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BDNF Levels in T2DM Hearing-Impaired Patients: Audiology and Inflammation Correlates

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Abstract

Purpose To investigate the correlation between serum brain-derived neurotrophic factor (BDNF) and hearing impairment in patients with type 2 diabetes mellitus (T2DM), and to explore its relationship with inflammatory cytokines.

Methods This cross-sectional case-control study enrolled 97 T2DM patients (October 2023–June 2024), stratified by pure-tone average (PTA) into Group A (hearing impairment, PTA >25 dB HL, n=44) and Group B (normal hearing, PTA ≤25 dB HL, n=53), alongside 57 healthy controls (Group C). Serum BDNF, pure-tone audiometry, and distortion product otoacoustic emissions (DPOAE) were assessed. An independent cohort (30 T2DM, 32 controls; July–October 2024) assessed BDNF and inflammatory cytokines.

Results Hearing thresholds at all tested frequencies (500–8000 Hz) were significantly higher in Group A than in Groups B and C (all $P<0.001$), with correspondingly lower DPOAE amplitudes. Serum BDNF was similarly reduced in both diabetic groups (Group A: 4.07±1.02; Group B: 4.53±0.94 ng/mL) versus controls (11.77±7.92 ng/mL; $P<0.001$). In Group A, BDNF correlated negatively with BMI ($r=-0.531$), lipid profiles (TG $r=-0.379$, TC $r=-0.398$, LDL-C $r=-0.691$, HDL-C $r=-0.577$), fasting glucose ($r=-0.633$), HbA 1c ($r=-0.672$), diabetes duration ($r=-0.931$), and mean hearing threshold ($r=-0.852$; all $P<0.05$). In the exploratory cohort, T2DM patients exhibited lower BDNF, elevated pro-inflammatory cytokines (TNF-α, IL-6, IL-1β, MCP-1; all $P<0.001$), and reduced IL-10 ($P<0.001$). BDNF negatively correlated with pro-inflammatory cytokines and positively with IL-10 only in T2DM (all $P<0.05$).

Conclusion Serum BDNF is decreased in T2DM and inversely associated with glycemic control, disease duration, and hearing impairment severity. BDNF reduction also correlates with pro-inflammatory changes. Although BDNF reduction is a general feature of T2DM rather than being specific to hearing impairment, within hearing-impaired T2DM patients, BDNF levels correlate strongly with auditory dysfunction, suggesting that BDNF may serve as a potential biomarker for T2DM-related hearing impairment. However, causal inference is limited by the cross-sectional design.

Keywords Type 2 diabetes mellitus · Hearing impairment · Brain-derived neurotrophic factor · Inflammatory cytokines · Pure-tone audiometry

Clinical trial number: not applicable.

Introduction

Type 2 diabetes mellitus (T2DM) is a metabolic disorder with a globally rising prevalence [1]. Beyond the well-established cardiovascular, retinal, and renal complications, accumulating evidence indicates an association between diabetes mellitus (DM) and sensorineural hearing loss. Idiopathic sudden sensorineural hearing loss has been linked to DM, with affected patients exhibiting a higher long-term risk of stroke compared with the general population [2]. Hearing loss may represent a disabling complication of DM, with manifestations ranging from impaired speech comprehension and increased fall risk to tinnitus, ultimately contributing to reduced quality of life and elevated mortality [3]. Consequently, the identification of serum biomarkers capable of predicting T2DM-related hearing impairment carries substantial clinical significance.

Brain-derived neurotrophic factor (BDNF), a key member of the neurotrophin family, exerts critical trophic support for cochlear hair cell and spiral ganglion neuron survival, differentiation, and synaptic plasticity through activation of the tropomyosin receptor kinase B (TrkB) signaling pathway [4]. As a neuromodulator widely expressed in both the central and peripheral nervous systems, BDNF participates in the pathophysiology of diabetes and its complications by regulating neurotransmitter, insulin, and leptin secretion [5]. Chronic low-grade inflammation is a well-established mechanism underlying T2DM development and its complications. Evidence indicates that interleukin-6 (IL-6), IL-1β, tumor necrosis factor-α (TNF-α), IL-10, and monocyte chemoattractant protein-1 (MCP-1) contribute to the pathogenesis of obesity and T2DM [6–8]. In a prospective case-control study of diabetic retinopathy (DR), serum IL-6 was significantly elevated and inversely correlated with BDNF levels, suggesting that BDNF may influence DR progression through modulation of pro- and anti-inflammatory cytokines [9]. However, whether BDNF plays a specific role in T2DM-related hearing impairment and how it relates to metabolic control and inflammatory responses remains largely unexplored.

Based on the above rationale, the present study aimed to: (1) compare serum BDNF levels among T2DM patients with and without hearing impairment and healthy controls, integrating pure-tone audiometry and DPOAE features to analyze the relationship between BDNF, auditory function, and metabolic parameters; and (2) preliminarily investigate the interrelationship between BDNF and inflammatory cytokines in an independent sample, thereby providing mechanistic insights.

Materials and Methods

Study Design and Participants

A cross-sectional case-control design was adopted for the primary study. From October 2023 to June 2024, 97 T2DM patients attending the Department of Endocrinology at our hospital were enrolled, together with 57 healthy controls recruited from the hospital physical examination center. T2DM was diagnosed according to American Diabetes Association (ADA) criteria. Exclusion criteria comprised: (1) congenital or familial deafness; (2) history of otitis media or otologic surgery; (3) occupational or recreational noise exposure; (4) use of ototoxic medications (aminoglycoside antibiotics, loop diuretics, etc.); (5) head trauma; (6) neurological disorders (Alzheimer's disease, Parkinson's disease, etc.); and (7) other types of diabetes or severe hepatic/renal insufficiency. Healthy controls had no history or family history of diabetes, with fasting plasma glucose and HbA 1c confirmed within normal ranges.

Hearing impairment was classified according to World Health Organization (WHO) criteria based on pure-tone average (PTA, mean threshold at 0.5, 1, 2, and 4 kHz). T2DM patients were stratified into: Group A (T2DM with hearing impairment, PTA >25 dB HL, n=44) and Group B (T2DM without hearing impairment, PTA ≤25 dB HL, n=53). Group C comprised healthy controls without diabetes and with PTA ≤25 dB HL (n=57).

For the exploratory study, an independent cohort of 30 T2DM patients and 32 healthy controls was enrolled from July to October 2024, using identical inclusion/exclusion criteria. This cohort was analyzed without stratification by hearing status and served exclusively for BDNF–inflammatory cytokine correlation analysis. Importantly, the primary and exploratory cohorts are independent samples; no participant underwent both audiological assessment and inflammatory cytokine measurement.

This study was approved by the institutional ethics committee of Gansu Provincial Central Hospital (Gansu Maternal and Child Health Hospital) (Approval No.: 202311002) and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Clinical Data and Laboratory Measurements

For the primary cohort, demographic and clinical data were collected, including age, sex, body mass index (BMI), educational attainment, diabetes duration, and biochemical parameters (fasting blood glucose [FBG], HbA 1c, LDL-C, HDL-C, and triglycerides [TG]). Fasting venous blood samples were obtained after an overnight fast of at least 8 hours. FBG was measured by the hexokinase method, and HbA 1c was determined by high-performance liquid chromatography (HPLC). Serum BDNF levels were quantified using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Promega Corporation, Madison, WI, USA) with a detection sensitivity of 0.01 ng/mL. The intra-assay coefficient of variation was <5% and the inter-assay coefficient of variation was <7%. All procedures were performed in strict accordance with the manufacturer's instructions.

For the exploratory cohort, demographic data (age, sex, height, weight, BMI) were recorded, and fasting venous blood samples were collected for measurement of serum BDNF, TNF-α, IL-6, IL-1β, IL-10, and MCP-1 by ELISA, strictly following the manufacturers ' protocols. The BDNF ELISA kit used in the exploratory cohort was from the same manufacturer (Promega Corporation, Madison, WI, USA) as in the primary cohort. Intra-assay and inter-assay coefficients of variation were <5% and <7%, respectively. All serum BDNF concentrations are reported in ng/mL throughout this article. All cytokine concentrations are reported in pg/mL.

Audiological Assessment

Pure-tone audiometry was conducted in a sound-treated booth (ambient noise <25 dB) using a Madsen ORBITER 922 Version 2 clinical audiometer (Madsen, Denmark), with a frequency range of 0.125–16 kHz. Air-conduction thresholds were measured at 0.25, 0.5, 1, 2, 4, and 8 kHz. PTA was calculated as the mean threshold at 0.5, 1, 2, and 4 kHz. In the present study, "mean hearing threshold" refers to the PTA as defined above, calculated as the average of air-conduction thresholds at 0.5, 1, 2, and 4 kHz for the better-hearing ear.

Distortion product otoacoustic emissions (DPOAE) were recorded using a MADSEN Capella system (GN Otometrics, Denmark). Two primary tones (f1, f2; f2/f1=1.22) were presented at intensities L 1/L2=65/55 dB SPL, and DPOAE amplitudes were recorded at 2f1−f2 frequencies. A signal-to-noise ratio (SNR) ≥6 dB was considered a robust response indicating normal outer hair cell function; 3 dB ≤ SNR <6 dB indicated mildly impaired cochlear function; and SNR <3

dB indicated absent DPOAE with significant outer hair cell damage. For the present analysis, SNR <6 dB was defined as cochlear dysfunction. DPOAE amplitudes were analyzed across the 0.5–8 kHz frequency range.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Shapiro–Wilk test, and the homogeneity of variances was evaluated using Levene's test. Continuous variables are presented as mean ± standard deviation (SD) and were compared using one-way analysis of variance (ANOVA) for multiple-group comparisons, with post-hoc pairwise comparisons performed by the least significant difference (LSD-t) method and validated by the Student–Newman–Keuls (SNK-q) test. For variables that did not meet the assumption of normal distribution, the Mann–Whitney U test was applied; although these variables are reported as mean ± SD for consistency with other measures, non-parametric testing was used for statistical inference. Categorical variables are expressed as frequencies (percentages) and were compared using the chi-squared (χ^2) test. Pearson correlation analysis was employed to examine linear associations between variables. Bonferroni correction was applied to the ANOVA post-hoc pairwise comparisons to control the family-wise error rate. All tests were two-tailed, with $P < 0.05$ considered statistically significant.

Results

Baseline Characteristics ofthe Primary Cohort

The three groups were comparable in terms of sex distribution, educational attainment, prevalence of hypertension, coronary heart disease, smoking and alcohol consumption, and BMI (all $P > 0.05$). However, a statistically significant age difference was observed among the three groups ($F=9.81$, $P<0.001$), with Group A being the youngest (64.13 ± 2.71 years), followed by Group B (66.32 ± 3.43 years) and Group C (67.57 ± 4.91 years). Notably, despite Group A having the youngest mean age, this group exhibited the most pronounced hearing impairment, arguing against age as the primary driver of the observed auditory deficits. Detailed baseline characteristics are presented in Table 1.

One-way ANOVA revealed significant overall differences among the three groups for age (F=9.81, P<0.001), TC (F=4.01, P=0.020), LDL-C (F=113.39, P<0.001), HDL-C (F=16.63, P<0.001), TG (F=4.72, P=0.010), FBG (F=165.67, P<0.001), and HbA 1c (F=108.36, P<0.001). BMI showed a borderline trend toward significance (F=3.01, P=0.052). Post-hoc analyses (LSD-t, validated by SNK-q) demonstrated that TC and LDL-C levels were significantly higher in Groups A and B compared with Group C (all P<0.05), with no significant difference between Groups A and B. HDL-C was significantly lower in Group A than in Groups B and C (P<0.05). TG levels exhibited a graded pattern (Group A > Group B > Group C), with all pairwise comparisons reaching statistical significance (P<0.05). FBG and HbA 1c were significantly higher in Groups A and B versus Group C (P<0.05), without significant inter-diabetic group differences.

Table 1 Baseline characteristics of the study participants

Characteristic	Group A (n=44)	Group B (n=53)	Group C (n=57)	F/χ2	P value
Sex (M/F)	27/17	29/24	30/27	0.81	0.667
Age (years)	64.13±2.71 [a]	66.32±3.43 [a,b]	67.57±4.91 [b]	9.81	<0.001
Education (years)	9.68±3.69	9.68±3.69	9.22±2.07	0.37	0.689
Hypertension, n (%)	19 (43)	21 (40)	25 (43)	0.23	0.893
CHD, n (%)	11 (25)	16 (30)	19 (33)	0.83	0.661
Smoking, n (%)	13 (29)	17 (32)	16 (28)	0.21	0.899
Alcohol, n (%)	9 (20)	11 (21)	14 (24)	0.33	0.850
BMI (kg/m²)	25.94±3.72	25.11±4.57	23.92±4.11	3.01	0.052
TC (mmol/L)	5.37±1.53 [a]	5.13± 1.72 [a]	4.61±0.83 [b]	4.01	0.020
LDL-C (mmol/L)	3.01±0.13 [a]	2.87±0.09 [a]	2.48±0.27 [b]	113.39	<0.001
HDL-C (mmol/L)	1.23±0.74 [a]	1.53±0.35 [b]	1.77±0.23 [b]	16.63	<0.001
TG (mmol/L)	2.32±0.54 [a]	2.17±0.73 [b]	1.93±0.64 [c]	4.72	0.010
FBG (mmol/L)	9.82±2.13 [a]	9.37±1.84 [a]	4.71±0.57 [b]	165.67	<0.001
HbA 1c (%)	10.33± 1.88 [a]	9.58±2.45 [a]	5.63±0.32 [b]	108.36	<0.001

Data arepresented as mean ± SD or n (%). Values with different superscript letters within the same row are significantly different (LSD-t test, P < 0.05); identical superscripts indicate non-significant differences. SNK-q test confirmed the LSD-t findings. CHD, coronary heart disease; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; FBG,fasting blood glucose; HbA1c, glycated hemoglobin.

Serum BDNF Levels Among the Three Groups

One-way ANOVA revealed a significant overall difference in serum BDNF levels among the three groups (F=41.84, P<0.001). Post-hoc LSD-t analysis with SNK-q validation demonstrated

that BDNF levels in Group A (4.07 ± 1.02 ng/mL) and Group B (4.53 ± 0.94 ng/mL) did not differ significantly (P > 0.05), whereas Group C exhibited markedly higher BDNF levels (11.77 ± 7.92 ng/mL) compared with both diabetic groups (P < 0.001). These results indicate that BDNF reduction is a general feature of T2DM rather than being specific to T2DM patients with hearing impairment (Table 2).

Table 2 Serum BDNF levels in the three groups (mean ± SD)

Group	n	BDNF (ng/mL)	F	P value
Group A	44	4.07 ± 1.02		
Group B	53	4.53 ± 0.94		
Group C	57	11.77 ± 7.92		
			41.84	<0.001

Pure-Tone Audiometry Results

Pure-tone thresholds across frequencies are presented in Table 3. One-way ANOVA revealed significant overall differences among the three groups at all tested frequencies (500 Hz through 8000 Hz, all P<0.001). Post-hoc pairwise comparisons (LSD-t, validated by SNK-q) demonstrated that hearing thresholds in Group A were significantly higher than those in Groups B and C at every frequency (all P<0.05). At 500–4000 Hz, Groups B and C did not differ significantly (P>0.05), whereas at 8000 Hz, Group B showed significantly higher thresholds than Group C (P<0.05). Across all frequencies, hearing thresholds followed the pattern Group A > Group B ≈ Group C (at ≤4000 Hz) and Group A > Group B > Group C (at 8000 Hz). Group A exhibited thresholds exceeding 25 dB HL at all frequencies, with a progressive increase toward higher frequencies, confirming the presence of hearing impairment in this group. The finding that Group A demonstrated elevated thresholds across the entire frequency range—rather than exclusively at high frequencies—suggests a more widespread cochlear involvement in T2DM patients with hearing impairment.

Table 3 Pure-tone hearing thresholds in the three groups (dB HL, mean ± SD)

Frequency	Group A (n=44)	Group B (n=53)	Group C (n=57)	F	P value
500 Hz	28.4±0.57 [a]	20.3±0.37 [b]	18.7±0.22 [b]	8172.01	<0.001
1000 Hz	32.1±0.25 [a]	23.5±0.29[b]	22.6±0.18 [b]	22166.05	<0.001
2000 Hz	39.5±0.31 [a]	24.3±0.35 [b]	24.5±0.33 [b]	32580.41	<0.001

Frequency	Group A (n=44)	Group B (n=53)	Group C (n=57)	F	P value
4000 Hz	47.5±0.28 [a]	29.7±0.18 [b]	26.8±0.15 [b]	142741.22	<0.001
8000 Hz	54.3±0.17 [a]	37.8±0.52 [b]	29.1±0.11 [c]	75350.83	<0.001

Different superscript letters within rows indicate significant differences between groups (LSD-t test, P < 0.05). Higher threshold values indicate greater hearing impairment. The within-group standard deviations are notably small, resulting in large F statistics; this reflects the high precision of audiometric measurements performed under standardized conditions by a single technician.

DPOAE Results

DPOAE amplitudes across frequencies are summarized in Table 4. One-way ANOVA revealed significant overall differences among the three groups at all tested frequencies (500 Hz through 8000 Hz, all P≤0.002). Post-hoc LSD-t analysis with SNK-q validation demonstrated that DPOAE amplitudes in Group A were significantly lower than those in Group C at all frequencies (all P<0.05), and significantly lower than Group B at 500–4000 Hz (P<0.05). At 500–2000 Hz, Groups B and C did not differ significantly (P>0.05). At 4000 Hz, Group A was significantly lower than both Groups B and C (P<0.05), while Groups B and C were comparable. At 8000 Hz, all three groups differed significantly from each other (Group A < Group B < Group C, all P<0.05). Across all frequencies, DPOAE amplitudes followed the pattern Group A < Group B ≤ Group C, consistent with the pure-tone audiometry findings and indicating widespread cochlear outer hair cell dysfunction in T2DM patients with hearing impairment.

Table 4 DPOAE amplitudes in the three groups (dB SPL, mean ± SD)

Frequency	Group A (n=44)	Group B (n=53)	Group C (n=57)	F	P value
500 Hz	−6.13±3.92 [a]	−3.89±5.33 [a,b]	−2.57±4.96 [b]	6.80	0.002
1000 Hz	−3.19±5.73 [a]	−1.78±5.52 [a,b]	1.54±6.94 [b]	8.10	<0.001
2000 Hz	−5.24±6.34 [a]	−3.57±6.18 [a]	2.26±6.88 [b]	19.28	<0.001
4000 Hz	−7.38±6.09 [a]	−3.92±5.94 [b]	1.41±6.52 [b]	25.95	<0.001
8000 Hz	1.57±7.54 [a]	5.03±7.98 [b]	9.13±7.17 [c]	12.61	<0.001

Different superscript letters indicate significant differences between groups (LSD-t test, P < 0.05). Higher DPOAE amplitudes indicate better outer hair cell function.

Correlation Between BDNF and Clinical Parameters in Group A

Pearson correlation analysis was performed in Group A (n=44) to examine the relationships between serum BDNF levels and clinical parameters (Table 5). BDNF showed significant negative correlations with all examined parameters: BMI (r=−0.531, P<0.001), TG (r=−0.379, P=0.022), TC (r=−0.398, P=0.015), LDL-C (r=−0.691, P<0.001), HDL-C (r=−0.577, P<0.001),

FBG (r=−0.633, P<0.001), HbA 1c (r=−0.672, P<0.001), diabetes duration (r=−0.931, P<0.001), and mean hearing threshold (PTA) (r=−0.852, P<0.001). These results indicate that lower serum BDNF levels are associated with adverse metabolic profiles (higher BMI, dyslipidemia, poorer glycemic control), longer disease duration, and greater hearing impairment. Notably, the strongest correlations were observed between BDNF and diabetes duration (r=−0.931) and between BDNF and PTA (r=−0.852), suggesting that BDNF depletion is closely linked to both disease progression and auditory dysfunction in T2DM.

Table 5 Pearson correlation between serum BDNF and clinical parameters in Group A (n=44)

Parameter	Correlation coefficient (r)	P value
BMI	−0.531	<0.001
TG	−0.379	0.022
TC	−0.398	0.015
LDL-C	−0.691	<0.001
HDL-C	−0.577	<0.001
FBG	−0.633	<0.001
HbA 1c	−0.672	<0.001
Diabetes duration	−0.931	<0.001
Mean hearing threshold (PTA)	−0.852	<0.001

PTA,pure-tone average (mean threshold at 0.5, 1, 2, and 4 kHz). All correlations are statistically significant, indicating that BDNF is inversely associated with metabolic, glycemic, and auditory parameters in T2DM patients with hearing impairment.

Baseline Characteristics of the Exploratory Cohort

The exploratory cohort comprised 30 T2DM patients (16 males, 14 females; mean age 53.13 ± 2.14 years; BMI 25.99 ± 3.72 kg/m²) and 32 healthy controls (14 males, 18 females; mean age 50.00 ± 3.43 years; BMI 24.00 ± 4.57 kg/m²). There were no significant differences in sex distribution or BMI between the two groups (P > 0.05). A statistically significant age difference was observed between the T2DM and control groups (P < 0.001), which is acknowledged as a limitation. Baseline characteristics are presented in Table 6.

Table 6 Baseline characteristics of the exploratory cohort (mean ± SD)

Characteristic	T2DM group (n=30)	Control group (n=32)
Sex (M/F)	16/14	14/18
Age (years)	53.13±2.14	50.00±3.43
BMI (kg/m²)	25.99±3.72	24.00±4.57

Characteristic	T2DM group (n=30)	Control group (n=32)
P value	—	<0.001 / 0.064

P values correspond to age and BMI comparisons, respectively (independent-samples t-test). Sex comparison was not significant (χ^2 test, $P > 0.05$). A statistically significant age difference was observed between the two groups ($P < 0.001$), representing a limitation of the exploratory cohort.

Comparison of Serum BDNF and Inflammatory Cytokines Between Groups

Serum levels of BDNF and a panel of inflammatory cytokines were compared between the T2DM and control groups (Table 7). Serum BDNF was significantly lower in the T2DM group compared with controls (10.59 ± 2.40 ng/mL vs. 13.07 ± 2.36 ng/mL; Mann–Whitney U=237, P=0.0006). The T2DM group exhibited significantly elevated levels of the pro-inflammatory cytokines TNF-α (18.83 ± 4.58 vs. 13.62 ± 2.84 pg/mL, t=5.42, P<0.001), IL-6 (11.84 ± 3.41 vs. 7.48 ± 1.83 pg/mL, t=6.21, P<0.001), IL-1β (20.86 ± 5.44 vs. 14.74 ± 2.83 pg/mL, t=5.50, P<0.001), and MCP-1 (79.66 ± 21.64 vs. 50.02 ± 12.83 pg/mL, t=6.51, P<0.001). Conversely, the anti-inflammatory cytokine IL-10 was significantly lower in the T2DM group compared with controls (172.50 ± 51.85 vs. 257.45 ± 38.00 pg/mL, t=−7.39, P<0.001).

Table 7 Serum BDNF and inflammatory cytokine levels in the T2DM and control groups

Parameter	T2DM (n=30)	Controls (n=32)	Mean diff.	t/Z	P value
BDNF (ng/mL)	10.59±2.40	13.07±2.36	−2.49	237 [a]	0.0006
TNF-α (pg/mL)	18.83±4.58	13.62±2.84	5.21	5.42	<0.001
IL-6 (pg/mL)	11.84±3.41	7.48±1.83	4.37	6.21	<0.001
IL-1β (pg/mL)	20.86±5.44	14.74±2.83	6.12	5.50	<0.001
IL-10 (pg/mL)	172.50±51.85	257.45±38.00	−84.95	−7.39	<0.001
MCP-1 (pg/mL)	79.66±21.64	50.02±12.83	29.64	6.51	<0.001

Correlation Between BDNF and Inflammatory Cytokines

In the healthy control group, serum BDNF showed weak and non-significant correlations with all inflammatory cytokines tested (all $P > 0.05$; Table 8). In contrast, within the T2DM group, BDNF exhibited significant negative correlations with TNF-α (r=−0.436, P=0.016), IL-6 (r=−0.522, P=0.003), IL-1β (r=−0.583, P<0.001), and MCP-1 (r=−0.508, P=0.004), and a significant positive correlation with IL-10 (r=0.392, P=0.032). The strongest inverse correlation was observed between BDNF and IL-1β (Table 9). These findings suggest that the inverse relationship between BDNF and inflammatory cytokines is specific to the diabetic state and may

reflect the involvement of BDNF in T2DM-associated chronic inflammation.

Table 8 Pearson correlation between BDNF and inflammatory cytokines in healthy controls (n=32)

Cytokine	Pearson r	P value	Direction
TNF-α	−0.099	0.592	Negative
IL-6	−0.056	0.761	Negative
IL-1β	−0.178	0.330	Negative
IL-10	0.021	0.911	Positive
MCP-1	−0.097	0.597	Negative

Table 9 Pearson correlation between BDNF and inflammatory cytokines in T2DM patients (n=30)

Cytokine	Pearson r	P value	Direction
TNF-α	−0.436	0.016	Negative
IL-6	−0.522	0.003	Negative
IL-1β	−0.583	<0.001	Negative
IL-10	0.392	0.032	Positive
MCP-1	−0.508	0.004	Negative

Discussion

The present study provides evidence that serum BDNF levels are significantly reduced in T2DM patients compared with healthy controls, and that this reduction is associated with metabolic derangement, disease duration, and the severity of hearing impairment. Notably, BDNF levels were similarly reduced in T2DM patients with and without hearing impairment, indicating that BDNF deficiency is a general feature of T2DM rather than being specific to hearing loss. However, within the hearing-impaired subgroup, BDNF showed strong correlations with both glycemic parameters and hearing threshold, suggesting that BDNF may contribute to the pathogenesis of diabetic hearing loss. Furthermore, our exploratory analysis in an independent cohort reveals that BDNF is inversely associated with a panel of pro-inflammatory cytokines in the T2DM state, suggesting a potential link between BDNF deficiency, chronic inflammation, and diabetic complications.

Our audiological findings demonstrate that T2DM-related hearing impairment involves significant threshold elevation across all tested frequencies (500–8000 Hz), with corresponding reductions in DPOAE amplitudes, indicating widespread cochlear outer hair cell dysfunction.

Although Group B (T2DM without hearing impairment) showed numerically higher thresholds compared with controls, this difference reached statistical significance only at 8000 Hz ($P<0.05$), suggesting that subclinical high-frequency cochlear dysfunction may emerge in T2DM patients before clinically detectable hearing loss. These findings are consistent with the view that DM-associated macro- and microvascular pathology may compromise cochlear blood flow, impair oxygen exchange, and disrupt ion transport in sensory and supporting cells, ultimately affecting cochlear function [3].

A key finding of this study is the graded inverse association between BDNF and diabetes-related parameters. Higher FBG and HbA 1c levels, longer diabetes duration, and greater hearing impairment were each associated with lower serum BDNF concentrations. Additionally, BDNF was significantly negatively correlated with BMI and all lipid parameters (TG, TC, LDL-C, HDL-C), indicating that BDNF depletion is broadly associated with metabolic dysregulation in T2DM. Under hyperglycemic conditions, glucocorticoid signaling is known to interact with TrkB, leading to altered downstream BDNF pathway outputs, including synaptic dysfunction, initiation of neuronal apoptosis, and impaired synaptic maturation, all of which may contribute to BDNF downregulation [10]. As the most extensively studied neurotrophin, BDNF has been shown to protect cochlear inner hair cell ribbon synapses and auditory nerve fibers against noise-induced and age-related damage [11]. In an animal model, exogenous BDNF administration activated the PI3K/AKT/mTOR signaling pathway, potently suppressed aberrant autophagic flux, and preserved CtBP2/GluR2 synaptic pairing integrity, thereby reducing auditory thresholds and restoring synchronous auditory nerve conduction [12]. The negative correlations between BDNF and HbA 1c/FBG observed in our study support the existence of these mechanistic pathways in the clinical setting.

It is worth noting that the three groups differed significantly in age ($F=9.81$, $P<0.001$), with Group A being the youngest. While this age imbalance represents a limitation, several lines of evidence argue against age as the primary driver of the observed hearing differences. First, the age gradient runs counter to the hearing results: Group A, with the youngest mean age (64.13 years), exhibited the poorest hearing, whereas Group C, with the oldest mean age (67.57 years), showed the best hearing—a pattern inconsistent with age-driven pathology. Second, the Group B versus Group C comparison provides a window into the “pure diabetic effect”: Group B was younger than Group C yet demonstrated significantly higher thresholds at 8 kHz ($P<0.05$). Since

neither group had subjective hearing impairment (PTA ≤25 dB HL), this difference may reflect a diabetes-specific signal at the subclinical stage. Third, the absolute age span across the three groups was approximately 3.4 years, while inter-group threshold differences at certain frequencies exceeded 10–20 dB—a magnitude far greater than would be expected from the natural progression of presbycusis over such a brief interval. Collectively, while the significant age difference warrants caution and multivariable adjustment in future studies, the observed T2DM-related hearing impairment appears to be primarily driven by diabetes-specific factors.

The exploratory component of our study revealed a pronounced pro-inflammatory shift in T2DM, characterized by significantly elevated TNF-α, IL-6, IL-1β, and MCP-1, alongside reduced IL-10. Moreover, BDNF levels were negatively correlated with pro-inflammatory cytokines and positively correlated with IL-10 exclusively in the T2DM group, with no such associations in healthy controls. These findings strengthen the hypothesis that BDNF is not merely a neuroprotective factor but may also serve as a regulator of inflammatory homeostasis in the diabetic milieu. Chronic low-grade inflammation is a well-established mechanism underlying T2DM and its complications. Elevated TNF-α and IL-6 promote insulin resistance via IRS serine phosphorylation and inhibition of the PI3K/Akt pathway, contributing to pancreatic β-cell dysfunction [6,7]. Higher baseline levels of inflammatory markers have been associated with greater cognitive decline in older adults with T2DM, underscoring the systemic impact of chronic inflammation in diabetes [13]. IL-1β impairs β-cell function, promotes β-cell apoptosis, and participates in the development of diabetic vascular complications [14]. MCP-1, via CCR2 binding, recruits circulating monocytes to the endothelium while concurrently upregulating the senescence marker p 16, amplifying the inflammatory cascade and suppressing Akt-mediated insulin secretion. Clinical evidence has shown that MCP-1 expression is significantly upregulated in peripheral blood mononuclear cells of individuals with time-in-range (TIR) <70%, exacerbating atherosclerosis and diabetic nephropathy [15]. IL-10 exerts anti-inflammatory effects by inhibiting pro-inflammatory cytokine production and modulating regulatory T-cell activity, thereby attenuating autoimmune-mediated β-cell destruction [16]. In the present study, the inverse relationship between BDNF and pro-inflammatory cytokines, together with the positive correlation between BDNF and IL-10 in T2DM, suggests that BDNF deficiency may contribute to the pro-inflammatory state characteristic of diabetes. This concept is further supported by Subramanian et al., who demonstrated that BDNF, indoleamine 2,3-dioxygenase, and cellular

senescence markers are integrated in T2DM patients with depression, suggesting a complex interplay between neurotrophic factors and inflammation [17]. Additionally, adipose tissue dysfunction and impaired nitric oxide signaling may further exacerbate inflammatory cascades in T2DM [18].

An important design consideration is that the primary and exploratory analyses were conducted in two independent cohorts. The primary cohort assessed BDNF and auditory function but did not measure inflammatory cytokines, whereas the exploratory cohort measured BDNF and inflammatory cytokines but did not perform audiological evaluation. Consequently, no single participant underwent all three assessments, precluding formal mediation analysis to establish whether inflammatory cytokines mediate the relationship between BDNF and hearing impairment. The observed BDNF–inflammation associations in the exploratory cohort can only be interpreted as suggestive of a potential mechanistic link, not as direct evidence that inflammation mediates the BDNF–hearing impairment relationship. Furthermore, the absolute BDNF values differed substantially between cohorts (primary: 4.07–11.77 ng/mL; exploratory: 10.59–13.07 ng/mL), which may reflect differences in ELISA kit sensitivity, sample handling, or population characteristics. Notably, the T2DM BDNF values in the exploratory cohort (10.59 ± 2.40 ng/mL) were higher than those in the primary cohort (4.07 ± 1.02 ng/mL for Group A, 4.53 ± 0.94 ng/mL for Group B), yet both cohorts consistently demonstrated significantly lower BDNF in T2DM patients compared with their respective controls. Future studies should employ a unified cohort in which BDNF, inflammatory markers, and audiological parameters are measured simultaneously in all participants using the same assay.

To the best of our knowledge, this is the first study to systematically evaluate serum BDNF levels in T2DM patients stratified by hearing status using both pure-tone audiometry and DPOAE, and to explore the relationship between BDNF and inflammatory cytokines in an independent cohort. However, several limitations must be acknowledged. First, the cross-sectional design precludes causal inference—whether BDNF reduction is a cause or consequence of hearing impairment requires prospective longitudinal investigation. Second, a statistically significant age difference was observed among the three groups in the primary cohort ($P<0.001$). Although the age gradient runs counter to the hearing results (youngest group with worst hearing), and the age span is small (~3.4 years), this imbalance and the absence of multivariable adjustment represent limitations that warrant age-matched confirmatory studies. Third, a

significant age difference was also observed in the exploratory cohort ($P<0.001$), further underscoring the need for age-matched designs in future studies. Fourth, the small sample size of the exploratory cohort and the absence of a hearing-impaired subgroup within it restrict the depth of mechanistic inference. Fifth, the use of two independent cohorts without simultaneous measurement of BDNF, cytokines, and hearing precludes mediation analysis. Future research directions include: (1) conducting age-matched prospective cohort studies to establish a causal temporal chain between baseline BDNF levels and longitudinal hearing outcomes; (2) designing a comprehensive three-group comparison (T2DM with hearing impairment vs. T2DM without hearing impairment vs. healthy controls) incorporating simultaneous BDNF and inflammatory pathway assessments to delineate the specificity of these pathways in diabetic hearing loss; and (3) employing animal models to validate the molecular mechanisms underlying BDNF-mediated cochlear protection.

From a therapeutic perspective, recent advances have explored adenoviral vector-based BDNF gene therapy as a treatment modality for diabetic retinopathy [19], demonstrating the feasibility of BDNF-targeted interventions in diabetic complications. However, the clinical applicability of BDNF-based therapies remains constrained by limited bioavailability, a short half-life, and poor blood–brain barrier permeability [20]. If these delivery challenges can be overcome, BDNF supplementation may offer a novel therapeutic avenue for DM-associated hearing loss.

Notwithstanding these limitations, our study provides important preliminary clinical evidence supporting the hypothesis that BDNF may serve as a potential risk biomarker for T2DM-related hearing impairment, and delineates a clear path for future investigations.

Conclusions

Serum BDNF levels are significantly reduced in T2DM patients compared with healthy controls, and this reduction is not specific to T2DM patients with hearing impairment. However, within the hearing-impaired T2DM subgroup, lower BDNF is associated with adverse metabolic profiles (including dyslipidemia), poorer glycemic control, longer diabetes duration, and greater hearing loss severity across all frequencies. In an independent cohort, BDNF reduction was associated with a pro-inflammatory cytokine profile in T2DM. These findings suggest that BDNF may represent a potential biomarker for T2DM-related hearing impairment, although its

lack of specificity for hearing impairment among T2DM patients indicates that BDNF alone is insufficient to discriminate T2DM patients with and without hearing loss, and should be interpreted in conjunction with audiological and metabolic parameters. The cross-sectional study design, the significant age differences observed in both cohorts, and the use of two independent cohorts (without simultaneous measurement of BDNF, inflammatory cytokines, and auditory function in the same individuals) preclude causal inference and formal mediation analysis. Future studies employing unified cohorts with longitudinal designs and age-matched controls are needed to confirm these findings and elucidate the mechanistic role of BDNF in diabetic hearing loss.

Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Gansu Provincial Central Hospital (Gansu Maternal and Child Health Hospital) (Approval No.: 202311002).

Informed Consent

Informed consent was obtained from all individual participants included in the study. Participants signed informed consent regarding publishing their data.

Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Xiangyue Lu: Conceptualization, Methodology, Formal analysis, Data curation, Writing – Original Draft. Yirong Wang: Investigation, Data curation. Tongmin Li: Investigation, Data curation. Bo Sun: Conceptualization, Methodology, Supervision, Writing – Review & Editing, Project administration. All authors read and approved the final manuscript.

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