

Plasma Glycated Albumin Levels Clearly Detect Hearing Loss and Atherosclerosis in Patients with Impaired Fasting Glucose

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Key Words

Hearing impairment · Impaired glucose tolerance · Atherosclerosis · Glycated albumin

Abstract

Objective: To describe the relationship between atherosclerosis and hearing thresholds in prediabetic patients with impaired fasting glucose (IFG) and to determine the efficacy of glycated albumin in predicting carotid artery atherosclerosis in patients with isolated IFG. **Subjects and Methods:** The study included 82 patients (aged 53.73–80 years) divided into two groups based on fasting glucose levels, the IFG group: 59 patients (32 females, 54.2%), and the normal fasting plasma glucose level group: 23 patients (12 females, 52.2%). Patients underwent audiological testing to determine hearing thresholds, and carotid intima-media thickness (CIMT) was measured using carotid artery Doppler sonography. Multivariate analyses were performed to determine whether or not the plasma glycated albumin levels could predict hearing loss and CIMT. **Results:** Patients in the IFG group (mean age: 59.8 ± 9.5 years) had higher hearing thresholds and pure-tone average scores (PTA) than those in the group with normal glucose levels (mean age: 56.2 ± 10.1

years) (left ear: 27.65 ± 8.85 vs. 25.75 ± 21.96 dB, $p = 0.021$; right ear: 29.22 ± 8.51 vs. 22.39 ± 6.99 dB, $p = 0.001$). The CIMT was significantly higher in the IFG group than the control group (0.75 ± 0.26 vs. 0.56 ± 0.16 mm, $p < 0.001$ for the left and 0.74 ± 0.26 vs. 0.51 ± 0.19 mm, $p < 0.001$ for the right carotid arteries). Glycated albumin levels were independently related with increased CIMT (left CIMT: $r = 0.32$, $p = 0.003$; right CIMT: $r = 0.42$, $p < 0.001$), and serum glycated albumin levels were significantly associated with PTA (left ear: $r = 0.28$, $p = 0.01$; right ear: $r = 0.30$, $p = 0.006$). **Conclusion:** Sensorineural hearing loss was more common in patients with IFG. Plasma glycated albumin levels were strongly correlated with CIMT and carotid plaques as a marker of atherosclerosis and with hearing impairment thought to develop due to atherosclerosis in patients with IFG.

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Introduction

Dysfunctional glucose homeostasis is a global problem with rapid progression [1]. Impaired fasting glucose (IFG) is one of the initial stages of glucose intolerance and affects 14.7% of the adult Turkish population [1]. Isolated

IFG is defined as fasting plasma glucose levels of 100–125 mg/dl (5.6–6.9 mmol/l) and a 2-hour postprandial plasma glucose level of <140 mg/dl (<7.8 mmol/l) [2].

Hyperglycemia results in serious vascular complications such as stroke and myocardial infarction due to atherosclerosis prior to the onset of overt diabetes mellitus [3, 4]. In the prediabetic period, serum glucose levels, along with glycosylated hemoglobin (HbA_{1c}) and the more recently popular glycated albumin, are thought to be the most important markers of the development of diabetic complications [5, 6].

Hyperglycemia with or without a diagnosis of diabetes mellitus may also affect hearing thresholds by provoking neuronal degeneration, resulting in sensorineural hearing loss at an early age [7, 8]. Therefore, the objectives of this study were to investigate the relationship between atherosclerosis and hearing thresholds in prediabetic patients with IFG and to test the hypothesis that glycated albumin is useful for predicting carotid artery atherosclerosis and hearing impairment in the isolated IFG population.

Subjects and Methods

This cross-sectional clinical study included 138 consecutive adult volunteer subjects who attended our Otorhinolaryngology Clinic. Exclusion criteria were patients diagnosed with ischemic brain damage, vertebrobasilar insufficiency, or otological diseases (such as benign paroxysmal positional vertigo, Ménière's disease or otosclerosis), type 1 and 2 diabetes mellitus, noise exposure, anemia, active thyroid disorders, history of liver or kidney diseases, alcohol usage, use of lipid-lowering or antidiabetic agents, malignancy, pregnancy, and obesity.

All investigations were performed in accordance with the Declaration of Helsinki on biomedical studies involving human subjects, and informed consent was obtained from all participating subjects. The study protocol was approved by the Ethics Committee of Ufuk University Medicine School, and written informed consent was taken from all participants.

Venous blood samples were taken for routine biochemical measurements after an overnight fasting period and centrifuged for 10–15 min at 2,500–3,000 rpm, and serum was separated by decantation. To determine fasting and postprandial glucose levels, plasma glucose levels were measured after an overnight fasting period of a minimum of 8 h. An oral glucose tolerance test using 75 g of glucose was performed to determine 2-hour postprandial glucose levels. Patients with overt diabetes or impaired glucose tolerance (fasting glucose levels >125 mg/dl or 2-hour postprandial glucose levels >140 mg/dl) were excluded according to the 2013 American Diabetes Association criteria [2]. Based on this, 56 patients were excluded.

Then, the remaining 82 patients were divided into two groups based on the fasting glucose levels. The IFG group included 59 patients (fasting plasma glucose levels between 100 and 125 mg/dl and postprandial plasma glucose levels <140 mg/dl), and the normal glucose group included 23 patients (fasting plasma glucose levels <100 mg/dl and postprandial plasma glucose levels <140 mg/dl).

Audiological Tests

Following a physical examination of the ear, audiological tests were performed, including pure tone audiometry (AC 33 Clinical Audiometer; Interacoustics, Assens, Denmark) and tympanometry (AZ 26 Clinical Audiometer; Interacoustics). In a totally isolated cabin, pure-tone averages (PTA) were determined using hearing thresholds between the frequencies of 500 and 8,000 Hz. The PTA was established as the simple arithmetic mean for frequencies 500, 1,000, 2,000, 3,000, 4,000, 6,000, and 8,000 Hz.

Speech discrimination scores were measured by calculating the percentage of 25 monosyllabic words correctly identified by the subjects at an easily detectable hearing level. The acoustic stapedius reflex was screened at 500, 1,000, and 2,000 Hz frequencies using a pure tone of 90 dB HL, and tympanograms of all patients were obtained using an instrument with a probe frequency of 226 Hz and an air pressure range of –200 to +200 mm H₂O in order to rule out middle ear diseases.

Ultrasonographic Measurement

Bilateral carotid artery Doppler measurements were taken by a single radiologist (G.K.A.) with 20 years of experience in Doppler sonography using a broadband linear probe with high frequencies and state of the art sonography equipment (Logic 7; General Electric Health Solutions, Little Chalfont, UK). The patients were positioned on the examination table in the supine position, and the radiologist evaluated the left and then right sides of the neck. B-mode and flow velocity measurements were taken beginning with the common carotid arteries and observing the internal carotid and vertebral arteries proximally in order using the color Doppler technique. Axial and longitudinal images were obtained when necessary. The transducer was aligned to the direction of blood flow when excessive kinking of the vessels was observed. Doppler angles were kept below 60°. Plaque characterization and the degree of stenosis were also evaluated if detected by B-mode sonography. Carotid intima-media thickness (CIMT) from the posterior wall was measured and tabulated.

Laboratory Measurements

Plasma glucose, albumin, glycated albumin, C-reactive peptide, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglyceride, aspartate transaminase, alanine transaminase, blood urea nitrogen, creatinine, and HbA_{1c} levels were measured using the blood samples taken after the overnight fasting.

Glycated albumin levels were measured in both groups using a Diazyme glycated serum protein reagent (GlycoGap®; Diazyme, Poway, Calif., USA). The Diazyme glycated serum protein assay uses proteinase K to digest glycated serum protein into low-molecular-weight glycated protein fragments. A microorganism-originated amadoriase was used to catalyze the oxidative degradation of the Amadori product glycated protein fragment to yield protein fragments or amino acids, glucosone, and H₂O₂. The H₂O₂ released was measured with a colorimetric Trinder end-point reaction. Absorbance at 600 nm is proportional to the concentration of glycated serum proteins [9]. The precision of the Diazyme glycated serum protein assay was evaluated based on the Clinical and Laboratory Standards Institute EP5-A guidelines. Measurements were calculated as micromoles/liter and given as a percentage of the ratio of albumin.

Table 1. Baseline characteristics of patients

	Patients with IFG (n = 59)	Patients without IFG (n = 23)	p value
Male/female, n (female %)	27/32 (54.2)	11/12 (52.2)	0.87
Age, years	59.8±9.5	56.2±10.1	0.15
Fasting plasma glucose, mg/dl	109.5±4.3	88.2±5.6	<0.001
HbA _{1c} , %	5.4±0.5	3.8±0.8	<0.001
Glycated albumin, %	15.85±3.71	13.66±4.21	<0.001
Systolic blood pressure, mm Hg	122.8±6.3	117.4±6.6	0.001
Diastolic blood pressure, mm Hg	81.2±6.5	77.7±6.6	0.03
Cholesterol, mg/dl	197.0±37.6	183.6±25.8	0.07
LDL, mg/dl	130.1±48.5	118.7±33.9	0.33
HDL, mg/dl	46.9±8.9	50.7±7.7	0.08
Triglyceride, mg/dl	132.0±60.8	109.5±39.3	0.06
Smoking history, n (%)	31 (52.5)	12 (52.2)	0.92
Hemoglobin, g/dl	13.8±1.4	14.0±1.2	0.41
Albumin, g/dl	3.9±0.4	3.9±0.4	0.60
C-reactive protein, mg/dl	2.7±1.6	2.1±1.3	0.08
Blood urea nitrogen, mg/dl	17.7±20.4	14.2±4.1	0.57
Creatinine, mg/dl	0.8±0.2	0.9±0.3	0.74
Aspartate transaminase, U/l	19.2±7.4	18.3±8.8	0.23
Alanine transaminase, U/l	19.1±10.9	19.2±8.5	0.61
Left CIMT, mm	0.75±0.26	0.56±0.16	<0.001
Right CIMT, mm	0.74±0.26	0.51±0.19	<0.001

Data are presented as means ± SD. LDL = Low-density lipoprotein; HDL = high-density lipoprotein.

Statistical Analysis

Data analysis was performed using PASW for Windows, version 21.0 (SPSS Inc., Chicago, Ill., USA). The distribution of variables was determined using the Kolmogorov-Smirnov test. Data are shown as means ± standard deviations or medians with ranges. Normally distributed variables were compared using the t test and nonnormally distributed variables using the Mann-Whitney U test. For categorical variables, a χ^2 test was used. Degrees of associations between continuous variables were calculated using Spearman's correlation coefficient. Multivariate analysis was performed for the variables which can affect hearing thresholds and atherosclerosis using linear regression. ROC analysis was used to determine the cutoff values of glycated albumin. A p value <0.05 was considered statistically significant.

Results

Baseline characteristics of the study population are summarized in table 1. There were no differences between the two groups regarding age and gender (p = 0.15 and 0.87, respectively). The plasma fasting glucose, HbA_{1c}, and glycated albumin levels were significantly higher in the IFG group. Total cholesterol and triglyceride levels, blood pressure measurements, and C-reactive

peptide levels were higher and high-density lipoprotein cholesterol measurements were lower in the IFG group (table 1).

The intra-assay coefficients of variation for plasma glycated albumin measurements were 0.8% for level 1 and 0.6% for level 2 and the interassay coefficients were 1.3% for level 1 and 1.0% for level 2. Based on the ROC analysis, the cutoff level for plasma glycated albumin that best predicted IFG was 14.89%. The area under the ROC curve was 0.788, with a sensitivity of 78% and a specificity of 74%.

CIMT measurements were significantly different between the IFG and control groups (0.75 ± 0.26 vs. 0.56 ± 0.16 mm, p < 0.01 for the left and 0.74 ± 0.26 vs. 0.51 ± 0.19 mm, p < 0.01 for the right carotid artery). Thirty-one (38.3%) patients with plaque formation in the carotid artery had higher plasma glycated albumin, fasting plasma glucose, HbA_{1c} levels, PTA scores, systolic and diastolic blood pressure levels, and ages than 51 (61.7%) patients without plaque formation (table 2).

The IFG group had higher hearing thresholds for all frequencies except 250 and 500 Hz for the left ear and all frequencies except 250 Hz for the right ear than those in

Table 2. Patient characteristics according to the presence of carotid artery plaque formation

	Patients with plaque formation in carotid artery (n = 31)	Patients without plaque formation in carotid artery (n = 51)	p value
Age, years	61.87±8.62	56.88±9.97	0.023
Fasting plasma glucose, mg/dl	107.26±8.59	101.27±11.32	0.027
HbA _{1c} , %	5.44±0.85	4.68±0.91	<0.001
Glycated albumin, %	16.49±6.64	12.72±4.62	0.003
PTA scores for left ear, dB	32.81±19.08	23.65±7.30	0.002
PTA scores for right ear, dB	32.58±8.49	24.11±7.06	<0.001
Systolic blood pressure, mm Hg	124.19±6.84	119.51±6.19	0.002
Diastolic blood pressure, mm Hg	82.42±6.31	78.82±6.60	0.02

Data are presented as means ± SD.

Table 3. PTA scores and speech discrimination scores

	Patients with IFG (n = 59)	Patients with normal glucose tolerance (n = 23)	p value
PTA scores for left ear, dB	27.65±8.85	25.75±21.96	0.021
PTA scores for right ear, dB	29.22±8.51	22.39±6.99	0.001
SDS for left ear, %	89.97±6.12	92.01±3.43	0.15
SDS for right ear, %	89.76±6.31	91.35±3.62	0.37

Data are presented as means ± SD. SDS = Speech discrimination scores.

the normal glucose group (fig. 1, 2). While average scores of pure tone in patients with IFG were also higher than in patients with normal fasting plasma glucose levels, the differences were not statistically significant for either the left or right ears (table 3).

Based on the ROC analysis, the cutoff level for plasma glycated albumin to predict plaque formation was 17.79%. The area under the ROC curve was 0.683, with a sensitivity of 61.3% and a specificity of 76.5%.

The correlations between glycated albumin, fasting plasma glucose, HbA_{1c} levels, and other parameters are shown in table 4. Of note, glycated albumin was significantly associated with CIMT ($r = 0.32$, $p = 0.003$ for left and $r = 0.42$, $p < 0.001$ for right CIMT) and hearing thresholds ($r = 0.28$, $p = 0.010$ for left and $r = 0.30$, $p = 0.006$ for right PTA scores).

Based on the multivariate analysis, the glycated albumin level was the only variable which was independently related to the increased CIMT (OR: 1.73, 95% CI:

1.04–2.89, $p = 0.03$). Similar results were obtained between glycated albumin levels and the presence of carotid plaque (OR: 1.15, 95% CI: 1.01–1.31, $p = 0.04$). When CIMT and glycated albumin were entered separately into the logistic regression analysis, both were found to be significantly associated with hearing loss (for glycated albumin, OR: 1.13, 95% CI: 1.02–1.24, $p = 0.02$; for increased CIMT, OR: 39.5, 95% CI: 2.7–565.0, $p = 0.007$).

Discussion

In this study, the hearing thresholds and average scores of pure tone were higher in prediabetic patients with IFG than patients with normal glucose tolerance. This appeared to be related to atherosclerosis. The CIMT, an important measure of atherosclerosis, was also found to be higher in patients with IFG than in patients with normal

Table 4. Correlations between different study parameters

	Age	CIMT of left carotid artery	CIMT of right carotid artery	Fasting plasma glucose	HbA _{1c}	Glycated albumin	PTA scores for left ear	PTA scores for right ear	Systolic blood pressure	Diastolic blood pressure
<i>Fasting plasma glucose</i>										
r value	0.20	0.43	0.45	n.a.	0.52	0.37	0.32	0.352	0.35	0.17
p value	0.07	<0.001	<0.001	n.a.	<0.001	0.001	0.003	0.001	0.001	0.13
<i>HbA_{1c}</i>										
r value	0.25	0.27	0.29	0.52	n.a.	0.52	0.15	0.25	0.31	0.21
p value	0.02	0.02	0.008	<0.001	n.a.	0	0.18	0.02	0.005	0.62
<i>Glycated albumin</i>										
r value	0.08	0.32	0.42	0.37	0.52	n.a.	0.28	0.30	0.08	-0.03
p value	0.49	0.003	<0.001	0.001	<0.001	n.a.	0.01	0.006	0.46	0.82
<i>CIMT of left carotid artery</i>										
r value	0.21	n.a.	0.85	0.43	0.27	0.32	0.64	0.64	0.26	0.2
p value	0.06	n.a.	<0.001	<0.001	0.15	0.003	<0.001	<0.001	0.02	0.07
<i>CIMT of right carotid artery</i>										
r value	0.23	0.85	n.a.	0.45	0.01	0.42	0.64	0.65	0.27	0.13
p value	0.04	<0.001	n.a.	<0.001	0.29	<0.001	<0.001	<0.001	0.013	0.25

n.a. = Not applicable.

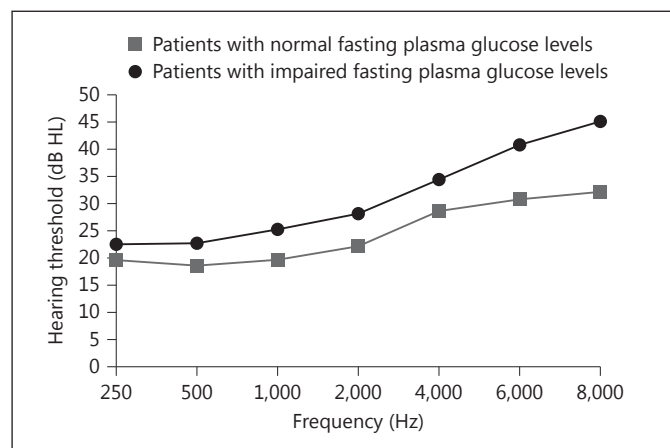


Fig. 1. Mean hearing thresholds for the left ear.

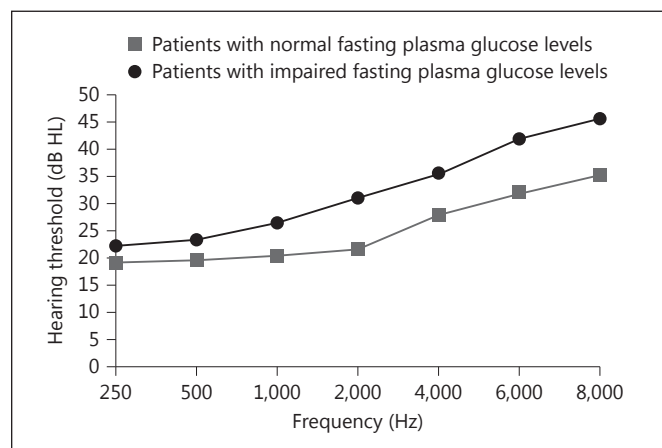


Fig. 2. Mean hearing thresholds for the right ear.

glucose levels and was associated with fasting glucose levels as well as HbA_{1c} and a newly studied biomarker, glycated albumin.

Diabetes-related hearing loss was first described several years ago as a progressive, bilateral, sensorineural impairment predominantly affecting the higher frequencies [10]. Previous studies also reported sensorineural hearing loss at high frequencies in diabetic patients [11–15].

However, no study has been conducted in prediabetic hyperglycemic patients investigating whether these patients have sensorineural hearing loss or not. In our study, we found that sensorineural hearing loss is present in prediabetic patients with IFG.

Our findings indicated that increased CIMT was an indicator of atherosclerosis in patients with IFG. More importantly, plasma glycated albumin levels, not fasting

glucose or HbA_{1c} levels, were significantly associated with CIMT. Atherosclerosis, a presumably important factor for hearing loss [16], develops before the onset of overt diabetes. Patients with IFG are known to be at increased risk of atherosclerotic events such as ischemic stroke and myocardial infarction. Even at early stages of glucose intolerance, glucose fluctuations provoke atherosclerosis and related complications [17, 18]. Therefore, glycated albumin could be considered a predictor of the presence of atherosclerosis.

In this study, the finding that glycated albumin had a stronger correlation with hearing thresholds than HbA_{1c} was similar to those of previous studies [5, 19–21]. Yoshiuchi et al. [19] and Suwa et al. [20] speculated that glycated albumin might be a better marker than HbA_{1c} for glycemic fluctuations due to the more rapid glycation reaction of albumin and the shorter turnover of serum albumin than hemoglobin [21]. Glycated albumin has been reported to be a possible predictor of CIMT and plaque formation in the carotid arteries [5].

In the present study, the finding that patients with carotid plaque had higher thresholds for hearing confirmed previous studies reporting that hearing impairment might also be associated with CIMT [22, 23], with atherosclerosis as a cause of hearing impairment. However, it should be kept in mind that patients with carotid plaque were older than their counterparts. Age might cause impairment in hearing thresholds as a result of presbycusis, but a multivariate analysis that included age showed a significant association between atherosclerosis and hearing loss.

Atherosclerosis which develops in the prediabetic stage appears to cause sensorineural hearing loss in patients with IFG. The significant association between CIMT, glycated albumin, and hearing thresholds in IFG patients could be because patients with IFG might have impaired hearing. Therefore, we can speculate that the association between atherosclerosis and hearing loss might be shown simply with a single blood test for glycated albumin, and increased glycated albumin levels in

patients with IFG might serve as a marker for atherosclerosis which leads to sensorineural hearing loss in this patient group.

In this study, we found a positive correlation between blood pressure and hearing thresholds. However, this association disappeared in the multivariate analysis. Accordingly, one of the main determinants of hearing loss was the presence of atherosclerosis, and hypertension did not seem to affect the hearing thresholds unless atherosclerosis was present. In a previous study, Agarwal et al. [24] reported that hearing loss could also be associated with cardiovascular disease risk factors such as hypertension. In addition, the well-known risk factor of smoking for atherosclerosis might also have affected our results and could have interacted with plasma glycated albumin levels [25]. However, this variable did not significantly differ between the study groups, and we thought that smoking would not affect our results significantly; this was also confirmed with multivariate analysis which included smoking as a parameter.

The limitations of this study were its cross-sectional design and the lack of otoacoustic emissions and auditory brainstem-evoked responses to evaluate whether the hearing loss was neural or strial.

Conclusion

In this study, sensorineural hearing loss was more common in patients with IFG. The IFG-related hearing loss could be due to atherosclerosis which began in the early stages of hyperglycemia. Higher plasma glycated albumin levels were strongly correlated with CIMT and carotid plaques as a marker of atherosclerosis. In addition, high plasma glycated albumin levels might predict the presence of hearing loss thought to develop due to atherosclerosis in IFG patients. We recommend a longitudinal study that could begin before the development of hyperglycemia.

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