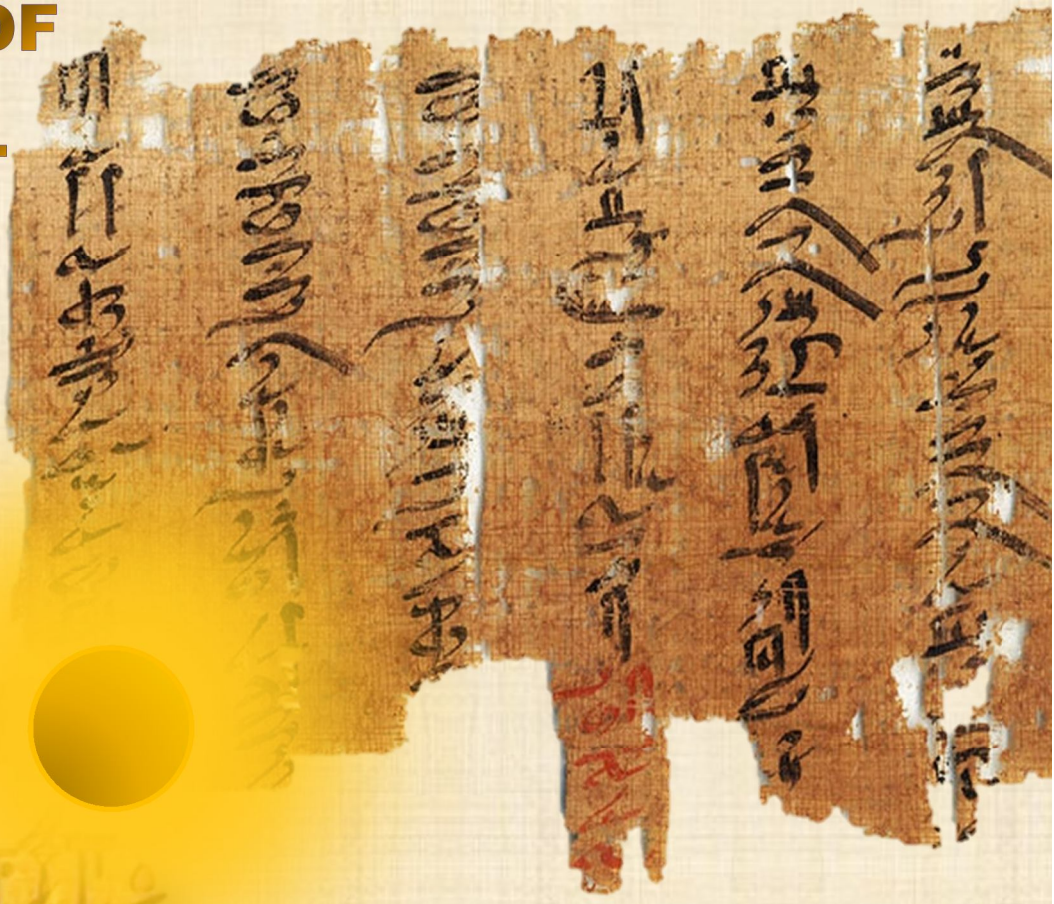
IJMA

International Journal of Medical Arts

VOLUME 2, ISSUE 4, AUTUMN 2020)



http://ijma.journals.ekb.eg/

Print ISSN: 2636 - 4174

Online ISSN: 2682 - 3780

International Journal of Medical Arts 2020; 2 [4]: 866-872.

Available online at Journal Website
https://ijma.journals.ekb.eg/
Main subject [Medicine[Audiology]] *

Original article

Audio-Vestibular Findings in Patients with Hyperuricemia

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Received at: August 08, 2020; **Revised at:** October 05, 2020; **Accepted at:** October 05, 2020

DOI: 10.21608/ijma.2020.38516.1153

ABSTRACT

Background: Hyperuricemia is a common biochemical disturbance in which serum concentration of uric acid exceeds the normal values which is 7.0 mg/dl in men and more than 6.0 mg/dl in women leading to deposition of monosodium urate [MSU] crystals in joints and soft tissues resulting in inner ear functions affection.

Aim of the work: To elaborate the effect of hyperuricemia on the peripheral hearing as well as peripheral vestibular functions.

Subjects and Methods: This study included 40 subjects with hyperuricemia and 40 healthy controls. Participants underwent serum uric acid assay, full history taking, basic audiological evaluation and vestibular evaluation.

Results: 37[92.5%] hyperuricemic subjects had normal peripheral hearing sensitivity, only 3[7.5%] had mild high frequencies sensori-neural hearing loss [SNHL] at 8 kHz. 31[77.5%] Hyperuricemic patients had normal peripheral vestibular functions, only 9[22.5%] subjects had BPPV; They also had higher serum uric acid [SUA] level. No correlation between duration of hyperuricemia and occurrence of BPPV.

Conclusions: The hyperuricemic subjects had a significant higher incidence of BPPV. Other investigations to detect early and subtle changes in cochlear function of hyperuricemic subjects were recommended.

Keywords: Audio-vestibular; Sensorineural hearing loss; Vertigo; Hyperuricemia, Uric Acid.

Please cite this article as: Al-Sobki MM, El-Zarea GA, Mahmoud AMA, Saad AAA. Audio-Vestibular Findings in Patients with Hyperuricemia. IJMA 2020; 2[4]:866-872. DOI: 10.21608/ijma.2020.38516.1153

* Main subject and any subcategories have been classified according to research topic.

INTRODUCTION

Hyperuricemia is a challenging medical condition, which caused by a biochemical disturbance [uric acid concentrations exceeds the normal value [6.8 mg/dL]]. Clinically, levels above 7.0 mg/dL is recognized as hyperuricemia[1].

In the human body, serum uric acid is the net product of a complex system. Urate is a byproduct of the metabolism of endogenous [mainly DNA and RNA] or exogenous [food-derivatives] purines. Urate itself cannot changed by further metabolism and thus must be eliminated by renal or intestinal routes [intestinal flora plays an important role]. The serum concentration is the net of the balance between these systems[2].

Hyperuricemia is associated with many systemic complications. Vascular system is one of the most vulnerable systems to harmful effects of hyperuricemia. The microvasculature of the cochlea is not an exception, as uric directly penetrate into outer hair cells [OHC] leading to stiffness of these cells with subsequent disturbances in OHC electrical motility responses that lead to auditory dysfunction[3]**. Singh and Cleveland[4]** found that, subjects suffered hyperuricemia were more likely to have hearing loss. They propose that, inflammation and oxidative stress pathways, are responsible for hearing loss among patients with hyperuricemia.

In neuro-otology clinics, it is very common to encounter the benign paroxysmal positional vertigo [BPPV][5]**.** It usually presented by a short, recurrent episodes of vertigo induced by certain positions of the head. Two mechanisms are responsible for BPPV; the first is known as "Canalithiasis theory" which proposed that, the otoconia are dislodged and arrives to one or more of semicircular canals, that lead to endolymphatic flow disturbances and results in vertigo. The second mechanism is known as "Capulolithiasis theory" which suggested that some particles were adherent to cupula [heavy cupula], these particles keeps the cupula from springing back to natural through its weights. BPPV can be recognized by the recommended criteria, and head repositioning represented an effective treatment[6,7].

For better prevention of BPPV, the identification of risk factors is a crucial component. Vitamin D-deficiency, old age and osteoporosis are among the potential risk factors[8]. Others reported hyper-uricemia as another risk factor[9,10]. Clarification of the potential association between hyperuricemia and BPPV is very important[11], potential association between hyperuricemia and sensori-neural hearing loss [SNHL] had been proposed with similar mechanisms as in BPPV[4].

AIM OF THE WORK

To elaborate the effect of hyperuricemia on the peripheral hearing as well as peripheral vestibular functions.

SUBJECTS AND METHOD

This prospective case-control study was performed at Audio-vestibular unit, Otorhinolaryng-ology Department [Al-Hussein University Hospital, Al-Azhar University] from December 2019 to June 2020. The local Research Ethical Committee approved the study protocol. A total of 80 subjects participated in the current work. They were divided into: 1] the study group, which comprised Forty patients, with hyperuricemia according to serum uric acid. They were selected from outpatient clinic of Rheumatology Department. They were **selected** according to the following criteria: age from 40 to 55 years old, both genders, and any current chronic medical disease or otological abnormality known to adversely affect hearing as chronic suppurative otitis media were **excluded**. Another 40 healthy individuals, matched with study group for age and sex were selected as a control group. After an informed consent, all selected subjects were exposed to complete history taking, clinical examination with specific attention to main-audio-vestibular manifestations. Serum uric acid measurements had been carried out at clinical pathology department [Al-Hussein University hospital] and values > 7 mg/dl were considered abnormal.

The audiological evaluation included **pure tone audiometry** [air conduction hearing threshold level for frequencies between 250-8000 Hz, and bone conduction hearing threshold level for frequencies between 500-4000 Hz. The threshold was taken as the faintest sound that the patient responds to 50% of the time], **speech audiometry** [Speech Reception Threshold [SRT] using Arabic spondee words, and Word Discrimination Scores [WDS] using Arabic phonetically balanced words[12]**, Immitancemetry** [tympanometry done at varying pressure ranging from +200 to - 400 mm H_2O, to evaluate the middle ear pressure and its compliance, and acoustic reflex threshold elicited both

ipsilaterally and contralaterally by pure tones of 500, 1000, 2000 and 4000 Hz-.

Vestibular evaluation included

[A] Vestibular office test:

I- Posture and Gait tests as described by **Goebel JA**, **Slattery** [13]**.** They include:

Tandom gait testing: is performed by stepping one foot in front of the other Romberg's test: The patient stands with feet together, arms folded and with eyes open then closed while the observer watches for swaying or movement of the feet to attain balance.

- The tandem Romberg test: The difference in this test is that the patient stands heel to toe rather than with feet together.
- Fukuda test: The test is performed by asking the subject to march in place with the arms extended straight out at the level of the shoulders. The test is done with and without vision. At least 50 steps are required to make a complete assessment.

II- Oculomotor Examination:

At first the eyes are examined for range of movement in different positions. Normally both eyes move together in the same direction and by the same amount.

- Spontaneous nystagmus: If present or not, it denotes movement of the eye without visual or vestibular stimulations.
- Smooth Pursuit: The subject was asked to visually track a slowly moving target, slowly back and forth in a sinusoidal fashion, to a maximum of 30° displacement from the midline while keeping his head stationary.
- Saccades test: The subject was asked to alternately fixate the examiner's nose and then finger without moving the head. The test was held at different locations at approximately 15 degrees away from primary position.
- Gaze-holding test: The subject was instructed to gaze at a fixed dot in different positions [central, horizontal and vertical positions], for about 15-20 seconds.
- Head impulse test HIT [head thrust test]: It consists of monitoring eye movements as the patient fixates on a stationary target. While the head is rotated to right or left unexpectedly using passive, small amplitude 10–20 degree, and high-acceleration head movement.

[B]- Videonystagmography [VNG] test battery:

Subjects had been instructed to refrain from any medications affect vestibular function for 48 hours before the tests.

I- Spontaneous nystagmus: Subject was asked to sit with head upright and the back is supported, spontaneous nystagmus observed in complete absence of any visual fixation. Minimum observation period is 30 seconds.

II- Gaze test: Subject was asked to fix his vision on the light bar, 20-degree eccentric position vertical and horizontal and the eye is kept in position for 20-30 seconds.

III- Oculomotor tests:

Subject was seated on test chair 1.5 meters from the center of the T.V.

- Saccadic test: Subject was instructed to follow the target that moves back and forth in jumping manner, such movements are of 5-30 degrees, Unpredicted, Start in the horizontal plane then to the vertical plane for 90 seconds.
- Smooth pursuit test: Subject asked to follow the target that moves back and forth in sinusoidal waveform, such movements are 20 degrees to right and 20 degrees to left and at various frequencies that ranges between 0.2 – 0.6 Hz.

Analysis of the test:

a. Gain which is normally the eye velocity is more or less similar to the target velocity.

b. Symmetry between eye movement and target movement.

- Optokinetic test: Subject asked to observe the multiple visual targets as they move across the light bar. These targets move in the 4 directions for 20 seconds for each direction at a rate 20 degree/second. Normally, nystagmus occurs with its slow phase with the direction of movement. Such nystagmus is evaluated for gain and asymmetry.

[C]- Positional tests:

It observed for different body and head position changes. There should be at least 30 seconds between 2 observations. These positions include supine, supine with head right, supine with head left, right side [Rt decubitus], and left side [Lt decubitus]. Normally, there is no nystagmus in all positions.

[D]- Positioning test:

- Dix-Hallpike maneuver: While the subject was on table in a sitting position, the subject's head was turned to the right [or the left] at 45º and the subject

was taken to the supine position. The patient is left in this position for 30 seconds. If there was no nystagmus the subject was returned to the sitting position. If nystagmus occurred, it was recorded and the subject returned to the sitting position after fading out of nystagmus.

[E]- Bi-thermal Caloric Testing:

The caloric test was performed by placing the subject in supine position, opening his eyes with the head elevated 30 degrees. Right ear cold: cold water stimulation 30˚C for 30 seconds. Left ear cold: cold water stimulation 30˚C for 30 seconds. Right ear warm: warm water stimulation 44˚C for 30 seconds. Left ear warm: warm water stimulation 44˚C for 30 seconds. Proper mental tasks were given and nystagmus was recorded. The goggles were then removed and the patient was asked to fixate on stationary target directly above for fixation suppression.

Statistical methods: Data entry and statistical analysis were performed using SPSS [statistical package of social science] version 21. Categorical data were expressed in numbers and percentage. Continuous normally distributed data were expressed in mean and standard deviation while non-normally distributed data were expressed in median and rang. The quantitative data were examined by Kolmogrov Smirnov test for normality of data. Student T test was used for continuous normally distributed data and Mann-Whitney [U] test for none normally distributed data. P<0.05 was considered significant[14].

A correlation coefficient [*r*] is a numerical measure of some type of correlation, meaning a statistical relationship between two variables. The Pearson product-moment correlation coefficient [*r*], is a measure of the strength and direction of the liner relationship between two variables divided by the product of their standard deviation. Correlation coefficient ranged from -1.0 to +1.0. The closer r is to +1 or -1 the more closely the two variables are related. If [*r*] is close to 0, it means there is no relationship between the variables.

RESULTS

Both study and control groups were comparable as regard to subject age and gender. The mean patient age of study group was 48.7±5.2 years, and 47.1±3.1 years for controls. Males were similarly distributed between two groups. All patients complaining from joint pain, hearing loss had been reported in 7.5%, tinnitus in 20.0%, vertigo in 22.5% and dizziness [unspecified] among 15.0%.

The mean SUA was 7.8±0.39, 8.2±0.12, 7.9±0.35, 8.1±0.34 and 7.7±0.33 mg/dl in patients with joint pain, hearing loss, tinnitus, vertigo, and dizziness [unspecified] respectively with positive correlation between SUA level and occurrence of vertigo [Table 1].

Basic audiological evaluation revealed that, the PTA [AC] was comparable between study and control groups at 0.25, 0.5, 1, 2, 4, 8 kHz [Table 2]. HF-SNHL was reported in 3 patients in study group [7.5%] and none in control group with no significant difference [Table 3]. In addition, there was no significant difference between study and control groups as regard to PTA [BC]. In the present work, there was positive, moderate and statistically correlation, between hearing threshold level at 8kHz and duration of disease [r=0.583, p =0.001] [Table 4]. In addition, both study and control groups were comparable as regard to speech audio-metry, ipsilateral and contralateral AR and audiological findings. The vestibular bedside tests ware done to 40 subjects, Dix-Hallpike was positive in 9 subjects [22.5%] [7 males and 2 females]. Fukuda test, spontaneous nystagmus, gaze test, smooth pursuit, saccade and HIT test were within normal. All tests VNG battery tests [Spontaneous nystagmus, Gaze test, oculomotor tests, positional tests and Bithermal caloric tests] were normal except 9 subjects [22.5%] with abnormal positioning test [Dix-Hallpike maneuver] results, revealed that 9 subjects with BPPV. Table [4] shows 9 subjects [22.5%] with abnormal results of Dix-Hallpike test [BPPV]. The Nystagmus is up-beating and torsional in the 9 subjects, directed to right side in 5 subjects [Rt Posterior BPPV] and directed to left side in 4 subjects [Lt Posterior BPPV].

In the current work, there was no significant difference between patients with positive and negative BPPV as regard to serum uric acid on the right or left sides and regarding duration of the disease. However, the total serum uric acid [on both sides] significantly decreased with absent BPPV [7.74±0.4] when compared to positive BPPV [8.06±0.3] [Table 5].

Table [1]: Correlation between SUA level and different presenting symptoms in the study group.

	Hearing loss	Tinnitus	Vertigo	Dizziness [Unspecified]
Correlation coefficient [r]	0.259	0.045	0.352	-0.089
P-value	0.106	0.791	0.026 **	0.585

Table [2]: Audiological findings in both groups.

	Study group		Control group	
	Mean	± SD	Mean	± SD
Pure Tone Average [AC]	21.15	4.2	19.17	3.5
Pure Tone Average [BC]	21.16	4.0	19.25	2.9
Speech Reception Test [SRT] average	20.1	4.6	18.75	2.2
Discrimination Score [WD%] average	99.7	1.3	100	0.0

Table [3]: Comparison between studied groups as regard HF-SNHL [at 8 kHz] at both ears.

HF-SNHL	Study [N = 40]	Control [N = 40]	MW	P-value
Absent	37 92.5%	20 100%	$X^2 = 1.6$	0.209 NS
Present	3 7.5%	0 0%		

Table [4]: Correlation between mean average of PTA and duration of disease in study group.

PTA	Correlation coefficient [r]	P-value
0.25 kHz	-0.084	0.623
0.5 kHz	-0.110	0.499
1 kHz	0.023	0.887
2 kHz	-0.005	0.976
4 kHz	-0.029	0.859
8 kHz	0.583	0.001 **

Table [5]: Relation of SUA levels as regard BPPV.

		BPPV		T	P-value
		Absent [n = 31]	Present [n = 9]		
SUA [mg/dl]	**Mean±SD**	7.74± 0.4	8.06± 0.3	2.3	0.026

DISCUSSION

The present study aimed to evaluate effects of hyperuricemia on peripheral audio-vestibular system. In the current work, hearing loss had been reported among 3 patients [7.5%] who had hyperuricemia. Their pure tone audiometry examination showed mild high frequencies SNHL at 8 kHz in both ears and this was in agreement with the study of **Samule et al. [15];** their cross-sectional study reported SNHL in 2 [6.9%] subjects. They concluded that hyperuricemia may affect the function of the cochlea with bilateral mild SNHL, although the differences are statistically non-significant. On the other hand, **Abdelkader et al.[16]** reported that, PTA threshold of the both ears were significantly higher in study group than control group at the frequencies of 2-8 kHz, with no differences in the PTA threshold between both ears in gouty patients. The percentage of patients with bilateral failed TEOAEs was significantly higher in gout group [50% versus 0%].

In this study, the 3 patients with high frequencies SNHL also had longest duration of hyperuricemia, this agree with the study of **Saini et al.[17];** they found positive correlation between duration of hyperuricemia and hearing loss especially at high frequencies. Also, in study of **Abdelkader et al.[16],** there was statistically significant positive correlation between the duration of hyperuricemia and audiological parameters. Patients with disease duration of more than 10 years had significantly higher TEOAEs values at 2000 Hz. In addition, patients with disease duration of more than 10 years had significantly higher PTA values at 2-8 kHz. **Saini et al.[17]** suggested that, hyperuricemia with crystal formation further lead to inflammatory response with accumulation of interleukins and neutrophils. As we are aware that any type of inflammatory response leads to increased vascular supply and edema subsequently, this inflammation forms a vicious cycle leading to decrease in blood supply by vascular injury and spasm. Later even in the healing phase, vascular injury continues by fibrotic changes in the tissue. In their study, they found significant difference between DPOAE S/N ratio. It was highly significant at 5 and 6 kHz. These observations suggest effect of

disease on cochlea in basal to apex pattern. Another study done by **Hamed and El-Attar[3],** support the vascular theory as a cause of SNHL in hyperuricemic patients. They measured common carotid artery intimal thickness and intracranial [middle cerebral and vertebral artery] blood flow through transcranial Doppler study. They found significant correlation in hyperuricemia, carotid intimal thickness, intracranial blood flow, and OAE. They concluded that hyper-uricemia leads to atherosclerosis and cochlear damage, especially in basal turn. They stated that atherosclerosis and direct hair cell stiffness are possible explanations regarding hyperuricemia-related hearing impairment. **Singh and Cleveland [4]** proposed that hyperuricemia-related inflammation and oxidative stress are the potential mechanisms linking gout to hearing loss in elderly.

It is known that presbycusis may begin as early as 30 years and it is becoming more prevalent with progression of age. Other factors that could contribute to SNHL are genetic, ototoxic medications, disease of ear, noise exposure and head tumor**.** It has been proposed that hyperuricemia could be a risk factor for SNHL[18]. Recently, many studies suggested new type of hearing loss called "Hidden Hearing loss". This type of hearing loss depending on "Synaptopathy theory", which is selective reduction in synapses connecting the Inner Hair Cells [IHCs] and their auditory nerve target. The term Hidden Hearing loss also been used by some to refer more generically to functional deficits, which are "hidden behind a normal audiogram"**.** This might denote subtle changes in auditory system still with normal audiogram[19]. Another case report of 64-year old woman presented with a right hearing loss for two years with no previous medical history and did not take any treatment. PTA revealed a right CHL with a 50 dB ABG, High-resolution CT on right temporal bone revealed calcified mass at the anterior part of the tympanic cleft. Pathological examination of excised mass revealed gouty tophi in ME[20]**.** According to V.N.G test battery results, Dix-Hallpike test revealed that 9 subjects [22.5%] in the study group presented with peripheral vertigo [BPPV], this percentage was in agreement with **Lin et al.[9];** they found 21% of total number of cases of BPPV to have hyperuricemia. 78% of BPPV patients are males, while 22% were females, with male to female affection ratio 3.5:1 which agree with ratio of Yang et al**[21].**

In the current work, Dix-Hallpike test analysis revealed that all cases of BPPV in this study were posterior canal. The nystagmus was characterized by short duration, delayed onset, torsional, upbeating and fatigable. Posterior BPPV is common according to study of **Agrawal and Parnes[22],** they said that the vast majority of all BPPV cases are of the posterior canal variant. Another study done by **Korres et al.[23],** produced a typical distribution of implicated canals in 122 cases diagnosed BPPV with 90% posterior, 8% lateral and 2% superior.

The right posterior BPPV cases represent 56.5% of BPPV cases and left posterior BPPV cases represent 44.5% of BPPV cases, which agree with study of **Celikbilek et al.[10],** which revealed that: among the most involved type of BPPV [PSCBPPV], the right side was affected in 26 patients [57.8%] and the left side in 19 patients [42.2%], which has no significant statistically difference. Another study, done by **Yousovich et al.[24]** explained why right PC-BPPV is most favorable than Lt PC-BPPV. Among the patients, 122 [52%] habitually sleep on right side. Of those, 102 [84%] were diagnosed with Rt PC-BPPV, while 82 [34%] patients habitually sleep on Lt side. Of those 53 [65%] were diagnosed with Lt PC-BPPV. This study suggested that favorable sleeping side will determine which side will affected if BPPV occurred. BPPV occurs by two suggested mechanisms, as described before: the "Canalithiasis theory" and "Cupulolithiasis theory"[6,7]**.**

The mean SUA level of all patients with BPPV significantly increased than those without BPPV [8.06 ± 0.3 vs 7.74±0.4 mg/dl respectively], which indicate significant difference. This is in agreement with study of **Celikbilek et al.[10]**. There was significant association between high SUA level and BPPV compared with control. Another meta-analysis done by **Yang et al.[21]** supported previous study done in Chinses population. Across this study, serum uric acid level was significantly higher among individuals with BPPV than among controls.

The mean SUA level of patients with right posterior BPPV is 8.02 ± 0.4 mg/dl, while the mean SUA level of patients with left posterior BPPV is 8.12 ± 0.26 mg/dl, which shows no statistical significant difference between serum UA levels as regard BPPV at right & left sides, which is in agreement with study of **Celikbilek et al.[10],** which revealed that SUA levels did not differ statistically in patients with posterior BPPV for either the right or left side.

The current work had some limitations, small sample size, limited time factor, lack investigations for inflammations and/or oxidative stress. However, we could conclud that, hyperuricemia is linked to increased risk of hearing loss, which usually bilateral, symmetrical and mild at high frequencies. The hearing threshold levels positively correlate with the duration of hyperuricemia level, and hyperuricemia had higher incidence of BPPV, with positive correlation between hyperuricemia and BPPV.

Financial and Non-financial Relationships and Activities of Interest:

None

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International Journal of Medical Arts

https://ijma.journals.ekb.eg/
Print ISSN: 2636-4174
Online ISSN: 2682-3780