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Effects of fasting on appetite-regulating hormones and hearing function in adults with type 2 diabetes mellitus

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Original Article

ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is known to affect multiorgan systems, including auditory function, with metabolic dysregulation playing a central role. Leptin and ghrelin, as metabolic hormones, are involved in energy homeostasis and neuroprotection, and may be influenced by fasting behavior. This study aimed to explore the associations between fasting practices, serum leptin and ghrelin levels, and hearing function in adults with T2DM.
Methods: A cross-sectional study was conducted involving 86 adults with T2DM, categorized into fasting (n=46) and non-fasting (n=40) groups. Serum leptin and ghrelin levels were measured using ELISA after an overnight fast. Hearing thresholds were assessed with pure-tone audiometry at 500, 1000, 2000, and 4000 Hz. Hearing loss was defined as a mean threshold >25 dB. Data were analyzed using Mann–Whitney U tests, Chi-Square tests, and logistic regression.
Results: The fasting group had significantly lower leptin (32.85 ± 31.03 ng/mL vs. 40.89 ± 23.40 ng/mL, p=0.012) and ghrelin levels (5.48 ± 3.37 ng/mL vs. 7.32 ± 3.32 ng/mL, p<0.001). Hearing thresholds were slightly lower in the fasting group (20.80 ± 8.10 dB vs. 23.32 ± 11.13 dB), though the difference was not statistically significant (p=0.192). However, the frequency of hearing loss was significantly lower in fasting participants (21.7%) than in non-fasting participants (37.5%, p=0.015). Logistic regression revealed that higher leptin levels increased the risk of hearing loss (OR = 1.023, 95% CI: 1.004 - 1.042, p = 0.015), whereas fasting status was protective (OR = 0.429, 95% CI: 0.197 - 0.935, p = 0.033). Ghrelin, age, and sex were not significant predictors.
Conclusion: Fasting may be associated with more favorable metabolic profiles and a lower frequency of hearing loss in individuals with T2DM. These findings suggest a potential protective role of structured fasting practices in auditory health, warranting further longitudinal studies to explore causality and underlying mechanisms.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and relative insulin deficiency, leading to hyperglycemia. Unlike type 1 diabetes, which is primarily autoimmune in nature, T2DM is often associated with lifestyle factors and genetic predisposition.[1] The pathogenesis involves complex interactions between genetic, environmental, and behavioral factors, resulting in impaired insulin action and secretion.[2]

Globally, the prevalence of T2DM has reached alarming levels. According to the World Health Organization (WHO), the number of people with diabetes rose from 108 million in 1980 to 422 million in 2014, with the majority of cases being T2DM.[3] The prevalence has been rising more rapidly in low and middle-income countries than in high-income countries.[4] In 2021, diabetes and kidney disease due to diabetes caused an estimated 2 million deaths worldwide.[5] A healthy diet, regular physical activity, maintaining a normal body weight, and avoiding tobacco

use are ways to prevent or delay the onset of T2DM.[6] Diabetes can be treated and its consequences avoided or delayed with diet, physical activity, medication, and regular screening and treatment for complications.[7] In Indonesia, the burden of T2DM is significant. The International Diabetes Federation (IDF) reports that in 2021, Indonesia had approximately 19 million adults with diabetes, ranking it among the top countries with the highest number of diabetes cases.[5,8] This underscores the urgent need for effective prevention and management strategies in the region.

Under normal physiological conditions, insulin facilitates glucose uptake into cells, maintaining blood glucose levels within a narrow range.[9] In T2DM, insulin resistance impairs this process, leading to elevated blood glucose levels.[10] Over time, pancreatic β-cell dysfunction exacerbates hyperglycemia, resulting in chronic metabolic disturbances.[11] The pathophysiology of T2DM involves multiple mechanisms, including insulin resistance, β-Cell Dysfunction, inflammation, and oxidative stress.[12] These disturbances not only affect glucose metabolism but also have systemic implications, contributing to various complications associated with T2DM.[13]

The regulation of appetite and energy balance is an intricate interplay of hormonal signals, with leptin and ghrelin at the centre of this system [14] Leptin, secreted mainly by adipose tissue, communicates with the hypothalamus to signal satiety, thereby suppressing food intake and stimulating energy expenditure. It plays a crucial role in sustaining long-term metabolic equilibrium.[15] Conversely, ghrelin, produced chiefly in the stomach, activates the hypothalamic pathway to enhance appetite, encourage food consumption, and promote fat accumulation, hence its description as the "hunger hormone".[16] In individuals with T2DM, the regulation of these hormones is often disrupted.[17] Although leptin levels are typically elevated due to excess adiposity, the hypothalamus becomes less responsive to its signals, resulting in ongoing hunger and progressive weight gain.[18] Ghrelin regulation may also be altered, further disrupting appetite control and overall energy stability.[19] These hormonal imbalances exacerbate metabolic dysfunctions in T2DM, highlighting the importance of understanding their roles in disease progression and management.

Hearing loss is an often overlooked complication of T2DM.[20] Studies have consistently shown that people with diabetes have a higher risk of developing hearing loss compared to non diabetic individuals.[21] The proposed mechanisms include chronic hyperglycemia leading to microvascular damages that compromises cochlear and auditory nerve perfusion,[22] diabetic neuropathy leading to impaired neural transmission,[23] and oxidative stress that damage cochlear hair cells.[24] Recent investigations have also pointed to a potential link between appetite-regulating hormones and auditory function.[25] The detection of leptin and ghrelin receptors within the inner ear indicates that hormonal dysregulation could directly affect cochlear function, although the precise pathways remain unclear.[26]

Fasting, particularly intermittent fasting, has received growing attention for its positive effects on metabolism and healthy ageing.[27] It stimulates autophagy, a cellular process that removes damaged components, thereby preserving β-cell integrity and improving insulin sensitivity.[28] Fasting has also been associated with telomere preservation, which may slow cellular ageing and reduce the risk of metabolic disorders such as T2DM.[29] Among diabetic individuals, fasting enhances insulin responsiveness, reduces systemic inflammation, and influences appetite-related hormonal activity.[30] Evidence further indicates that intermittent fasting can lower circulating leptin levels and restore leptin sensitivity,thereby improving energy regulation and metabolic homeostasis.[31]

Given the interplay between metabolic health, hormonal regulation, and auditory function, fasting may offer a multifaceted approach to managing T2DM and its complications. By modulating leptin and ghrelin levels, fasting could improve appetite control and energy homeostasis. Additionally, activating autophagy and reducing oxidative stress may protect cochlear structures, potentially mitigating hearing loss in individuals with T2DM. Despite the growing body of evidence on the benefits of fasting in metabolic health, its specific effects on appetite-regulating hormones and hearing function in T2DM remain underexplored. This study aims to investigate the impact of fasting on serum leptin and ghrelin levels and auditory

function in adults with T2DM. By comparing fasting and non-fasting individuals, we seek to elucidate potential mechanisms through which fasting may influence metabolic and auditory outcomes, providing insights for holistic management strategies in T2DM.

METHODS

Study design

This was an analytical observational study with a cross-sectional design, conducted from May to June 2024 in Malang, Indonesia. Participants were recruited consecutively from community-based health screening programs held in collaboration with the Department of Internal Medicine, Brawijaya Academic Hospital. Eligible participants were adults aged 18-65 years with a confirmed diagnosis of Type 2 Diabetes Mellitus (T2DM). The fasting group consisted of individuals who, in addition to receiving standard antidiabetic treatment, regularly practiced voluntary fasting. Fasting practices included Islamic sunnah fasting (e.g., Monday-Thursday fasting, Dawud fasting, and other regular religious fasts) or intermittent fasting. Intermittent fasting is a dietary pattern characterized by repeated intervals, typically 16 to 48 hours, during which energy intake is substantially reduced or entirely absent. Several variations exist, including alternate-day fasting (complete caloric abstinence on fasting days), alternate-day modified fasting (more than 60% reduction in caloric intake on fasting days), and time-restricted eating practices implemented on two nonconsecutive days per week. In contrast, periodic fasting involves longer periods of restricted intake, generally spanning 2-21 days or more.[32] In the present study, although fasting practices among participants showed variability, the operational definition of fasting was standardized as an abstinence period of 8-16 consecutive hours before blood sampling and audiometric examination. This criterion was adopted to ensure uniformity across participants and to reflect the most common fasting duration observed in routine Islamic sunnah and time-restricted eating practices.

Population and sample

The study population comprised adult patients diagnosed with T2DM, defined according to the following criteria: (1) ongoing antidiabetic treatment; (2) fasting blood glucose ≥126 mg/dL; (3) random blood glucose ≥200 mg/dL; (4) inpatient discharge diagnosis of diabetes mellitus; or (5) outpatient clinical diagnosis confirmed by a physician. Consecutive sampling was applied to enroll 86 eligible participants who met the inclusion criteria. Participants were then categorized into two groups: those practicing routine fasting (n = 46) and those who did not engage in any regular fasting (n = 40).

Data collection

Demographic data, including age and sex, were recorded through structured interviews. Venous blood samples were collected from all participants in the morning following a minimum 8-hour fast to ensure accurate hormonal measurements. Serum was isolated and analyzed for leptin and ghrelin concentrations using validated enzyme-linked immunosorbent assay (ELISA) kits (Catalog No. ab100581 for leptin and ab100592 for ghrelin, Abcam, Cambridge, UK), according to the manufacturer's instructions. Audiometric examination was conducted using the Interacoustics Clinical Audiometer AD629 to assess air- and bone-conduction thresholds. All assessments were performed in a certified soundproof booth with ambient noise levels maintained below 40 dB. Hearing thresholds were measured at 500, 1000, 2000, and 4000 Hz, and the average hearing threshold for these speech frequencies was calculated. Hearing was classified as normal if the average threshold was $\leq$25 dB and as impaired if >25 dB, based on World Health Organization criteria.[33]

Data analysis

All statistical analyses were performed using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation (SD) and

compared between groups using the Mann-Whitney U test due to non-normal distribution. Categorical variables such as sex and hearing loss incidence were analyzed using Pearson's chi-square test. To further evaluate the independent association of leptin, ghrelin, age, sex, and fasting status with hearing loss, binary logistic regression analysis was performed. The results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). A p-value of < 0.05 was considered statistically significant.

Ethical statement

The study protocol was reviewed and approved by the Health Research Ethics Committee of Universitas Brawijaya (Approval No. 112/EC/KEPK/2024). All participants provided written informed consent before enrollment. Data confidentiality was maintained throughout the study in accordance with the Declaration of Helsinki.

RESULTS

The fasting and non-fasting groups were generally comparable in terms of demographic and baseline metabolic characteristics. A total of 86 individuals with Type 2 Diabetes Mellitus (T2DM) were included in this study, accounting for 172 ears (Table 1). Of these, 46 participants (92 ears) were in the fasting group, while 40 participants (80 ears) and 40 participants (80 ears) were in the non-fasting group. Table 1 summarizes the clinical and laboratory characteristics between the two groups. Participants in the fasting group had a significantly higher mean age (56.32 ± 5.85 years) than those in the non-fasting group (53.35 ± 6.32 years; p = 0.001). Serum leptin levels were significantly lower in the fasting group (32.85 ± 31.03 ng/mL) compared to the non-fasting group (40.89 ± 23.40 ng/mL; p = 0.012). Similarly, serum ghrelin levels were significantly lower in the fasting group (5.48 ± 3.37 ng/mL) than in the non-fasting group (7.32 ± 3.32 ng/mL; p < 0.001). Mean hearing threshold was slightly lower in the fasting group (20.80 ± 8.10 dB) than in the non-fasting group (23.32 ± 11.13 dB); however, the difference was not statistically significant (p = 0.192).

Table 1. Comparison of age, hormonal markers, and hearing thresholds between fasting and non-fasting groups

Variable	Fasting (n=92 ears)		Non fasting (n=80 ears)		Total (n=172 ears)		p-value
	Mean	SD	Mean	SD	Mean	SD	
Age (years)	56.32	5.85	53.35	6.32	54.94	6.24	0.001*
Leptin (ng/mL)	32.85	31.03	40.89	23.40	36.59	27.96	0.012*
Ghrelin (ng/mL)	5.48	3.37	7.32	3.32	6.33	3.4	0.000*
Hearing Threshold (dB)	20.80	8.1	23.32	11.13	21.97	9.69	0.192

Note: Mann-Whitney U test was used. *Statistically significant at p < 0.05.

When examining sex distribution and hearing outcomes, we observed that fasting participants were less likely to have hearing loss than non-fasting participants. The distribution of sex and hearing loss status between the two groups is shown in Table 2. The fasting group consisted of 15 males and 31 females, while the non-fasting group included 6 males and 34 females. The difference in sex distribution was statistically significant (p = 0.007). Regarding hearing loss status, 10 participants in the fasting group had hearing impairment, compared to 15 in the non-fasting group. This difference was statistically significant (p = 0.015), indicating a lower frequency of hearing loss among fasting participants.

Table 2. Sex and hearing loss distribution between fasting and non-fasting groups

Variable	Fasting (n=46 people)	Non Fasting (n=40 people)	Total (n=86 people)	p-value
Sex				
Male	15	6	21	0.007*

Variable	Fasting (n=46 people)	Non Fasting (n=40 people)	Total (n=86 people)	p-value
Female	31	34	65	
Total	46	40	86	
Hearing Loss Distribution				
Hearing Loss	10	15	25	0.015*
No Hearing Loss	36	25	61	
Total	46	40	86	

Note: Pearson chi-square test was used. *Statistically significant at $p < 0.05$.

Logistic regression analysis was conducted to evaluate the association between appetite-regulating hormones, demographic factors, and fasting status with the risk of hearing impairment in adults with T2DM. The overall model was statistically significant ($\chi^2 = 17.26$, df = 5, $p = 0.004$), explaining 9.5%-13.6% of the variance in hearing outcomes (Cox & Snell $R^2 = 0.095$; Nagelkerke $R^2 = 0.136$). Leptin levels were significantly associated with higher odds of hearing impairment (OR = 1.023; 95% CI = 1.004 - 1.042; p = 0.015), while fasting status was associated with reduced risk (OR = 0.429; 95% CI = 0.197 - 0.935; p = 0.033). Gender showed a borderline effect (OR = 2.567; 95% CI = 0.987 - 6.677; p = 0.053), whereas ghrelin and age were not significant predictors.

Table 3. Logistic Regression Analysis of Factors Associated with Hearing Impairment

Variable	B	SE	Wald	p-value	OR (Exp(B))	95% CI for OR
Leptin	0.022	0.009	5.878	0.015*	1.023	1.004 - 1.042
Ghrelin	-0.044	0.065	0.467	0.494	0.957	0.843 - 1.086
Age	0.008	0.029	0.085	0.771	1.008	0.953 - 1.068
Gender (Male vs Female)[a]	0.943	0.488	3.738	0.053	2.567	0.987 - 6.677
Fasting (Yes vs No)[a]	-0.846	0.397	4.535	0.033*	0.429	0.197 - 0.935
Constant	0.999	1.813	0.303	0.582	2.715	

Note: OR = Odds Ratio; CI = Confidence Interval; SE = Standard Error. [a]Reference group = female (for gender) and non-fasting (for fasting). Leptin, ghrelin, and age were treated as continuous variables. *Statistically significant at $p < 0.05$.

DISCUSSION

This study explored the potential association among fasting practices, leptin and ghrelin levels, and hearing outcomes in adults with T2DM. Logistic regression analysis demonstrated that fasting status was independently associated with a reduced risk of hearing loss, even after adjustment for age, sex, leptin, and ghrelin. In particular, lower leptin concentrations were significantly associated with hearing outcome, whereas ghrelin and age were not. These findings suggest that fasting may exert beneficial effects on auditory health through metabolic and neuroendocrine pathways, possibly mediated by leptin regulation. Although the difference in average hearing thresholds between the groups did not reach statistical significance, the observed trend supports the hypothesis that fasting-induced metabolic adaptations may influence neuroendocrine regulation and auditory health in diabetic populations. In the following sections, we discuss the physiology and pathophysiology of leptin and ghrelin in both healthy individuals and those with T2DM, including how fasting influences their regulation. We also integrate our study findings into these mechanisms. In addition, we briefly explore the roles of autophagy and telomere shortening, two cellular processes critically affected by fasting. Furthermore, we examine the clinical implications of fasting and the importance of auditory screening in the context of T2DM progression. Finally, we address the limitations of our study and outline directions for future research.

The observed association between fasting status and lower hearing loss prevalence may, in part, be explained by hormonal adaptations. One of the most relevant pathways involves leptin regulation. Leptin is a 16-kDa adipokine predominantly secreted by white adipose tissue

and plays a vital role in energy homeostasis, appetite regulation, and neuroendocrine function.[34] Since its discovery in 1994,[34] leptin's physiological roles have extended beyond metabolism,[35] influencing immune responses,[36] reproductive functions,[37] and neural processes,[36] including auditory system regulation.[38,39] Leptin receptors (Ob-R), belonging to the class I cytokine receptor family, exist in multiple isoforms (Ob-Ra through Ob-Rf), with the long isoform (Ob-Rb) primarily responsible for intracellular signaling.[40] These receptors are widely expressed in the hypothalamus, mediating leptin's anorexigenic effects. They are also found in peripheral organs such as pancreatic β-cells, liver, skeletal muscle, and structures within the inner ear.[38,41,42] In adipose tissue, leptin modulates lipogenesis and lipolysis via autocrine and paracrine signaling. Within the cochlea and brainstem auditory nuclei, leptin receptors are believed to exert neuroprotective and anti-inflammatory effects, suggesting a novel link between metabolic hormones and sensory regulation.[43,44]

In individuals with normal glucose metabolism, leptin functions as a feedback signal to the hypothalamus, indicating adequate energy reserves, thereby reducing food intake and increasing energy expenditure.[38] Binding of leptin to Ob-Rb activates the JAK2-STAT3 signaling pathway, influencing transcriptional regulators such as proopiomelanocortin (POMC) and suppressing orexigenic neuropeptides like neuropeptide Y (NPY) and agouti-related peptide (AgRP).[40] Furthermore, leptin supports neurogenesis and synaptic plasticity, potentially by modulating brain-derived neurotrophic factor (BDNF) and other neurotrophic factors.[45] However, in T2DM, leptin signaling is frequently impaired. Despite elevated circulating leptin levels due to increased adiposity, leptin resistance, particularly at the hypothalamic level, disrupts satiety signaling, resulting in persistent hyperphagia and aggravated insulin resistance.[46,47] This resistance may be driven by defective leptin transport across the blood-brain barrier, impaired Ob-Rb signaling, suppressor of cytokine signaling 3 (SOCS3) overexpression, and endoplasmic reticulum stress in hypothalamic neurons.[48] Consequently, the homeostatic and neuroprotective effects of leptin are diminished in diabetic individuals.

Altered leptin signaling in T2DM has implications for the auditory system.[49] Research indicates leptin may protect cochlear structures by modulating inflammation, oxidative stress, and synaptic function. Animal models deficient in leptin or leptin signaling exhibit increased susceptibility to cochlear damage, likely due to disrupted mitochondrial metabolism, glutamate excitotoxicity, and reduced hair cell resilience.[50] Additionally, leptin may influence microvascular health and endothelial function within the stria vascularis, a critical region for maintaining the endocochlear potential necessary for hearing.[51] In diabetic patients, particularly those with poor glycemic control, hyperleptinemia and leptin resistance may worsen microvascular complications and neurodegeneration in auditory pathways.[52] Novita et al. (2024) found a significant correlation between serum leptin levels and shifts in auditory thresholds in T2DM patients, suggesting leptin dysregulation as an independent risk factor for diabetes-associated hearing loss.[52,53] Chronic inflammation and oxidative stress, hallmark features of diabetes, further impair leptin's reparative capacity in the cochlea, contributing to progressive sensorineural hearing loss.[54]

The observed reduction in leptin levels among fasting participants aligns with previous findings that caloric restriction and intermittent fasting decrease leptin production, primarily by reducing adipose tissue activity and enhancing insulin sensitivity.[55] This decline is especially relevant in T2DM, where elevated leptin is associated with persistent low-grade inflammation and vascular complications, including those affecting cochlear function.[56] Therefore, the lower leptin concentrations in the fasting group may reflect a more favorable metabolic profile that mitigates the risk of such complications.

In addition to leptin, ghrelin also plays a vital role in energy balance and neural protection, which may contribute to auditory outcomes in T2DM. Ghrelin is a 28-amino-acid peptide hormone secreted mainly by the stomach, with additional expression in peripheral tissues such as the pancreas, kidneys, and small intestine. Identified in 1999 as the endogenous ligand for the growth hormone secretagogue receptor (GHS-R), ghrelin is well-known for stimulating appetite and promoting energy storage.[54] Emerging evidence also implicates ghrelin

in neuroprotection, immune modulation, and potentially auditory function. The ghrelin receptor (GHS-R1a) is widely distributed in the central nervous system, particularly in the hypothalamus, hippocampus, and brainstem. It is expressed in peripheral tissues, including adipose tissue, pancreas, cardiovascular tissue, and sensory organs such as the cochlea.[57,58] In the brain, ghrelin modulates feeding behavior, memory, and neuroplasticity, while in peripheral organs it influences insulin secretion, lipid metabolism, and mitochondrial function.[59]

In healthy individuals, ghrelin levels rise during fasting and fall after eating, promoting hunger and preparing the body for nutrient assimilation. This rhythmic secretion is essential for maintaining energy balance. Ghrelin primarily acts through GHS-R1a to stimulate NPY- and AgRP-expressing neurons in the hypothalamus, thereby promoting food-seeking behavior and adiposity.[60] Additionally, ghrelin exerts anti-inflammatory and antioxidative effects in central and peripheral tissues; however, its specific influence on the inner ear has not been fully elucidated.[61] In T2DM, however, ghrelin dynamics are significantly disrupted. Patients exhibit lower circulating levels of acylated ghrelin, the biologically active form, compared to healthy controls.[62] This decline likely results from insulin resistance, chronic inflammation, and hyperinsulinemia, which collectively impair ghrelin synthesis and secretion by gastric X/A-like cells.[63] Reduced ghrelin activity may contribute to appetite dysregulation, poor glycemic control, and worsening metabolic imbalance.

The consequences of ghrelin dysregulation in T2DM extend beyond metabolism and may impact sensory systems, particularly the auditory apparatus. Ghrelin may support cochlear hair cells and spiral ganglion neurons by engaging neuroprotective pathways that interact with cholinergic mechanisms, including the α9/α10 nicotinic acetylcholine receptors,[64] which have been suggested as potential targets for improving auditory function. Experimental animal studies demonstrate that ghrelin administration attenuates cochlear cell apoptosis, reduces oxidative damage, and promotes regeneration after acoustic trauma or ototoxic injury.[65] In T2DM patients, reduced ghrelin levels may heighten vulnerability of auditory structures to damage from hyperglycemia-induced oxidative stress, vascular insufficiency, and inflammation. Diabetic microangiopathy and mitochondrial dysfunction in the cochlea may be aggravated by the lack of ghrelin's protective signaling, leading to progressive sensorineural hearing loss.[66] Additionally, low ghrelin levels may impair neurovascular coupling in the auditory cortex, further degrading auditory perception and processing.[67]

Interestingly, ghrelin levels in this research were significantly lower in the fasting group, which contrasts with studies reporting increased ghrelin during short-term fasting.[68] However, long-term or habitual fasting, such as religious fasting or structured health regimens, may induce hormonal adaptations resulting in a new homeostatic balance and overall decreased circulating ghrelin.[69] The protective role of ghrelin in the auditory system, particularly its anti-inflammatory and anti-apoptotic effects demonstrated in animal models,[69,70] supports the hypothesis that reduced ghrelin levels linked to chronic fasting may still contribute to hearing preservation.

Beyond hormonal regulation, fasting also activates cellular maintenance pathways, particularly autophagy, which may indirectly influence auditory resilience. Autophagy is a highly conserved catabolic process that maintains cellular homeostasis by degrading and recycling damaged organelles, misfolded proteins, and pathogens via lysosomal degradation.[71] Derived from the Greek "auto" (self) and "phagy" (eating), autophagy functions as a survival mechanism activated by stressors such as nutrient deprivation, oxidative stress, and infection. This process not only contributes to energy balance but also regulates cell survival, aging, immunity, and neuroprotection.[72]

Under normal physiological conditions, basal autophagy facilitates the routine turnover of cytoplasmic components, preventing the accumulation of dysfunctional mitochondria and other organelles. It begins with the formation of a phagophore, a double-membrane structure that engulfs targeted cytosolic material, which matures into an autophagosome. The autophagosome then fuses with lysosomes to form autolysosomes, where degradation and recycling occur.[73] In neurons and sensory cells, where component turnover is limited, autophagy is critical for long-

term function and cellular integrity. In T2DM, autophagy is often dysregulated; chronic hyperglycemia, insulin resistance, and metabolic inflammation impair the autophagic process at multiple stages, resulting in defective clearance of damaged organelles and proteins.[74] Pancreatic β-cells, highly reliant on autophagy, become particularly vulnerable, contributing to dysfunction, reduced insulin secretion, and increased apoptosis.[75] Similar defects in liver, muscle, and adipose tissue promote lipid accumulation, mitochondrial dysfunction, and inflammatory signaling, characteristic of T2DM pathophysiology.[76]

The impact of autophagy impairment in T2DM extends to sensory organs, including the auditory system. The cochlea, particularly vulnerable to oxidative stress, inflammation, and energy imbalance, relies on autophagy in hair cells and spiral ganglion neurons to clear damaged mitochondria and maintain synaptic integrity.[77] Diabetic models show that reduced autophagic activity correlates with increased cochlear cell death, disrupted neurotransmission, and progressive hearing loss.[78] Accumulation of autophagy substrates such as p62 and damaged mitochondria in diabetic auditory tissues suggests impaired autophagic flux, not merely reduced initiation.[79]

Emerging evidence increasingly indicates that autophagy dysregulation in individuals with T2DM is closely associated with disruptions in hormonal homeostasis, particularly involving leptin and ghrelin. Leptin, a hormone primarily secreted by adipose tissue to signal satiety, modulates autophagic processes via AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin (mTOR) signaling pathways. Under physiological conditions, leptin supports cellular resilience by promoting autophagy in metabolically active tissues such as neurons and hepatocytes.[80] However, in the context of T2DM, leptin resistance undermines these protective mechanisms, resulting in suppressed autophagy and increased susceptibility to oxidative damage.[81] Conversely, ghrelin plays a dual role in metabolic regulation and neuroprotection. This orexigenic hormone facilitates autophagy by activating AMPK and inhibiting mTOR, a key suppressor of autophagic pathways. In neuronal tissues, ghrelin-induced autophagy promotes mitochondrial turnover and mitigates apoptosis.[82] In diabetic conditions, reduced ghrelin activity impairs these protective effects, further disrupting autophagic processes and contributing to both metabolic dysfunction and neurodegeneration, including in cochlear structures.[83] Consequently, strategies aimed at restoring leptin and ghrelin balance in T2DM may indirectly enhance autophagic activity and offer neuroprotective benefits for auditory tissues.

Another biological mechanism influenced by fasting is telomere dynamics, which have been linked to both aging and metabolic control. Telomeres is the repetitive nucleotide sequences (TTAGGG) at the ends of chromosomes. They serve as protective caps that preserve chromosomal integrity during cell division. Their progressive shortening is a natural part of cellular aging and plays a pivotal role in cellular senescence, genomic instability, and apoptosis, especially in high-turnover tissues. Under normal physiological conditions, telomere length is maintained within a narrow range by the enzyme telomerase, particularly active in germline and stem cells. In contast, fmost somatic cells exhibit minimal telomerase activity and therefore experience gradual telomere attrition over time.[84] In individuals with T2DM, telomere shortening is significantly accelerated. Several mechanistic pathways underlie this phenomenon. Chronic hyperglycemia and insulin resistance, hallmark features of T2DM, contribute to increased oxidative stress and low-grade systemic inflammation, both of which exacerbate telomere erosion.[85] High levels of reactive oxygen species (ROS) directly damage telomeric DNA, which is particularly sensitive to oxidative stress due to its high guanine content. Moreover, persistent metabolic stress in T2DM enhances cell turnover in metabolically active tissues such as pancreatic β-cells, vascular endothelium, and neurons, leading to cumulative telomere depletion.[86]

Recent studies have increasingly highlighted the effects of telomere shortening in specific organs, including the auditory system. The cochlea, a highly metabolic structure in the inner ear, relies heavily on mitochondrial integrity and redox balance. Shortened telomeres in cochlear cells, especially in spiral ganglion neurons and hair cells, may impair cellular regeneration and

heighten susceptibility to oxidative damage, ultimately contributing to sensorineural hearing loss (SNHL) in diabetic populations.[87] Experimental models have shown that telomere attrition in auditory neurons leads to early onset auditory dysfunction, mirroring clinical observations in elderly diabetic patients with compromised hearing thresholds.[88]

Leptin and ghrelin, two pivotal hormones in energy homeostasis, also interact with telomere dynamics and may influence auditory health, particularly in the context of T2DM. Leptin, secreted primarily by adipocytes, not only regulates appetite but also modulates immune function and oxidative stress. However, in T2DM, hyperleptinemia and leptin resistance disrupt these regulatory roles. Elevated leptin levels have been linked to telomere shortening by promoting pro-inflammatory cytokines such as TNF-α and IL-6, which, in turn, accelerate cellular senescence and damage.[89] Furthermore, the chronic inflammatory milieu in T2DM, potentiated by leptin dysregulation, may exert detrimental effects on cochlear cells, amplifying the risk of diabetic hearing impairment. Conversely, ghrelin has been shown to exert protective effects on cellular aging processes. Ghrelin possesses antioxidant and anti-inflammatory properties, and its reduced levels in T2DM may limit these protective effects. Ghrelin administration in experimental models has been found to reduce oxidative DNA damage, improve mitochondrial function, and attenuate telomere shortening.[90] Given the expression of ghrelin receptors in the cochlea and auditory pathways, it is plausible that this hormone modulates telomere integrity and auditory function. However, further investigation is needed in human models.

Fasting, both intermittent and religious, is emerging as a promising non-pharmacological intervention in the management of Type 2 Diabetes Mellitus (T2DM).[91,92] Numerous studies have demonstrated its potential to improve glycemic control, reduce insulin resistance, modulate hormonal profiles such as leptin and ghrelin, and mitigate systemic inflammation, all of which are crucial in preventing the vascular and neural complications commonly associated with diabetes. Among these complications, sensorineural hearing loss remains under-recognized despite growing evidence of its prevalence in the diabetic population.[93] Diabetes-related hearing loss is thought to result from chronic hyperglycemia-induced microangiopathy, oxidative stress, and neural degeneration within the cochlea and auditory pathways. Several cohort studies have confirmed a significantly higher incidence of hearing impairment among individuals with T2DM compared to non-diabetic controls.[20,94,95] Importantly, poor glycemic control correlates with a greater degree of auditory dysfunction.[96] This suggests that any intervention capable of stabilizing blood glucose and improving insulin sensitivity, such as fasting, could offer protective effects against hearing deterioration.

Fasting modulates metabolic signaling pathways, enhances autophagy, and reduces oxidative stress, all of which are implicated in the pathophysiology of diabetic complications, including those affecting the auditory system. Studies have shown that intermittent fasting can preserve mitochondrial function and neural integrity, particularly in metabolically sensitive tissues like the inner ear.[97,98] Additionally, fasting-associated reductions in leptin and improvements in ghrelin signaling have been linked to neuroprotection, suggesting a protective hormonal environment for cochlear structures.[99] Despite these promising mechanisms, clinical protocols seldom integrate fasting as part of comprehensive diabetes care, and hearing loss remains inadequately addressed in routine screenings. This highlights the urgent need for standardized auditory screening programs in the management of T2DM. Early identification of subclinical hearing changes through pure-tone audiometry or otoacoustic emissions can facilitate timely interventions and prevent functional impairment, particularly in older adults and those with long-standing diabetes. Moreover, patient education should emphasize the systemic nature of diabetes, including its potential to affect hearing. Health providers should advocate for periodic auditory evaluations, especially in patients with poorly controlled T2DM, and consider personalized fasting interventions when appropriate. Incorporating such strategies into diabetes management plans could improve quality of life and reduce long-term complications. Fasting holds significant promise as an adjunctive approach to managing T2DM and preventing its lesser-known complication, hearing loss. However, further interventional

studies are warranted to define optimal fasting protocols, evaluate long-term auditory outcomes, and solidify guidelines for integrating hearing screenings into diabetes care.

The lower frequency of hearing loss observed in the fasting group may be attributed to cumulative physiological effects, including better hormonal regulation, decreased oxidative stress, and improved vascular health. Previous studies have linked diabetes-related auditory impairment to small-vessel disease and to neuropathy affecting the auditory nerve.[100,101] Fasting has been shown to ameliorate these processes by enhancing endothelial function and decreasing the accumulation of advanced glycation end-products (AGEs).[102] These mechanisms may help explain the beneficial patterns noted in this study.

Although a favorable trend was noted, the correlation between fasting and hearing thresholds did not reach statistical significance. This could be due to sample size limitations or variations in participants' adherence to fasting routines. Additionally, the potential auditory benefits of fasting may require extended periods to manifest, beyond the observational window of this study. Age was also inversely associated with fasting status, suggesting that younger individuals were more likely to engage in regular fasting. Since aging is an established risk factor for hearing decline, this demographic difference may have influenced the findings.[103]

Another notable observation was the significant association between fasting and sex, with a higher proportion of female participants in the fasting group. This may reflect social or behavioral norms, such as greater involvement of women in religious observances or health-promoting behaviors. However, it also introduces the possibility of hormonal or physiological differences by sex that could impact both hormone profiles and auditory outcomes, considering established differences in leptin and ghrelin responses between men and women.[104,105]

Taken together, these mechanisms suggest that structured fasting could confer metabolic and neuroprotective benefits, with potential implications for clinical practice in the management of T2DM. From a public health perspective, these findings may inform non-pharmacological strategies aligned with Sustainable Development Goal 3, which seeks to promote health and well-being across the lifespan. Encouraging culturally relevant lifestyle practices, such as intermittent or religious fasting, may may be a cost-effective way to support sensory health among individuals with chronic diseases, particularly in settings with limited access to healthcare resources. Recognizing the interplay between metabolic and sensory systems could inform more integrated models of care for people with T2DM and related conditions.

Nevertheless, several limitations of the study should be acknowledged.. The cross-sectional design does not permit causal inferences. Additionally, fasting status was self-reported and not objectively verified, which may introduce recall bias. Other factors, such as diet composition, diabetes duration, and glycemic control, were not measured and may have influenced both hormonal status and hearing function. Finally, the relatively small sample size may reduce the generalizability of the findings. Despite these constraints, this research offers preliminary insights that can guide future longitudinal and interventional studies on the metabolic pathways connecting fasting and auditory health.

CONCLUSION

This study identifies a potential association between routine fasting practices and reduced serum leptin and ghrelin levels, as well as a lower prevalence of hearing loss among adults with T2DM. Although mean hearing thresholds did not differ significantly, the hormonal trends and lower occurrence of auditory impairment in the fasting group suggest that metabolic regulation may play a role in preserving auditory function. These findings underscore the importance of integrating culturally accepted lifestyle interventions, such as intermittent or religious fasting, into diabetes care strategies. Furthermore, they highlight the need to incorporate routine hearing screening in diabetic management protocols, particularly in resource-limited settings where early detection of sensory decline is often overlooked. Future longitudinal studies are warranted to explore the causal pathways linking fasting, endocrine modulation, and hearing preservation.

CONFLICT OF INTEREST

The author declare no conflicts of interest in relation to the design, execution, analysis, or publication of this study. This research was funded by an internal grant from the University of Brawijaya, which had no role in the study design, data collection, interpretation of results, or the decision to submit this manuscript for publication. The author confirm that they have no financial ties, consultancy roles, or proprietary interests with any external entities, companies, or organizations that could be construed as influencing the integrity of the study.

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DATA AVAILABILITY

The data supporting the findings of this study are not publicly available due to ethical restrictions and the confidentiality agreement with participants. However, de-identified data may be made available upon reasonable request to the corresponding author, provided that such access complies with institutional and ethical guidelines. Requests for access to the dataset should include a clear research purpose. They will be considered on a case-by-case basis, subject to approval by the Health Research Ethics Committee of the Faculty of Medicine, University of Brawijaya.

SUPPLEMENTAL DATA

Supplementary material associated with this article includes the anonymized raw dataset, detailed descriptions of the fasting patterns reported by participants, and the full audiometric threshold values across tested frequencies for both ears. These files have been uploaded as supplementary material during the submission process and are available in their original format without tracked changes or annotations. While these materials are not essential to the main text, they provide additional context and transparency for readers interested in methodological details and raw data interpretation. All supplementary files are clearly labeled and include appropriate captions to facilitate independent review. For ethical and confidentiality reasons, no personal identifiers are included. Any requests for clarification or extended access to the supplementary dataset may be directed to the corresponding author and will be considered on a case-by-case basis in accordance with institutional guidelines.

AUTHOR CONTRIBUTIONS

The sole author, KDN was responsible for the entire research process, including conceptualization, study design, data collection, laboratory and audiometric assessments, statistical analysis, interpretation of results, and the drafting and finalization of the manuscript.

DECLARATION OF USING AI IN THE WRITING PROCESS

The author affirms that the conception, design, data analysis, and interpretation presented in this manuscript are entirely the product of the author's independent clinical and academic expertise. No generative AI platforms were used to create, draft, or revise the core scientific content. Limited use of AI-assisted technologies, such as for language clarity and reference formatting, was employed solely to enhance technical consistency during the final

stages of manuscript preparation. The author remains fully responsible for the accuracy, integrity, and originality of all content submitted for publication.

LIST OF ABBREVIATIONS

AI: Artificial Intelligence; dB: Decibel; ELISA: Enzyme-Linked Immunosorbent Assay; HL: Hearing Loss; Hz: Hertz; IF: Intermittent Fasting; PTA: Pure Tone Audiometry; SD: Standard Deviation; SPSS: Statistical Package for the Social Sciences; T2DM: Type 2 Diabetes Mellitus; WHO: World Health Organization.

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