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Whole blood viscosity and its association with the presence and severity of hearing loss and other microangiopathies in Indian patients with type 2 diabetes mellitus

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Abstract

Background/Aims: Although studies correlating idiopathic sensorineural hearing loss (SNHL) to whole blood viscosity (WBV) have been conducted, no such study has been done in diabetic patients in whom WBV is said to be altered. Therefore, we aimed to investigate the potential association between calculated WBV and the presence and severity of SNHL and other microangiopathies in Indian patients with type 2 diabetes mellitus (T2DM).

Methods: A cross-sectional study was carried out in the Kasturba Medical College (KMC) group of hospitals among individuals who were older than 18 years and had T2DM. The included patients underwent pure-tone audiometry, ophthalmoscopy, monofilament test, and routine blood investigations for diabetes. WBV was derived using hematocrit and total protein with a validated formula.

Results: Of the total 60 participants, 73.3% had SNHL, which was predominantly bilateral and moderate. There was a statistically significant association between glycemic control and the degree of SNHL. The associations between SNHL and HbA1C levels and random plasma glucose were both statistically significant ($P = .001$). The statistical association between WBV and the degree of SNHL was not significant ($P = .056$). Although higher mean blood viscosity was noted in individuals with diabetic retinopathy and neuropathy than those without, the associations between blood viscosity and the presence of retinopathy, neuropathy, and nephropathy were not statistically significant ($P = .238$, $P = .621$, and $P = .656$; respectively). Finally, the associations between WBV and glycemic control were also not significant ($P = .652$ for random plasma glucose and $P = .928$ for HbA1C).

Conclusion: This study concludes that SNHL is highly prevalent in diabetes, and poor glycemic control is associated with its worsening. Elevations in WBV, if present, are not affected by poor glycemic control and do not appear to significantly contribute to the development of complications of the microvasculature in T2DM.

Keywords: diabetes, microangiopathies, blood viscosity, hearing loss, cochleopathy

Introduction

Diabetes is a complex multisystem disorder that has commonly been known to result in vascular diseases, both macrocirculatory and microcirculatory, and despite revolutionary improvements in the treatment and management of diabetes, these chronic effects have become a leading cause of mortality and morbidity.[1]

Microangiopathy is an integral feature of diabetes mellitus, and it may manifest as retinopathy, neuropathy, nephropathy, or skin changes.[1] Extensive research exists pertaining to diabetic retinopathy, nephropathy, and neuropathy. However, cochleopathy and hearing loss have often been overlooked as microvascular complications of diabetes. Although the existence and increased prevalence of hearing loss in diabetes has been

We, the authors declare that we do not have any competing interests.

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Ethics: The study protocol was submitted to and approved by the Institutional Ethics Committee of Kasturba Medical College (Manipal Academy of Higher Education), Mangalore (IEC KMC MLR 04-16/96).

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established, further elaboration on the magnitude and cause of this complication is greatly needed.[2-5]

Hearing loss in people living with diabetes is said to be sensorineural deafness that is bilateral, gradually progressive, and affects predominantly the higher frequencies.[2,6] However, early sensorineural loss and unilateral sudden hearing loss have also been reported.[7,8]

The existence of diabetes-related hearing loss carries with it the possibility of yet another complication: diabetic vestibulopathy.[9] In severe cases, impaired proprioception could lead to impaired balance and gait in people living with diabetes.

Altered blood flow properties have been implicated in the aetiopathogenesis of the vascular complications of diabetes.[10,11] These include an increase in blood and plasma viscosity and altered red cell deformability.[12-14] Unlike the retina, the cochlea and its microcirculation are virtually impossible to examine visually. The correlation between altered blood viscosity and the extent of hearing loss, if any, can provide some insight into the state of the cochlear microcirculation in people living with diabetes.

While studies correlating idiopathic/sudden sensorineural hearing loss (SNHL) to serum viscosity have been conducted,[15,16] no such study has been done in diabetic patients in whom whole blood viscosity (WBV) is said to be altered. Still, India is well on the way to being crowned the "diabetes capital of the world," and we are projected to have up to 79.4 million individuals with diabetes by 2030.[17]

Therefore, we aimed to investigate the potential association between calculated WBV and the presence and severity of SNHL and other microangiopathies in Indian patients with type 2 diabetes mellitus (T2DM).

This study model intends to test the hypothesis that altered WBV could contribute to the development and/or progression of SNHL and other microangiopathies in T2DM. We will also test if glycemic control exerts an influence on both WBV and the severity of SNHL.

Materials and methods

A cross-sectional study was carried out in the Kasturba Medical College (KMC) group of hospitals, in Mangalore, India, among individuals who were older than 18 years and had T2DM diagnosed as per the American Diabetes Association criteria.

All the patients seeking treatment at KMC group of hospitals who fulfilled the inclusion criteria and who gave informed consent were chosen for the study. The exclusion criteria included individuals younger than 18 years, history of hearing loss before the onset of diabetes or family history of hearing loss, history of chronic noise exposure, history of any ear disease/perforation of the tympanic membrane, history of ototoxic drug usage over the past 2 months (streptomycin, gentamicin, tobramycin, kanamycin, erythromycin (IV), neomycin, cisplatin, furosemide, ethacrynic acid, deferoxamine, quinine, and aspirin), patients using cranial nervous system sedatives, patients with a history of trauma to the head or ear, or patients who did not give informed consent.

The study protocol was submitted to the Institutional Ethics Committee of Kasturba Medical College (Manipal Academy of Higher Education), Mangalore (IEC KMC MLR 04-16/96).

After obtaining the approval of the ethics committee, approval was taken from the heads of the respective hospitals. The study patients were provided with a patient information sheet, and the purpose of the study was explained.

Detailed history of patients was taken, and a detailed examination of the external auditory canal, tympanic membrane, and cranial nerves was performed. The Rinne test and Weber test were performed to test the acuity of hearing. The examination for diabetic peripheral neuropathy was carried out by an initial clinical examination where the deep tendon reflexes and peripheral sensations (fine touch, crude touch, joint position sense, vibration sense, and stereognosis) were tested. This was followed by the monofilament test using a Semmel Weinstein monofilament. The examination for diabetic retinopathy was done using a Welch Allyn ophthalmoscope.

Blood samples were collected by venepuncture for the analysis of random blood glucose using the COBAS 6000 (C501) analyzer taking the normal reference range as 70–140 mg/dL. The hematocrit level was analyzed using Beckman Coulter LH 780, taking the normal reference range for men as 40–50% and for women as 36–46%. The HbA1C level was analyzed using the Biorad Variant 2 Turbo, taking the reference ranges up to 6% as normal, 6.10–7.00% as prediabetes, 7.10–8.00% as diabetes mellitus, and 8.10% and above as poor control. The serum total protein was measured using the COBAS 6000 (C501) analyzer, taking the normal reference range as 6.0–8.3 g/dL. Serum creatinine was analyzed using the COBAS 6000 (C501) analyzer, taking the normal reference range as 0.4–1.4 mg/dL. Urine samples were collected in a sterile container for the estimation of urine microalbuminuria using the COBAS 6000 (C501) analyzer, taking the normal reference range as less than 20 mg/L. WBV (cP) was calculated using plasma protein concentration (TP; g/L) and hematocrit (HCT; %) at a high shear rate (208 seconds^{-1}) and a low shear rate (0.5 seconds^{-1}), by the formula WBV (208 seconds^{-1}) = [0.12 × HCT] + [0.17 × (TP-2.07)] and WBV (0.5 seconds^{-1}) = [1.89 × HCT] + [3.76 × (TP-78.42)].[18-21]

Following daily calibration, pure-tone audiometry was carried out in a soundproof room using a Piano Inventis audiometer. The transducers used were the TDH 39 Supra Aural Head phones and the Radio Ear B 71 bone vibrator. The Modified Hughson-Westlake procedure recommended by the American Speech and Hearing Association (ASHA 1978) was used to estimate the threshold. The threshold was determined based on the American National Standard Institute (ANSI). The threshold was obtained across all the frequency octaves (250 Hz–8000 Hz), and using the modified Goodman classification of severity of hearing loss, the degree of hearing loss was assessed. The degrees of hearing loss are categorized based on air conduction pure-tone averages at 500, 1000, 2000 Hz, and 4000 HZ. Hearing loss ranges that were considered were −10–25 dB as hearing within normal limits, 26–40 dB as mild hearing loss, 41–55 dB as moderate hearing loss, 56–70 dB as moderately severe hearing loss, 71–90 dB as severe hearing loss, and above 90 dB as profound hearing loss.

Data were analyzed using descriptive statistics. A statistical package SPSS version 25.0 was used to perform Chi-squared or Student T tests when applied. $P < .05$ was considered to be statistically significant.

Results

Of the total 60 participants, 40 (66.7%) were male. A total of 11 (18.3%) participants were younger than 40 years, 14 (23.3%) participants were between age 40–50 years, 18 (30%) participants were between the age 50–60 years, and 17 (28.3%) participants were older than 60 years. The mean age of the study population was 53 years. It was reported that 18 (30%) participants had been living with diabetes for less than 5 years,

33 (55%) participants had been living with diabetes for between 5 to 10 years, and 9 (15%) participants had been living with diabetes for more than 10 years (Table 1).

Among the 60 participants, 16 (26.7%) participants had no SNHL while 44 (73.3%) had SNHL of various degrees (Table 2). Of the total 44 participants who had sensorineural hearing loss, 14 (23.3%) had mild hearing loss, of whom 11 (18.3%) participants had unilateral hearing loss, and 3 (5%) participants had bilateral hearing loss. A total of 24 (40%) participants had moderate hearing loss, of whom 3 (5%) had unilateral hearing loss and 21 (35%) had bilateral hearing loss. A total of 6 (10%) participants had severe hearing loss which affected both ears. There were no participants with moderately severe or profound hearing loss.

Individuals with a normal hearing (N = 16) had a mean WBV of 15.29 ± 1.60 centipoise. The participants with a mild hearing loss (N = 14) had a mean WBV of 14.75 ± 1.97 centipoise while the participants with moderate hearing loss (N = 24) had a mean WBV of 15.92 ± 1.43 centipoise. It was also found that participants with severe hearing loss (N = 6) had a mean WBV of 16.62 ± 0.87 centipoise. The above association between the degree of hearing loss and WBV was not statistically significant (Table 3; $P = .056$).

The glycemic control of the study participants was assessed in terms of random plasma glucose (RPG) and glycated hemoglobin (HbA1C). Participants with a normal hearing (N = 16) had a mean RPG of 161.68 mg/dL ± 22.54. Individuals with a mild hearing loss (N = 14) had a mean RPG of 213.92 mg/dL ± 33.30. It was also found that, study participants with a moderate hearing loss (N = 24) had a mean RPG of 242.29 mg/dL ± 37.76 while study participants with a severe hearing loss (N = 6) had a mean RPG of 277.50 mg/dL ± 43.90. The statistical association between the degree of hearing loss and glycemic control was significant (Table 4; $P = .001$).

The mean HbA1C level of participants with normal hearing (N = 16) was reported to be 6.89% ± 0.32. The participants with a mild hearing loss (N = 14) had a mean HbA1C of 7.58 % ± 0.61 while the participants with a moderate hearing loss (N = 24) had a mean HbA1C of 8.1 % ± 0.55. In addition to this, participants with a severe hearing loss (N = 6) had a mean HbA1C of 8.9 % ± 0.45. There was a significant statistical association between the degree of hearing loss and HbA1C levels (Table 5; $P < .001$).

Normoglycemic patients (70–140 mg/dL) had a mean WBV of 15.82 cP, which was higher than that of hyperglycemic patients (15.54 cP). The association between WBV and RPG was not statistically significant (Table 6; $P = .652$).

Participants below the standard target levels of HbA1C (N = 18) had a mean WBV of 15.65 cP ± 1.76, whereas participants within standard target levels (N = 26) had a mean WBV of 15.45 cP ± 1.52. In addition to this, participants with above the standard target level (N = 16) had a mean WBV of 15.58 cP ± 1.81. There was no significant association between WBV and HbA1C levels (Table 7; $P = .928$).

Of the total 60 participants, the 38 participants (63.3 %) in whom diabetic retinopathy was present had a mean WBV of 15.74 cP ± 1.54 (Table 8). The 22 participants (36.7%) who did not have diabetic retinopathy had a mean WBV of 15.22 cP ± 1.80. This was not statistically significant ($P = .238$). A total of 42 participants with urine microalbuminuria had a mean WBV of 15.48 cP ± 1.58, whereas 18 participants without urine microalbuminuria had a mean WBV of 15.69 cP ± 1.83. This was also not statistically significant ($P = .656$). A total of 43 participants who had a positive monofilament test had a mean WBV of 15.61 cP ± 1.68 while the 17 participants with a normal monofilament test had a mean WBV of 15.38 cP ± 1.60. This was also not statistically significant ($P = .621$).

Table 1

Demographic and clinical characteristics of the study population.

Characteristic	Frequency (N = 60)	Percent (%)
Sex		
Male	40	66.7
Female	20	33.3
Total	60	100
Age		
<40 years	11	18.3
40–50 years	14	23.3
50–60 years	18	30.0
>60 years	17	28.3
Total	60	100
Duration of diabetes		
<5 years	18	30
5–10 years	33	55
>10 years	9	15
Total	60	100

Table 2

Prevalence and degree of sensorineural hearing loss among the participants.

Degree of sensorineural hearing loss	Frequency (N)	Percent (%)
Normal	16	26.7
Mild	14	23.3
Unilateral	11	18.3
Bilateral	3	5
Moderate	24	40
Unilateral	3	5
Bilateral	21	35
Severe	6	10
Unilateral	0	0
Bilateral	6	10
Total	60	100

Discussion

This study found a 73.3% prevalence of SNHL, which is consistent with the findings of Rajendran et al[7] (73.3%), who also had a sample of 60 patients.[2] Friedman also showed a 55% prevalence in his study. Kakarlapudi et al[5] found a higher prevalence of hearing loss in diabetic patients (13.1%) when compared with the nondiabetic controls (10.3%). Shafeeq et al[22] reported a 62.65% prevalence of SNHL. In a systemic review and meta-analysis conducted by Olubunmi et al, involving the results of 18 studies, incidence ranging between 44% and 69.7% was found among patients with T2DM.[23] The variation in these results could be due to heterogeneity in the methods and populations within the studies. However, existing literature has

Table 3

Association between the degree of hearing loss and whole blood viscosity.

Degree of SNHL	Mean WBV (cP)	Standard deviation	*P* Value
Normal	15.29	1.60	$P = .056$
Mild	14.75	1.97	
Moderate	15.92	1.43	
Severe	16.62	1.87	

Table 4

Association between the degree of hearing loss and glycemic control.

Degree of SNHL	Mean RPG (mg/dL)	Standard deviation	*P* Value
Normal	161.68	22.54	$P = .001$
Mild	213.92	33.30	
Moderate	242.29	37.76	
Severe	277.50	43.90	

Table 6

Association between whole blood viscosity (WBV) and random plasma glucose (RPG) levels.

Random plasma glucose	Mean WBV	Standard deviation	*P* Value
Within reference range of 70–140 mg/dL (N = 1)	15.82	—	$P = .652$
Abnormal (N = 59)	15.54	1.66	

extensively proven a higher prevalence in people with diabetes compared with nondiabetic individuals.[2-5]

For example, in a study conducted by Bhaskar et al, audiometry in 57 patients with T2DM and 50 matched controls revealed a 78.2% incidence of SNHL in T2DM compared with 38% among nondiabetics. Progressive, bilaterally symmetrical hearing loss of gradual onset was the most common pattern seen, but asymmetric patterns were also reported. No significant correlation was found between sex of the participants and hearing loss.[24] Similarly, in our study, the hearing loss was reported to be predominantly moderate and bilateral. Rajendran et al,[2] reported bilateral mild to moderate SNHL in people living with diabetes, predominantly affecting the higher frequencies. Shafeeq et al,[22] also reported predominantly moderate hearing loss in their study. This hearing loss can be attributed to various causes, broadly categorized as microangiopathic, neuropathic, or a combination of both.[25]

Considering changes in the hemorheology (measured in terms of calculated whole blood viscosity) to be the cause for development of microangiopathy and the subsequent hearing loss, the following hypotheses were presented:

A) Hypothesis: Higher WBV is likely to be associated with higher degree of SNHL.

The study showed that patients with moderate and severe SNHL had raised mean WBV when compared with patients with normal hearing or mild SNHL. However, this association was found to be statistically insignificant and did not support the above hypothesis.

B) Hypothesis: Higher WBV is likely to be associated with presence of diabetic retinopathy/neuropathy/nephropathy.

Although participants with diabetic retinopathy had a higher mean WBV (15.74 cP) than those without it (15.22 cP), the statistical association was not significant ($P = .238$), as opposed to a study conducted by Lowe et al,[26] who reported a significant association ($P < .05$) in T2DM with and without retinopathy. Turczynnski et al,[27] also found a positive correlation between elevation in blood/plasma viscosity and severity of retinopathy. Similarly, patients with diabetic neuropathy showed greater mean WBV than those without. These findings have led us to suggest that there may be other additional mechanisms underlying the development of these complications of diabetes. The authors have stated that basement membrane thickening in capillaries of affected organs as seen by Smith et al[28] and Fukushima et al[29] in the inner ear and by Williamson and Kilo in retinal blood vessels[30] could be responsible for the development of diabetic complications. Another theory for this occurrence is due to oxidative stress that arises from hyperglycemia induced overproduction of reactive oxygen species and the subsequent activation of the polyol pathway, protein kinase C production, and inactivation of antiatherosclerotic enzymes among others, which leads to inflammation, persistent expression of proinflammatory genes, and defects in ischemia-induced angiogenesis.[31] It is also believed that an altered cell metabolism, such as sorbitol overproduction in cells with high intracellular glucose, leads to swelling and osmotic damage of neural cells, therefore causing these complications.[32] Another theory is that the depletion of myo-inositol leads to a decreased motor nerve conduction velocity, thereby causing the diabetic complications.[33] Finally, it can also be explained by reduced oxygen transport resulting from increased HbA1C, which has a high affinity for oxygen and hence low oxygen release.[34] Considering all the above mechanisms, the development of these complications can be multifactorial.

In our study, we found that poor glycemic control was directly linked to the occurrence of SNHL. Similar findings were reported by in the articles by Kurien et al,[3] Sumathi et al,[35] Sunkum et al,[36] and by Panchu.[37] Thus, HbA1C levels above the normal are associated with worsening of hearing, possibly due to sustained hyperglycemia leading to more damage to the microcirculation by the mechanisms postulated above.

The findings of this study did not corroborate with the hypothesis that poor glycemic control was directly linked to higher WBV. Conversely, Cinar et al[38] reported a 25% rise in blood viscosity with a 300 mg/dL rise in mean blood glucose value. Irace et al[39] reported higher blood viscosity associated with higher blood glucose among groups of normoglycemic and prediabetic patients. This disparity may be due to variations in methodology such as the sample size and the direct measurement of blood viscosity.

Our study used calculated or derived viscosity as the primary measure, as opposed to direct measurement used in other studies. This can be a significant limitation that reduces the precision of the estimates and the likelihood of obtaining significant results. To address this limitation, further research is needed to explore this association using direct measurement in both people living with diabetes and matched controls. Such studies could help to strengthen the validity of the findings and provide more precise estimates of the associations. Further studies on the role of other

Table 5

Association between the degree of hearing loss and HbA1C levels.

Degree of SNHL	Mean HbA1C level	Standard deviation	*P* Value
Normal	6.98	0.32	$P < .001$
Mild	7.58	0.61	
Moderate	8.10	0.55	
Severe	8.90	0.45	

Table 7

Association between whole blood viscosity and HbA1C levels.

HbA1C category	Mean WBV	Standard deviation	*P* Value
Below standard target levels (N = 18)	15.65	1.76	$P = .928$
Within standard target levels (N = 26)	15.45	1.52	
Above standard target levels (N = 16)	15.58	1.81	

Table 8

Association between whole blood viscosity (WBV) and the presence of diabetic retinopathy, nephropathy, and/or neuropathy.

Diabetic microangiopathy	Percent (%)	Mean WBV	Standard deviation	*P*-value
Diabetic retinopathy				
Present (N = 38)	63.3	15.74	1.54	*P* = .238
Absent (N = 22)	36.7	15.22	1.80	
Diabetic nephropathy				
Urine microalbumin present (N = 42)	70	15.48	1.58	*P* = .656
Urine microalbumin absent (N = 18)	30	15.69	1.83	
Diabetic neuropathy				
Positive monofilament test (N =4 3)	71.7	15.61	1.68	*P* = .621
Normal (N = 17)	28.3	15.38	1.60	

mechanisms of microvascular complications are also suggested. Our study also had other limitations such as the small sample size and the fact that age-related hearing loss (presbyacusis) could have contributed to the SNHL in our population.

Conclusion

In our study, elevated WBV was not associated with the prevalence and degree of SNHL, retinopathy, nephropathy, or neuropathy. However, there was a high prevalence of SNHL in patients with diabetes, being predominantly moderate in degree and bilateral. Higher HbA1C levels were also linked to worsening of hearing in patients with diabetes. Therefore, we recommend that patients with diabetes should be routinely screened for SNHL by their health care providers.

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