells systems [1, 10–12]; (2) crosstalk between the VIII nerve fibres [13–15]; (3) ionic imbalance in the cochlea [11, 16, 17]; (4) dysfunction of cochlear neurotransmitter systems [14, 16, 17]; (5) heterogeneous activation of the efferent system [10, 13, 17]; (6) heterogenous activation of Type I and II cochlear afferents [1, 10, 13, 17].

The 'discordant damage hypothesis' postulates that tinnitus is generated in the part of the basilar membrane characterized by preserved IHCs and damaged or temporarily dysfunctional OHCs [18–20]. This hypothesis explains the occurrence of tinnitus in patients without hearing loss, as diffuse damage of up to 30 % of OHCs can occur without any associated detectable hearing loss [18]. An OHC's damage could be identified using Transient Otoacoustic Emission (TEOAE).

In the last years many aetiological factors have been studied and considered as potential causes of tinnitus and/or co-factors (i.e. vascular disease, diabetes, hypertension, autoimmune disorders, and degenerative neural disorders) [12, 22, 23]. All these conditions could be responsible for a periodic hypoxia/re-oxygenation with a consequent oxidative stress, endothelial dysfunction, and activation of the inflammatory cascade [24]. These noxious stimuli can activate the sympathetic nervous system, depress parasympathetic activity, provoke oxidative stress and systemic inflammation, activate platelets, and impair vascular endothelial cochlear function.

In Italy different regional programmes are applied to achieve the goal of an early tinnitus detection and prevention and the initiatives are still left to individual hospitals.

The aim of this study was to determine the distribution of risk factors associated with tinnitus analyzing their role in the development of tinnitus and the effects of their interaction; to evidence the importance of a suitable and adequate clinical and audiologic assessment to avoid those modifiable risk factors responsible for cochlear dysfunction and tinnitus onset.

## Materials and methods

The study was designed as a matched case–control study on 134 subjects, 87 males and 47 females, ranging from 14 to 85 years of age, who were visited at the Audiology Section of the Department of Bio-technology of Palermo University.

All patients underwent careful medical history (to identify audiological pathologies and other health diseases) and otological examination by otolaryngologists. Subjects with cranio-facial abnormality (CFA), syndromes associated with HL, history of ototoxic drugs administration, otosclerosis, acoustic neuroma, chronic otitis, previous myringotomy, ventilation tube insertion, tympanoplasty, and coexisting psychiatric disorders were excluded from this study.

The study protocol was completely explained to patients and written informed consent was obtained from each subject. The study design was approved by the Palermo University Human Research Ethics Committee.

Data for each patient were collected regarding: age (seven age groups: ≤20, from 21 to 30, 31 to 40, 41 to 50, 51 to 60, 61 to 70 and >70), sex, Body Mass Index (BMI—kg/m$^2$ categories: <21.0, 21.0–22.9, 23.0–24.9, 25.0–26.9, 27.0–29.9, ≥30), neck circumference (<40 cm; ≥40 cm), tobacco smoking, feeling fatigued or headache (Yes/No) and self reporting snoring (Yes/No). Comorbidity such as hypertension (systolic BP [SBP] <140 mmHg or diastolic BP [DBP] <90 mmHg, SBP 140–159 mmHg or DBP 90–99 mmHg, SBP 160–179 mmHg or DBP 100–109 mmHg, SBP ≥180 mmHg or DBP ≥110 mmHg), diabetes (Yes/No), coronary heart disease (Yes/No), and hyperlipidemia (lipid profile: total cholesterol level and HDL level) were also investigated. All patients underwent d-ROMs test that study the levels of reactive oxygen metabolites (ROM) in blood plasma and serum. Specifically the d-ROMs test is based on spectrophotometer studies on increases in red colour intensity after the addition of a small quantity of human blood to a solution of *N*,*N*-diethylparaphenylendiamine (chromogen), buffered to pH 4.8. Such colouring is attributed to the formation, via oxidation, of the cation radical of the amine which formation is due to alkoxyl and peroxyl radicals. These latter derive from the reaction of the $Fe^{2+}$ and $Fe^{3+}$ ions released by proteins in acidic condition as created in vitro [25]. Reference values of d-ROMs test expressed by Carratelli Units (CARR U—1 CARR U corresponds to 0.08 mg of $H_2O_2$/dL), are between 250 and 300 CARR U independently on gender and age; values higher than 300 CARR U indicate, after a borderline bracket (301–320 CARR U), progressively increasing levels of oxidative stress: 321–340 CARR U—low level oxidative stress; 341–400 CARR U—middle level of oxidative stress; 401–500 CARR U—high level of oxidative stress; >500 CARR U—very high level of oxidative stress [25].

The sample was divided in two groups: subjects with tinnitus (cases) and subjects without tinnitus (controls).

Multi-frequency audiometry (considering the frequencies 0.25–0.5–1–2–3–4–6–8–9–10–11.2–12.5–14–16 kHz), impedenzometry and transient-evoked otoacoustic emissions (TEOAE diagnostic) were performed for each ear.

Audiometric threshold was considered as the pure tone average for the frequencies 0.5–1–2–4 kHz ($PTA_{0.5–4\ kHz}$) and divided in: normal hearing (<20 dB); light hearing loss (21–40 dB); moderate hearing loss (41–70 dB); severe hearing loss (71–90 dB); profound hearing loss (>90 dB). Piano Plus VRA by Inventis S.r.l. (two separate and identical channel; frequency range: 125–8,000 Hz; 8–20 Hz) was used for testing the subjects.

TEOAE measurements were evaluated in reproducibility (expressed as the correlation between two waveforms, namely for responses stored in buffers A and B, acquired alternately) and were done using defined criteria as response detection in 4/5 different frequency bands (1, 1.5, 2, 3, and 4 kHz); a minimum signal-to-noise ratio (SNRs) of 6 dB for each frequency band was chosen. The instrument used was the 'SENTIERO by Path Medical GmbH', that is based on the nonlinear cross-correlation method (ILO88) of TEOAE recording. The TEOAE diagnostic was conducted by placing a small probe tip from the 'Path Medical' (3.9 mm diameter × 11.7 mm) inside the patient's ear canal; when powered on, the instrument initiated a routine self-calibration before recordings were made. The click rate was approximately 97 per second and each stimulus (at the probe loud-speaker output) consisted of a single 80 μs square pulse. To eliminate passive mechanical artefact from the recorded waveform, stimuli were presented in blocks of four stimuli: three small positive polarity stimuli followed by one big negative polarity stimulus three times as large. Click peak stimulus level was 80 dB SPL. Emissions elicited from the outer hair cells in response to the clicks were picked up by the internal microphone of the equipment and were windowed and filtered to remove unwanted signals; all response data outside a window from 5 to 13 ms, after the stimulus, were removed to eliminate the stimulus signal.

Cases compiled the Tinnitus Handicap Inventory (THI) to evaluate the perceived severity of tinnitus and its impact on life. This tool is a 25-item survey that is composed of three subscales: a functional subscale (12 items), an emotional subscale (8 items) and a catastrophic response subscale (5 items) which address role and physical functioning, psychological distress, desperation and loss of control, respectively. Each item has 3 potential answers with "yes" assigned 4 points, "sometimes" 2 points, and "no" 0 points. This leads to a total score ranging from 0 (indicating no tinnitus handicap) to 100 (indicating the worst patients' annoyance). Classically it grades five categories of tinnitus severity: slight (0–16); mild (18–36); moderate (38–56); severe (58–76); catastrophic (78–100).

The audiologic measurements of tinnitus included pitch masking (matching the frequency of the tinnitus with a variety of stimuli) and loudness matching (estimating the loudness of tinnitus with a pure tone or noise); the difference between the hearing threshold and the sensation level was considered tinnitus loudness (0–5, 5, 10, 15, > 15 dB above the hearing threshold).

Statistical analysis was performed with Matlab® computer programme; $\chi^2$ test, *t* test, Fisher's exact test, logistic odds ratio (or) and Mantel–Haenszel test were used, following usual conditions of application.

## Results

### Study sample

The patients examined were 132 but 12 subjects were excluded from the study because of CFA (1 case), history of ototoxic drugs administration (5 cases), otosclerosis (2 cases), chronic otitis (3 cases) and previous tympanoplasty (1 case); 120 subjects were included in the cohort studied.

The age range of patients was from 14 to 85 years old, with a mean age of 57.6 years ± 13.15. The 79.16 % of subjects were >50 years old; 77 (64.16 %) patients were males and 43 were females with a male/female ratio of 1.79 (Table 1).

Forty-six subjects (38.33 %) suffered from tinnitus; of them, 31 were males (67.39 %) while 15 were females (male/female ratio 2.06). Of the 74 patients of the control group, 46 (62.16 %) were males and 28 were females with a male/female ratio of 1.64 ($P = 0.5$). With mean age values of 58.10 ± 13.28 and 57.34 ± 13.12, respectively, for cases and controls, it resulted in no statistical difference among the groups ($P = 0.98$).

### Clinical characteristics

The 22.5 % (27/120) of the total cohort had a BMI value at risk for health (>30 $kg/m^2$); of them 21 suffered from tinnitus while 7 were controls (Table 1). Tinnitus patients had higher BMI values contrasting with controls, with the 43.47 % (20/46) of tinnitus group with BMI ≥30 with regards to the 9.46 % (7/74) of control group ($P < 0.0001$).

Even if the 74.16 % of the cohort presented a neck circumference value <40 cm (89 subjects, 26 with tinnitus and 63 controls), the 43.48 % of tinnitus group had a neck circumference value ≥40 cm with respect to the 14.86 % of controls ($P < 0.0001$).

No statistical difference was found among the groups in the distribution of tobacco smoking ($P = 0.85$).

Feeling fatigue or headache was reported by the 39.17 % (47/120) of patients; the distribution among

**Table 1** Clinical characteristics of the cohorts; tinnitus patients Vs control group: statistical analysis

| | Total cohort *N* (%) | Tinnitus patients *N* (%) | Controls *N* (%) | Statistical analysis | |
|---|---|---|---|---|---|
| | 120 (100) | 46 (38.33) | 74 (61.67) | *or* (*P*) 95 %CI | $\chi^2$ (*P*) |
| Sex | | | | 1.26 (0.5) 0.58–2.73 | 0.34 (0.5) |
| Male | 77 (64.16) | 31 (67.39) | 46 (62.16) | | |
| Female | 43 (35.84) | 15 (32.61) | 28 (37.84) | | |
| Age (years) | | | | | |
| Mean ± standard deviation | 57.6 ± 13.15 | 58.10 ± 13.28 | 57.34 ± 13.12 | *t* test = 0.3 (0.7) | |
| Range | 14–85 | 14–85 | 14–85 | | |
| ≤50 | 25 (20.84) | 9 (19.56) | 16 (21.62) | 1.13 (0.78) 0.35–2.20 | 0.07 (0.78) |
| >50 | 95 (79.16) | 37 (80.44) | 58 (78.38) | | |
| ≤20 | 2 (1.66) | 1 (2.17) | 1 (1.35) | | 0.989 (0.98) |
| 21–30 | 1 (0.83) | 0 (−) | 1 (1.35) | | |
| 31–40 | 9 (7.5) | 3 (6.52) | 6 (8.1) | | |
| 41–50 | 13 (10.83) | 5 (10.87) | 8 (10.81) | | |
| 51–60 | 51 (42.5) | 19 (41.3) | 32 (43.24) | | |
| 61–70 | 29 (24.16) | 12 (26.08) | 17 (22.97) | | |
| >70 | 15 (12.5) | 6 (13.04) | 9 (12.16) | | |
| Body mass index (BMI) (kg/m$^2$) | | | | | |
| <30 | 93 (77.7) | 26 (56.53) | 67 (90.54) | 7.36 (<0.0001) 2.38–19.47 | 18.83(<0.0001) |
| ≥30 | 27 (22.3) | 20 (43.47) | 7 (9.46) | | |
| <21.0 | 6 (5) | – | 6 (8.11) | | 52.4 (<0.0001) |
| 21.0–22.9 | 40 (33.33) | 2 (4.35) | 38 (51.35) | | |
| 23.0–24.9 | 36 (30) | 16 (34.78) | 20 (27.02) | | |
| 25.0–26.9 | 3 (2.5) | – | 3 (4.05) | | |
| 27.0–29.9 | 8 (6.66) | 8 (17.39) | – | | |
| ≥30 | 27 (22.5) | 20 (43.47) | 7 (9.46) | | |
| Neck circumference | | | | 4.41 (<0.0001) 1.85–10.47 | 12.1 (<0.0001) |
| <40 | 89 (74.16) | 26 (56.52) | 63 (85.14) | | |
| ≥40 | 31 (25.84) | 20 (43.48) | 11 (14.86) | | |
| Tobacco smoking | | | | 0.93 (0.035) 0.43–2.00 | 0.035 (0.85) |
| Yes | 43 (35.87) | 16 (34.79) | 27 (36.49) | | |
| No | 77 (64.16) | 30 (65.21) | 47 (63.51) | | |
| Feeling fatigued or headache | | | | 7.49 (<0.0001) 3.27–17.15 | 24.9 (<0.0001) |
| Yes | 47 (39.17) | 31 (67.39) | 16 (21.63) | | |
| No | 73 (60.83) | 15 (32.61) | 58 (78.37) | | |
| Self reporting snoring | | | | 3.13 (0.04) 0.98–9.99 | 4.01 (0.04) |
| Yes | 99 (82.5) | 42 (91.31) | 57 (77.02) | | |
| No | 21 (17.5) | 4 (8.69) | 17 (22.98) | | |
| Hypertension | | | | 12.14 (<0.0001) 5.04–29.23 | 35.75 (<0.0001) |
| Yes | 48 (40) | 34 (73.91) | 14 (18.91) | | |
| No | 72 (60) | 12 (26.09) | 60 (81.09) | | |
| SBP <140 mmHg or DBP <90 mmHg | 72 (60) | 12 (26.09) | 60 (81.09) | | |
| SBP 140–159 mmHg or DBP 90–99 mmHg | 14 (11.66) | 10 (21.73) | 4 (5.41) | | 36.0 (<0.0001) |
| SBP 160–179 mmHg or DBP 100–109 mmHg | 25 (20.83) | 17 (36.95) | 8 (10.81) | | |

**Table 1** continued

| | Total cohort *N* (%) 120 (100) | Tinnitus patients *N* (%) 46 (38.33) | Controls *N* (%) 74 (61.67) | Statistical analysis | |
|---|---|---|---|---|---|
| | | | | *or* (*P*) 95 %CI | $\chi^2$ (*P*) |
| SBP ≥180 mmHg or DBP ≥110 mmHg | 9 (7.5) | 7 (15.21) | 2 (2.70) | | |
| Diabetes | | | | 1.72 (0.33) 0.56–5.26 | 0.91 (0.33) |
| Yes | 14 (11.66) | 7 (15.21) | 7 (9.46) | | |
| No | 106 (88.34) | 39 (84.79) | 67 (90.54) | | |
| Coronary heart disease | | | | 0.57 (0.31) 0.19–1.73 | 1 (0.31) |
| Yes | 18 (15) | 5 (10.87) | 13 (17.56) | | |
| No | 102 (85) | 41 (89.18) | 61 (82.44) | | |
| Hypercholesterolemia | | | | 7.56 (<0.0001) 2.97–19.25 | 20.7 (<0.0001) |
| Yes | 30 (25) | 22 (47.82) | 8 (10.80) | | |
| No | 90 (75) | 24 (52.17) | 66 (94.59) | | |
| <200 mg/dl | 90 (75) | 24 (52.17) | 66 (89.2) | | 21.9 (<0.0001) |
| 200–239 mg/dl | 19 (15.83) | 15 (32.60) | 4 (5.4) | | |
| ≥240 mg/dl | 11 (9.16) | 7 (15.21) | 4 (5.4) | | |
| Total cholesterol level (mg/dl) | | | | | |
| Mean ± standard deviation | 178.75 ± 42.60 | 199.24 ± 48.45 | 166.22 ± 33.00 | *t* test = 4.37 (<0.0001) | |
| Range | 101–315 | 103–315 | 101–250 | | |
| HDL level (mg/dl) | | | | | |
| Mean ± standard deviation | 47.19 ± 12.88 | 45.41 ± 13.00 | 48.24 ± 12.85 | *t* test = 1.16 (0.2) | |
| Range | 28 – 86 | 30 – 86 | 28 – 86 | | |
| <40 mg/dl | 35 (29.16) | 16 (34.78) | 19 (25.67) | 1.54 (0.38) 0.69–3.44 | 1.94 (0.38) |
| 40–59 mg/dl | 60 (50) | 23 (50) | 37 (50) | | |
| ≥60 mg/dl | 25 (20.84) | 7 (15.21) | 18 (24.32) | | |
| d-ROM test (CARR U) | | | | | |
| Mean ± standard deviation | 323.29 ± 56.87 | 331.11 ± 59.54 | 318.43 ± 55.0 | *t* test = 1.18 (0.23) | |
| Range | 215–480 | 215–456 | 215–480 | | |
| ≤400 | 105 (87.5) | 38 (82.61) | 67 (90.54) | 2.02 (0.03) 0.68–5.99 | |
| >400 | 15 (12.5) | 8 (17.39) | 7 (9.46) | | |
| <300 CARR U | 42 (35) | 14 (30.43) | 28 (37.84) | | 10.7 (0.03) |
| 300–320 CARR U | 22 (18.33) | 4 (8.69) | 18 (24.32) | | |
| 321–340 CARR U | 20 (16.66) | 7 (15.22) | 13 (17.57) | | |
| 341–400 CARR U | 21 (17.5) | 13 (28.26) | 8 (10.81) | | |
| 401–500 CARR U | 15 (12.5) | 8 (17.39) | 7 (9.46) | | |
| >500 CARR U | – | – | – | | |

groups evidenced significant differences with the 67.39 % of tinnitus group positive to this factor in respect to the 21.63 % of controls ($P < 0.0001$). Also the 'self reporting snoring' reported by the 82.5 % of the cohort evidenced a higher percentage among tinnitus patients with regards to controls (91.31 Vs 77.02 %; $P = 0.04$).

Hypertension was present in 73.91 % of tinnitus group contrasting with 18.91 % of controls ($P < 0.0001$) with tinnitus patients more at risk of suffering a severe hypertension ($P < 0.0001$). Diabetes and coronary heart disease were found, respectively, in the 11.66 % (14/120) and the 15 % (18/120) of the cohort without significant difference between cases and controls ($P > 0.05$).

Hypercholesterolemia resulted more frequently among patients affected by tinnitus (47.82 %) than controls (10.80 %) ($P < 0.0001$). Particularly serum cholesterol values ≥240 mg/dl were evidenced in the 15.21 and 5.4 % of cases (mean values of 199.24 ± 48.45 mg/dl) and control group (mean values of 166.22 ± 33.00 mg/dl), respectively ($t = 4.37$; $P < 0.0001$). The analysis of HDL

**Table 2** Audiological characteristics of the cohorts: Tinnitus population Vs Control group: analysis statistical

| | Total cohort *N*(%) | Tinnitus Patients (G1) *N*(%) | Controls (G2) *N*(%) | Statistical analysis |
|---|---|---|---|---|
| Hearing of population | 120 | 46 (38.34) | 74 (61.66) | $\chi^2 = 18.82$ ($P < 0.0001$) or = 5.64 95 % CI = 2.51–12.68 |
| Normal Hearing | 76 (63.33) | 18 (39.13) | 58 (78.38) | |
| Hearing Loss | 44 (36.67) | 28 (60.87) | 16 (21.62) | |
| Bilateral | 39 | 27 | 12 | |
| Unilateral | 5 | 1 | 4 | |
| Hearing threshold | 120 | 46 | 74 | $\chi^2 = 22.7$ ($P < 0.0001$) |
| Normal hearing | 76 (63.33) | 18 (39.13) | 58 (78.38) | |
| Light HL | 38 (31.66) | 22 (47.82) | 16 (21.62) | |
| Moderate HL | 6 (5) | 6 (13.04) | – | |
| Severe HL | – | – | – | |
| Profound HL | – | – | – | |
| Hearing threshold | mean (dB) ± stand. dev | | | *t* test (*P*) |
| Frequency (kHz) | | | | |
| 0.25 | 18.04 ± 6.41 | 17.77 ± 8.43 | 18.2 ± 4.77 | 0.5 (0.61) |
| 0.5 | 18.7 ± 7.31 | 19.51 ± 10.13 | 18.2 ± 4.77 | 1.35 (0.18) |
| 1 | 19.72 ± 9.47 | 22.17 ± 13.75 | 18.2 ± 4.77 | 3.22 (0.001) |
| 2 | 20.97 ± 10.32 | 24.07 ± 15.18 | 19.05 ± 4.56 | 3.76 (<0.001) |
| 3 | 21.95 ± 11.48 | 27.47 ± 16.56 | 18.51 ± 3.66 | 6.34 (<0.001) |
| 4 | 27.68 ± 13.95 | 37.55 ± 17.98 | 21.55 ± 4.19 | 10.39 (<0.001) |
| 6 | 31.25 ± 16.46 | 43.04 ± 21.44 | 23.91 ± 3.89 | 10.59 (<0.001) |
| 8 | 35.56 ± 21.14 | 53.75 ± 22.84 | 24.25 ± 8.27 | 14.29 (<0.001) |
| 9 | 46.04 ± 34.08 | 67.17 ± 31.43 | 32.9 ± 28.71 | 8.66 (<0.001) |
| 10 | 49.56 ± 34.34 | 71.9 ± 31.89 | 35.67 ± 27.94 | 9.24 (<0.001) |
| 11.5 | 53.54 ± 35.82 | 80.21 ± 30.85 | 36.95 ± 27.84 | 11.22 (<0.001) |
| 12.5 | 58.77 ± 39.8 | 92.01 ± 30.79 | 38.1 ± 29.45 | 13.55 (<0.001) |
| 14 | 61.33 ± 44.36 | 101.52 ± 29.77 | 36.35 ± 31.8 | 15.8 (<0.001) |
| 16 | 65.27 ± 46.48 | 111.14 ± 24.55 | 36.75 ± 31.69 | 19.21 (<0.001) |
| TEOAE responses[a] | | | | |
| Invalid | 52 (43.33) | 23 (50) | 29 (39.18) | $\chi^2 = 1.35$ ($P = 0.24$)or = 1.5595 % CI = 0.74–3.26 |
| Valid | 68 (56.67) | 23 (50) | 45 (60.82) | |
| Valid | 68 (100) | 23 (100) | 45 (100) | $\chi^2 = 1.58$ ($P = 0.28$) |
| Bilateral | 20 (29.41) | 9 (39.13) | 11 (24.44) | |
| Monolateral | 48 (70.59) | 14 (60.87) | 34 (75.6) | |
| Ears (*n*) | | | | |
| Total | 88 (100) | 32 (100) | 56 (100) | $\chi^2 = 0.23$ ($P = 0.98$) |
| Right | 42 (47.72) | 15 (46.87) | 27 (48.21) | |
| Left | 46 (52.28) | 16 (53.13) | 29 (51.79) | |

[a] response detection in 4/5 different frequency bands with signal-to-noise ratio (SNRs) >6 dB HL

levels evidenced values ≥40 mg/dl (serum recommended levels according to American Heart Association) in the 70.84 % (85/120) of the total sample (range 28–86 mg/dl); of them 55 patients were controls (55/74, 74.32 %). Tinnitus patients had lower HDL levels (mean value of 45.41 ± 13.00 mg/dl) with respect to controls

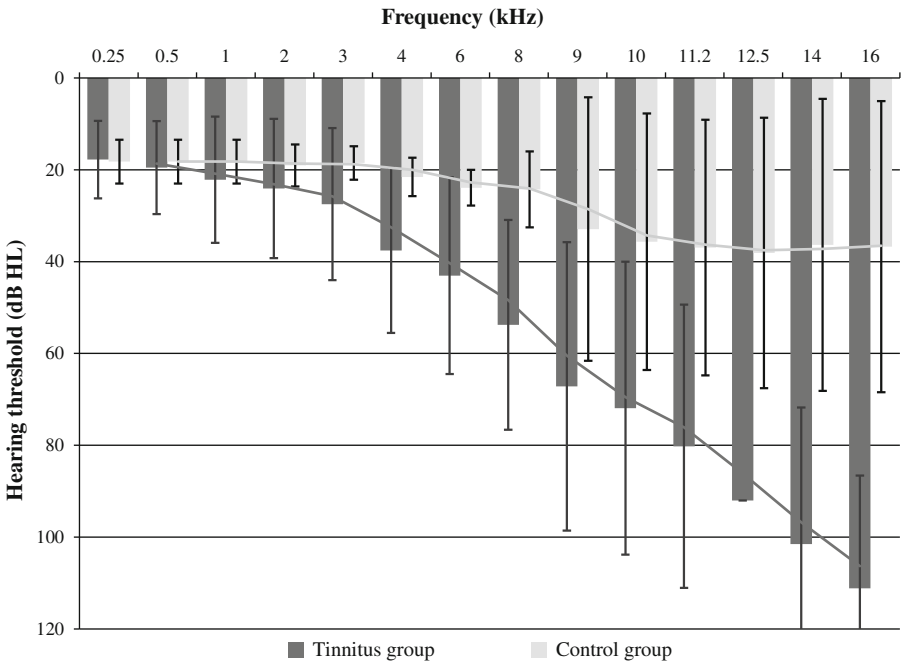


**Fig. 1** Hearing threshold levels in tinnitus and control groups

(48.27 ± 12.81 mg/dl), but without any significant difference ($P = 0.24$).

The study of presence/absence of comorbidity among the patients examined evidenced that 14 cases and 30 controls resulted positive for a specific disorder. Of the 30 patients with more than 1 comorbidity, the 86.66 % were affected by tinnitus ($P < 0.0001$).

The risk of tinnitus increases 15-fold when hypertension and BMI $\geq$30 kg/m$^2$ coexist ($G.or = 8.45$); of 8 times when subjects are smokers and affected by hypercholesterolemia ($G.or = 5.08$). Finally the risk of tinnitus increases 3.5-fold in patients with diabetes and concomitant hypercholesterolemia ($G.or = 2.71$).

The analysis of reactive oxygen metabolites (ROM) levels showed mean values of 331.10 ± 59.53 CARR U for tinnitus group and 318.43 ± 55.0 CARR U for controls ($P = 0.23$). Specifically the distribution of the six categories of oxidative stress resulted normal in 30.43 and 37.83 %, borderline in 8.69 and 24.32 %, low in 15.22 and 17.57 %, middle in 28.26 and 10.81 %, high in 17.39 and 9.46 % for case and control groups, respectively ($P = 0.03$).

## Audiological evaluation

The 63.33 % (76/120) of the total cohort had a normal hearing while the 36.67 % (44/120) was affected by hearing loss (39 bilateral and 5 unilateral). Particularly 28 (60.87 %) patients with tinnitus were hearing impaired in respect to 16 (21.62 %) controls ($P < 0.0001$). Also the distribution of the SNHL degree evidenced significant differences with the 100 % of moderate SNHL subjects belonging to tinnitus population ($P < 0.0001$) (Table 2).

Multi-frequency audiometry showed a normal hearing for the frequencies 0.25, 0.5 and 1 kHz, a slight HL for the frequencies 2, 3, 4, 6 and 8 kHz and a moderate HL for the frequencies 9, 10, 11.5, 12.5, 14 and 16 kHz (Fig. 1); patients with tinnitus presented a more severe hearing impairment, especially for high frequencies ($P \leq 0.001$).

According to the defined criteria, 'response detection in 4/5 different frequency bands' at SENTIERO TEOAE diagnostic, the 56.66 % (68/120) of the total cohort presented valid TEOAE responses; of them 23 patients were affected by tinnitus (50 % of tinnitus group) and 45 were controls (60.82 % of control group) without significant statistical difference among the groups ($P = 0.24$). Valid responses were detected bilaterally in 9 cases and in 11 controls for a total of 32 and 56 ears, respectively, for tinnitus and control group ($P = 0.24$). Figure 2 shows the mean values, medians and range of SNRs relative to tinnitus and control groups; a significant difference was observed between tinnitus population and controls with the first group characterized by lower SNRs mean values ($P < 0.05$). Specifically 1, 1.5 and 2 kHz frequencies resulted not impaired (SNRs ratio >6 db HL) while the 3 and 4 kHz resulted significantly impaired with a SNRs ratio <6 dB HL.

The risk of tinnitus increases in presence of a SNHL ($P < 0.0001$) when hearing loss is associated with age >50 years ($G.or = 3.79$), with hypercholesterolemia and hypertension ($G.or = 1.57$), with coronary heart disease and hypercholesterolemia ($G.or = 1.57$) and with diabetes,

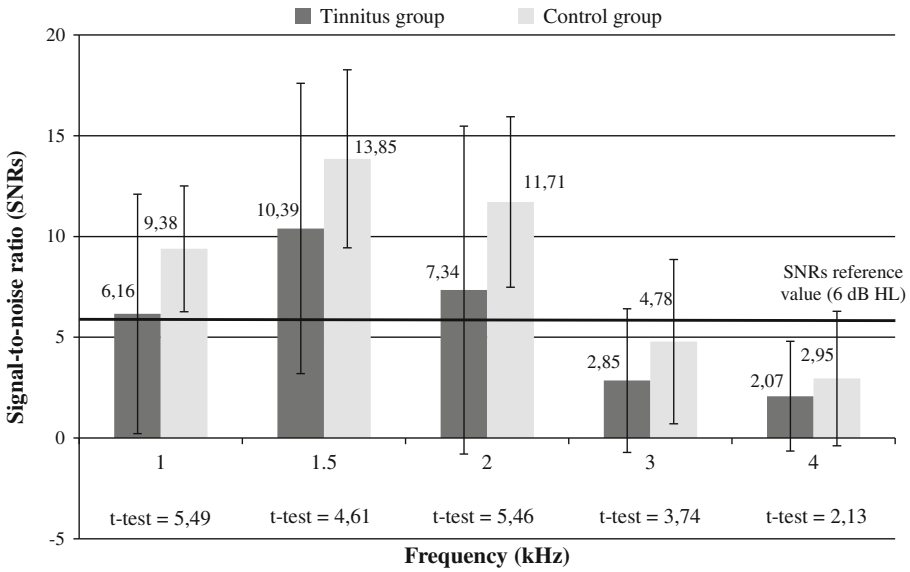


**Fig. 2** TEOAE diagnostic: signal-to-noise ratio (SNRs); means ± standard deviations in tinnitus and control groups; *t* test ($P < 0.05$). Tinnitus group: 1 kHz: 6.16 ± 5.93 dB HL; 1.5 kHz: 10.39 ± 7.20 dB HL; 2 kHz: 7.34 ± 8.13 dB HL; 3 kHz: 2.85 ± 3.55 dB HL; 4 kHz: 2.07 ± 2.72 dB HL. Control group: 1 kHz: 9.38 ± 3.12 dB HL; 1.5 kHz: 13.85 ± 4.41 dB HL; 2 kHz: 11.71 ± 4.22 dB HL; 3 kHz: 4.78 ± 4.08 dB HL; 4 kHz: 2.95 ± 3.33 dB HL

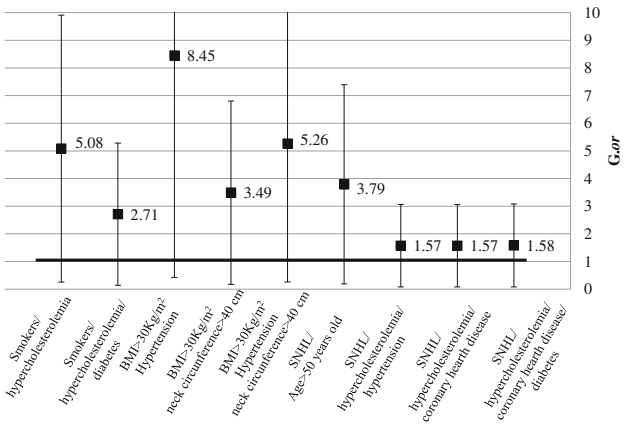


**Fig. 3** Global odds ratio (*G.or*) and 95 % confidence intervals (CI) for joint effect of determinants among tinnitus patients

coronary heart disease and hypercholesterolemia ($G.or = 1.58$) (Fig. 3).

Tinnitus characteristics

Tinnitus (Table 3) was referred as bilateral only in one patient (2.18 %) and unilateral in 45 patients (97.82 %); in the right ear in 19 subjects (41.30 %), in the left ear in 26 subjects (56.52 %).

The 84.78 % of patients reported their tinnitus as a pure tone, instead of the 15.22 % who reported it as a narrow band.

The tinnitus frequency, measured by the pitch-matching test, was matched to high frequencies (>4 kHz) in 80.43 % of cases (37/46), to middle frequencies (1–3 kHz) in the 17.39 % (8/46) of cases and not identifiable only in one subject (2.18 %).

The loudness of tinnitus perceived by patients was: 0–5 dB above the hearing threshold in the 54.34 % of cases (25/46), 10 dB above the hearing threshold in the 26.08 % of cases (12/46), 15 dB above the hearing threshold in the 8.69 % of cases (4/46) and above 15 dB in the 10.86 % of cases (5/46).

Concerning tinnitus annoyance and its impact on quality of life, the study of THI score (mean value of 41.04 ± 21.12) evidenced a slight grade in the 15.22 % (7/46), a mild grade in the 32.6 % (15/46); a moderate grade in the 21.73 % (10/46) a severe grade in the 26.08 % (12/46) and a catastrophic grade in the 4.35 % (2/46) of patients affected by tinnitus.

No correlation between tinnitus annoyance (THI score) and tinnitus loudness ($r^2 = 0.104$), tinnitus frequency ($r^2 = 0.0135$) and hearing threshold ($r^2 = 0.0014$) was observed.

## Discussion

Tinnitus is a multifactorial symptom, which can be induced by all types of hearing loss as well as by clinical, somatic disorders and pharmaceutical drugs. Axelsson and Barrenas described different diseases which were associated with tinnitus and the main causes leading to tinnitus [26] such as sex and elderly.

Many reports like those of Johansson et al. [29], Palmer et al. [30], Fabijanska et al. [31], Martines et al. [27] and Shargorodsky et al. [23] reported a minimally higher prevalence for male suffering from tinnitus than for female; it seems to be confirmed in our cohort.

Epidemiological data have generally supported a strong association between tinnitus and increasing age; in

**Table 3** Tinnitus characteristics and correlation index relative to THI score

| Factors | Tinnitus populations | | Correlation matrix for THI score |
|---|---|---|---|
| | *N* | (%) | |
| Tinnitus localization | | | $r = 0.32$ |
| Unilateral right | 19 | (41.30) | |
| Unilateral left | 26 | (56.52) | |
| Bilateral | 1 | (2.18) | |
| Head | – | (–) | |
| Subjective judgment of tinnitus | | | $r = 0.29$ |
| Pure tone | 39 | (84.78) | |
| Narrow band | 7 | (15.22) | |
| Undetermined | – | (–) | |
| Tinnitus pitch | | | $r = 0.23$ |
| High-pitched | 37 | (80.43) | |
| Middle-pitched | 8 | (17.39) | |
| Low-pitched | – | (–) | |
| Undetermined | 1 | (2.18) | |
| Tinnitus frequency (kHz) | | | $r = 0.013$ |
| 1 | 6 | (13.04) | |
| 2 | 2 | (4.35) | |
| 4 | 8 | (17.39) | |
| 6 | 10 | (21.73) | |
| 8 | 11 | (23.91) | |
| 9 | 2 | (4.35) | |
| 10 | 3 | (6.74) | |
| 11.2 | 1 | (2.18) | |
| 12.5 | 3 | (6.74) | |
| Tinnitus loudness | | | $r = 0.10$ |
| 0–5 dB | 25 | (54.34) | |
| 10 dB | 12 | (26.08) | |
| 15 dB | 4 | (8.69) | |
| >15 dB | 5 | (10.86) | |
| Undetermined | – | (–) | |
| THI | | | – |
| Mean + standard deviation | 41.04 ± 21.12 | | |
| SCORE | | | |
| Slight | 7 | (15.22) | |
| Mild | 15 | (32.60) | |
| Moderate | 10 | (21.73) | |
| Severe | 12 | (26.08) | |
| Catastrophic | 2 | (4.35) | |

particular, tinnitus affects more frequently subjects between 61 and 70 years of age followed by patients between 41 and 50 years of age [3, 4, 9, 27–30]. With a prevalence of 80.44 % and a mean age of 58.10 ± 13.28, our data evidenced the highest percentage of tinnitus after the age of 50 years (Table 1). Therefore, the identification of the main risk factors and co-factors of tinnitus should help to reduce them before the age of 50 years to lower tinnitus incidence.

In line with the literature data our results evidenced that tinnitus in 60.87 % of cases is accompanied by SNHL while the auditory dysfunction was present only in the 21.62 % of control group ($P < 0.0001$) [2–5, 11, 14, 16, 20, 23, 27, 28]. Specifically, of the 76 subjects with normal hearing, 58 corresponding to 76.31 % were controls ($P < 0.001$). Table 2 reports the average hearing threshold levels for each frequency relative to tinnitus and control groups; it is clear that patients suffering from tinnitus presented higher hearing thresholds with respect to controls, particularly for the frequencies above 4 kHz ($P < 0.001$); it confirmed that patients with tinnitus had a worse cochlear dysfunction than control group especially in the cochlear basal turn, where high frequencies are represented, as suggested in CD/1 mice by Riva et al. and Hwang et al. [24, 32].

Because SNHL and tinnitus are usually associated, it was previously suggested that some of the factors that are responsible for hearing loss are also responsible for the tinnitus onset (i.e. vascular diseases, diabetes, hypertension, autoimmune disorders, and degenerative neural disorders); Sindhusake et al. [21, 22], Shargorodsky et al. [23], Lazarini et al.[33] and Nondahl et al. [34] hypothesized that reduced basal and functional capillarity rarefaction could be an additional risk factor of impaired peripheral perfusion and dysfunction of cochlear hair cells [21–23, 33, 34].

Our findings are in line with those from the EHLS [34] and agree with the ''clinical dictum'' of Shargorodsky that some clinical conditions are responsible for hearing loss and tinnitus [23, 35]. In fact, according to Fransen et al. who demonstrated, in a multicenter study of 2008, a strong association between morphometric characteristics (high body weight and high BMI score) and SNHL, we observed, a higher BMI score and a higher neck circumference value in patients with tinnitus than control group ($P < 0.0001$) [23, 36]; additionally, in presence of BMI ≥30 kg/m$^2$ and neck circumference ≥40 cm, the risk of developing tinnitus increases fivefold ($G.or = 3.49$; $P = 0.003$) (Fig. 3). Fransen et al. [36–38] confirmed also the Framinghan study (1993) and the study of Brant et al. which suggested a strong association between SNHL, cardiovascular diseases, high value of systolic blood pressure and hypercholesterolemia. Shargorodsky et al., studying an American population composed by adults with BMI ≥30 kg/m$^2$, hypertension, diabetes mellitus and dyslipidemia, demonstrated a correlation between these disorders and tinnitus [23]. Also our data supported these findings, with a clear association between hypertension and/or hypercholesterolemia and tinnitus ($P < 0.0001$); the joint effect of

hypertension and BMI $\geq$30 kg/m$^2$ increases 15-fold the risk of tinnitus (*G.or* = 8.45) (Fig. 3).

The role of smoking in the tinnitus onset is still controversial. Rosenhall et al., Cruickshanks et al., Fransen et al. and Uchida et al. found an association between hearing levels and smoking, while on the other hand, no association was found in the Framingham cohort [36, 37, 39–41]. From our results smoking is not a risk factor for tinnitus ($P = 0.85$), even if the interaction of smoking–hypercholesterolemia increases 8-fold the risk of developing tinnitus (*G.or* = 5.08; $P = 0.003$), as well as the risk of tinnitus increases 3.5-fold when subjects are smokers and suffer also from diabetes and hypercholesterolemia (*G.or* = 2.71; $P = 0.0001$).

Recently Riva et al. and Hwang et al. [23, 32] demonstrated, in a mouse model of age-related hearing loss (the CD/1 mice), a higher production of reactive oxygen species that would be responsible for cochlear degeneration through a transient ischemia, vasospasm, thrombosis, embolism, hypercoagulation and altered vascular characteristics in the labyrinth. To confirm this theory, all patients underwent d-ROM test, an oxidative stress testing that is of fundamental importance for preventive medicine and health care, disease management as well as the control of relevant therapies during pathologies. Even if a statistical difference in the d-ROM test mean values was not found ($P = 0.23$), a ROM level <320 CARR U was observed in the 62.16 % of controls with respect to the 39.12 % of tinnitus group ($P = 0.03$); it supports the role of oxidative stress as risk factor for hearing loss and tinnitus in humans [23, 32].

Cochlear activity was also studied through TEOAE diagnostic that gives us information relative to the normal activity of OHCs. The choice of the TEOAE records was taken because they are able to detect, through a reduction of SNRs values, potential sub-clinical cochlear lesions not evidenced at classic audiometry; from the analysis of the TEOAE responses a valid test was evidenced only in the 50 % of tinnitus population with regards to the 60.82 % of controls (Table 2). Moreover, Fig. 2 shows that tinnitus subjects, presenting low mean values of SNRs, had a more OHCs-altered functionality than controls ($P = 0.0001$ for 1, 1.5, 2, 3 kHz; $P = 0.03$ for 4 kHz).

The effects of tinnitus on quality of life are highly individualized, so that personality characteristics may predispose some people to experience tinnitus as a ''distressing'' symptom. The 30.43 % of patients affected by tinnitus has sleep disturbances and difficulty with any daily activity while no significant correlation was found between the level of tinnitus intensity measured by matching procedure and the tinnitus annoyance. It may support the actual theory that the patient's reaction to tinnitus cannot be classified as a simple function of its psychoacoustic aspects but rather as a complex interaction between acoustic phantom symptoms, somatic attention and depressive symptoms; moreover, the subjective judgment of tinnitus intensity was $\geq$10 dB above the hearing threshold in the 45.63 % of tinnitus group, suggesting that most patients seek for specialist examination when the symptom is already disturbing [42, 43].

## Conclusions

Because tinnitus and SNHL are often associated disorders, it is reasonable that factors responsible for hearing loss are also likely to have caused tinnitus; our data suggest that several factors either individually or jointly are associated with tinnitus. Ageing, BMI >30 kg/m$^2$, high values of neck circumference, hypertension and hypercholesterolemia are significantly associated with tinnitus; the effect of smoking becomes significant when associated with hypercholesterolemia; the joint effects of >2 medical disorders increases significantly the risk of tinnitus (i.e.: 15-fold when coexisting hypertension and BMI >30 kg/m$^2$, *G.or* = 8.45; 3.5-fold in smokers with concomitant diabetes and hypercholesterolemia *G.or* = 2.71).

Comprehensive knowledge of tinnitus risk factors could assist in the management of tinnitus, as well as providing a solid research evidence base for the delivery of tinnitus-related healthcare. These data are also needed to guide policy decisions that shape public health practice in relation to tinnitus treatment and management. It is possible that timely health interventions to reduce or limit exposure to specific environmental/lifestyle factors and/or better managing conditions such as age-related hearing loss could reduce the incidence of tinnitus. Education and guidance on the modifiable risk factors found in this study could contribute to minimizing this condition in populations.

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