



Evaluation Of Otolith Organs Functions in Patients Suffering from Vitamin D Deficiency

1159

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Abstract

Background: Vitamin D has been linked to hearing and balance. Since Many studies found a relationship between vitamin D deficiency and semicircular canals causing BPPV, it's expected to find Otoliths dysfunction in patients with hypovitaminosis D.

Material: To evaluate otoliths functions, two study groups and a control group (25 subjects in each group) based on serum vitamin D level went under evaluation with cVEMPs and oVEMPs and DHI questionnaire.

Results: High prevalence of abnormal ocular vestibular-evoked myogenic potentials (oVEMPs) and cervical vestibular-evoked myogenic potentials (cVEMPs) in the study group (delayed latencies or even absent response). Higher DHI scores was found in the study groups in comparison to the control group. Correlation was found between vitamin D and (cVEMPs, oVEMPs, and DHI score).

Conclusion: Vitamin D deficiency may be associated with development of otolith dysfunction affecting both the utricle and the saccule.

Keywords: Otolith organs, vitamin D deficiency

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1. Introduction

Vitamin D is a fat-soluble vitamin that plays a role in many physiological processes. Hence its receptor is found in almost every tissue, regulates the functions of hundreds of genes and is essential for growth and development; the interest in studying vitamin D and its effects on physiological processes has accelerated dramatically (Bikle, 2014).

Hypovitaminosis D is mainly attributed to lifestyle and environmental factors that reduce exposure to sunlight, which is required for vitamin D production in the skin. Very few foods naturally contain vitamin D and foods that are fortified with vitamin D are often inadequate to satisfy vitamin D requirements (Nair & Maseeh, 2012). Although receiving a great amount of sunlight in The Middle East, including Egypt, vitamin D deficiency is endemic due to inadequate exposure to sunlight and avoidance of extremely hot sun (Al-Mohaimed et al., 2012).

Vitamin D participates in the regulation of calcium and phosphorus found in the body and plays an important role in maintaining proper bone structure. Several studies emphasized the important role of vitamin D for the normal vestibular, hearing functions and inner ear development (Kwon, 2016). Studies on mice with a mutated vitamin D receptor gene have shown that it is associated with progressive SNHL (Zou et al., 2009). Other studies suggested that vitamin D receptor deficiency in mice is associated with balance dysfunction which may be relevant to poor balance and posture control in humans with low levels of vitamin D (Minasyan et al., 2009).

Many studies have demonstrated an association between idiopathic BPPV, and abnormal calcium metabolism caused by decreased serum vitamin D. The possible disturbance in vestibular endolymph Ca^{2+}

level resulting in formation of abnormal otoconia (Joeng et al., 2013). If vitamin D deficiency results in otoconial abnormalities in the utricle, and possibly the saccule, otolith dysfunction would be expected (Sanyelbhaa H & Sanyelbhaa A, 2015; Talebi et al., 2018). For otolith function assessment, vestibular evoked myogenic potentials (VEMP); both ocular VEMP (oVEMP) and cervical VEMP (cVEMP) are widely used clinical tools (Nagai et al., 2015).

Aim of the work

- Vitamin D deficiency is very common in Egypt and worldwide and there are only few studies on its effect on otolith organ's functions.
- to evaluate otolith organs functions in patients with vitamin D deficiency. Using a combination of Dizziness handicap inventory questionnaire (DHI) and both c & o (VEMPs) results would be a valuable addition to the vestibular assessment battery in those patients.

2. Subjects and methods

Subjects

Seventy-five subjects were included in this study. They were selected among those performing serum level assessment of 25-hydroxy vitamin D either for routine checkup, which is quite common in Egypt due to the high prevalence of vitamin D deficiency, or due to non-otologic complaints, e.g., lethargy, bone aches, hair fall, etc.

Control group:

The group consisted of 25 healthy subjects of both genders ranging in age from 20 to 50 years with Serum level of 25(OH) D (>20 ng/mL).



Study group:

It consisted of fifty adults (25 in each subgroup) of both genders and age matched with the control group.

Subgroup I:

Adults with Serum level of 25(OH) D (<12 ng/mL).

Subgroup II:

Adults with Serum level of 25(OH) D (12-20ng/mL).

All subjects fulfilled the following criteria:

- Subjects of both genders.
- Ranging in age from 20 to 50 years.
- Normal middle ear functions.
- No history of neurological disorder or head trauma.
- No history of other systemic disorders that affect balance
- (e.g., neurological diseases, uncontrolled hypertension, renal failure, hepatic cell failure)
- No Cervical lesions that could limit neck motion, which would prevent subjects from participation in (cVEMPs) recording.
- No Conductive hearing loss that abolishes VEMPs.

Investigations were performed in Audiology Unit, ORL Department, Zagazig University, Egypt, after obtaining a written consent from each participant after an approval from the Institutional Ethical Committee.

Equipment:

- COBAS 6000's module e601 by electro-chemiluminescence immunoassay using Roche Cobas vitamin D total assay reagent.
- Sound treated room.
- Two channel diagnostic audiometer, Madsen, model Orbiter 922.

- Immittancemeter, Madsen model "Zodiak 902".
- Otometrics model "ICS chartr EP 200".

Methodology:

All subjects enrolled in the current study underwent:

1. **Complete history taking** including personal, medical, otological and detailed dizziness history.
2. **Otological examination** to exclude external ear diseases.
3. **Basic audiological evaluation:**

Conventional pure tone audiometry including air conduction for octave frequencies from 250Hz to 8000Hz and bone conduction for octave frequencies from 500Hz to 4000Hz.

Speech audiometry including speech reception threshold testing (SRT) and word discrimination testing (WD %).

Immittancemetry including both tympanometry and acoustic Reflex thresholds which were elicited contralaterally using pure tones of 500, 1000, 2000 and 4000 Hz to ensure normal middle ear functions.

4. Vestibular evaluation including:

a. **The Arabic questionnaire version of the Dizziness Handicap Inventory (DHI):**

Jacopson and Newman (1990) developed the dizziness handicap inventory (DHI) in 1989. It was translated in Arabic language by **El-Gohary et al. (2000) (table1)** All the subjects were asked to answer this questionnaire, which consisted of 25 questions to quantify the impact of dizziness on everyday life. These questions were



designed to evaluate the patient functionally, physically, and emotionally.

The scoring involved the following: a (yes) response was given 4 points, (sometimes) response was given 2 points and 0 point for (no). Total maximum possible score was 100% for a significant self-perceived handicap, 0% suggested no handicap.

In attempt to evaluate the degree of handicap, a score up to 25% is considered mild handicap. (25%-50%) was moderate handicap, (50%-75%) was moderately severe and (>75%) was severe handicap.

Table (1): DHI questionnaire in Arabic language

*ضع دائرة على (دائما) او (احيانا) او (لا) لكل سؤال.
 *اجب هذه الاسئلة كما تنطبق عليك فقط

P	لا	احيانا	دائما	1-هل النظر الى اعلى يزيد الدوار
E	لا	احيانا	دائما	2-هل تشعر بالإحباط بسبب هذه المشكلة
F	لا	احيانا	دائما	3-هل قلت من اعمالك واسفارك بسبب الدوار
P	لا	احيانا	دائما	4-هل السير في ممشي ضيق كمسير ماركت مثلا يزيد الدوار
F	لا	احيانا	دائما	5-هل تجد صعوبة في القيام من السرير او الذهاب اليه
F	لا	احيانا	دائما	6-هل قلت من انشطتك الاجتماعية مثل الخروج للنزهة او الزيارات الاجتماعية
F	لا	احيانا	دائما	7-هل هل تجد صعوبة في القراءة بسبب الدوار
P	لا	احيانا	دائما	8-هل زيادة المجهود او الرياضة تزيد الدوار
E	لا	احيانا	دائما	9-هل تخشى الخروج بمفردك بسبب الدوار
E	لا	احيانا	دائما	10-هل تشعر بالحرج امام الاخرين بسبب الدوار
P	لا	احيانا	دائما	11-هل تشعر بالدوار عندما تحرك راسك بسرعة
F	لا	احيانا	دائما	12-هل تبعد عن الاماكن المرتفعة بسبب الدوار
P	لا	احيانا	دائما	13-هل تشعر بالدوار عندما تنقلب في السرير
F	لا	احيانا	دائما	14-هل بسبب الدوار لا تستطيع زيادة ضغط العمل المكلف به
E	لا	احيانا	دائما	15-هل تخشى ان يظن الناس أنك تتعاطي مهدئات او ما شابه
F	لا	احيانا	دائما	16- هل بسبب الدوار تخشى المشي بمفردك
P	لا	احيانا	دائما	17- هل النزول من السلم يزيد الدوار
E	لا	احيانا	دائما	18- هل تجد صعوبة في التركيز بسبب الدوار
F	لا	احيانا	دائما	19- هل تجد صعوبة في المشي في الظلام
E	لا	احيانا	دائما	20- هل تشعر بالخوف من البقاء بمفردك بالمنزل
E	لا	احيانا	دائما	21- هل تشعر أنك أصبحت معاقا بسبب الدوار
E	لا	احيانا	دائما	22- هل أصبحت بسبب الدوار سريع الانفعال مع اقاربك واصدقائك
E	لا	احيانا	دائما	23- هل اصابك الدوار بالاكنتاب
F	لا	احيانا	دائما	24- هل أثر الدوار عليك في القيام بمسؤولياتك
P	لا	احيانا	دائما	25- هل الانحاء يزيد الدوار

Functional (f) score ____ Emotional (E) score ____ Physical (P) score ____ TOTAL _

(El-Gohary et al., 2000)

b. Office tests:

❖ Dix-Hallpike maneuver:

- While the subject was on table in a sitting position, his head was oriented 45 degrees toward the ear to be tested
- While supporting the head, the examiner rapidly placed the patient's head into a hanging position with his neck extended 20 degrees below the level of the examining table. below the horizontal, maintaining the initial rotation of the head for 30 seconds while his eyes were being watched for nystagmus using Frenzel glasses.
- If there was no nystagmus the subject was returned to the sitting position. If nystagmus occurred, it was recorded, and the subject was returned to the sitting position after fading out of nystagmus (Dix & Hallpike, 1952).

❖ Supine roll test:

- It was performed by rotating the patient's head from neutral to one side while the patient was lying supine. In a positive test, horizontal nystagmus would be observed.
- After waiting for any nystagmus or vertigo to subside the test was

performed to the opposite side (McClure, 1985).



c. Vestibular evoked myogenic potentials measurements:

❖ **cVEMPs:**

- **Subjects:**

• the supine patient held their head up unsupported, using the anterior neck muscles then rotated his head towards the side opposite to the stimulated ear. Subjects were instructed to relax between runs of acoustic stimulation (**Rosengren, 2015**).

- **Electrode montage:**

• The position of the active electrode was placed on the middle part of the SCM muscle. While the reference electrode was placed over the upper sternum and the ground on the forehead (**Sheykholeslami and Kaga, 2002**).

- **Stimulus parameters:**

• Five hundred Hz tone burst stimulus was delivered to the tested ear at an intensity of 95 dB nHL.

• The analysis time for each response was 100 ms.

• One hundred and fifty sweeps were the average for each run.

• Band-pass filtered between 10 and 1000 Hz.

• Repetition rate was 5.1/second.

- **Data analysis:**

• The first positive peak occurring around a latency of 13 ms was marked as p1 and the first negative peak following the p13 was marked as n1 occurring around a latency of 23ms.

• The positive (p1) and the negative peaks (n1) from all recorded traces were identified according to their latencies.

• measuring the amplitude of the wave from peak to trough (p1-n1).

• At least two consecutive traces were recorded from each side to verify reproducibility.

- **Asymmetry Ratio was calculated as the following:**

• Using the formula: $100 \left[\frac{(AR-AL)}{(AR+AL)} \right]$

(AR is the amplitude of p1-n1 on the right side; AL is the amplitude of p1-n1 on the left side).

▪ Asymmetry ratio shows the relationship between side differences in VEMPs. Interaural difference (IAD) ratios have been shown to range from 0% to 35% in normal healthy adults regardless of the method used to account for muscle activity (**Rosengren et al., 2010**).

oVEMPs:

- **Subjects:**

• The patient was instructed to lay supine and maintain 30 degrees upward gaze, keep gazing upward at a fixed mark in the ceiling while hearing the stimulus (**Kantner & Gürkov, 2014**).

- **Electrode montage:**

• The active electrode was placed just inferior to the center of the lower eyelid. The reference electrode was positioned on the cheek at a point 1–2 cm below the positive one while the ground electrode was positioned over the forehead, based on the montage suggested by (**Todd et al., 2007**).

- **Stimulus parameters:**



- utilizing similar stimulus parameters of (c VEMP), the stimulus was delivered to the tested ear (the contralateral ear to the measured eye) (Murofushi and Kaga, 2009).

Data analysis:

- The first negative peak occurring around a latency of 10 ms was marked as n1 and the first positive peak following the n10 was marked as p1 occurring around a latency of 15ms.
- The peak latencies of n1, p1 and peak-to-peak amplitudes (n1-p1) were measured for all participants in all groups.

The interaural differences of n1 and p1 latency and AR were calculated similarly to cVEMP (Rosengren et al., 2010).

3. Results

In the present study there was no statistical difference between study and control groups in age and gender distribution (table 1), The study groups (group I, II) had statistically significant lower 25-hydroxyvitamin D levels than the controls. Subjects included in the study had different reasons for assessment of serum level of vitamin D. Either as a part of routine check-up, a part of lab investigation for IVF, suffering from hair fall, painful joints, back, muscles, suffering from fatigue or dizziness. There was a significant association between: -fatigue and group I.

-bone and joint pain and group II.

-dizziness and group I, II.

-Hair fall and the control group.

no statistically significant difference among groups as regards pure tone thresholds, Speech Reception Thresholds (SRT), Word Discrimination scores (WD) and Acoustic Reflexes at different frequencies

200 traces in the study groups, four registered for each subject. Regarding

oVEMPs, 28 traces were abnormal, 20 traces were with delayed latencies while 8 traces were absent. Regarding cVEMPs, 22 traces were abnormal, twenty-two traces were with delayed latencies and no absent responses.

There was no statistically significant difference between study and control groups as regards cVEMP latencies (table 2), peak amplitude (table 3), and asymmetry ratio (table 4).

Delayed peaks were significantly associated with group I and group II (table 5).

Vit D was significantly negatively correlated with P13, N23 peak latencies of cVEMPs (table 6).

There were significant differences regarding oVEMPs n10 and p15 latencies ($p < 0.05$) at both right and left ears among studied groups (table 7).

there was no statistically significant difference between all case groups as regards oVEMPs amplitude (table 8) and asymmetry ratio (table 9) among studied groups.

The oVEMPs' delayed peaks were significantly associated with group I and group II, and no response significantly associated with group I (table 10).

vitamin D was significantly negatively correlated with P15 & N10 peak latencies of oVEMPs (Table 11).

Group I was significantly higher as regards all parameters and total DHI score with no significant difference between group I and group II (table 12).

vitamin D significantly negatively correlated with Total DHI, Functional and Physical (table 13).



Table (1): Age and sex distribution among studied groups

		Group I (<12 ng/ml)	Group II (12-20 ng/ml)	Control (>20 ng/ml)	F	P	
Age	Mean± SD	28.78±6.43	33.72±7.25	30.36±9.48	2.913	0.089	
	Range	20-45	23-47	20-49			
Sex	Male	N	5	1	3		
		%	20.0%	4.0%	12.0%		
	Female	N	20	24	22	3.03	0.22
		%	80.0%	96.0%	88.0%		
Total		N	25	25	25		
		%	100.0%	100.0%	100.0%		

table shows no statistically significant difference as regards age and sex in all participants.

Table (2): The cVEMPs peak latencies (right and left ears) in different study groups:

		Group I	Group II	Control	F/Kruskal Walis	P
Right ear	P13 latency (msec.)	16.07±1.08 14.5-18	15.59±0.99 14-17.5	16.15±1.03 14.8-18.6	1.914	0.155
	N23 latency (msec.)	23.88±1.68 21.6-27.3	24.10±1.83 20-26.8	24.56±2.79 20-30	0.684	0.508
Left ear	P13 latency (msec.)	15.94±1.73 13.8-20.5	15.47±1.24 13.5-18.0	16.36±0.90 15-18	2.512	0.088
	N23 latency (msec.)	24.32±2.50 21.5-29.3	23.74±2.30 20.5-27.83	22.56±5.20 9-27.8	1.609	0.207

This table shows that there was no statistically significant difference between study and control groups as regards cVEMPs latencies.

Table (3): The cVEMPs amplitude (right and left ears) in different study groups:

		Group I	Group II	Control	F/Kruskal Walis	P
Right ear	P1-N1 Amplitude (uv)	252.60±85.6 72.3-493.3	286.46±96.3 72.3-510.5	290.69±95.6 126.9-597.1	1.902	0.055
Left ear	P1-N1 Amplitude (uv)	266.48±95.36 43.8-507.7	283.13±91.25 51.1-546.1	291.20±88.6 100.7-761.4	1.854	0.067

This table shows that there was no statistically significant difference between study and control groups as regards peak amplitude.



Table (4): The cVEMPs asymmetry ratio (right and left ears) in different study groups:

	Group I	Group II	Control	F/Kruskal Walis	P
Asymmetry (%)	11.92±3.58 1-28	10.13±2.85 0-28	13.56±5.63 0-31	2.542	0.099

This table shows that there was no statistically significant difference between study and control groups as regards asymmetry ratio.

Table (5): Distribution of cVEMPs peak latency among studied groups

			Group I	Group II	Control	X ²	P
p13	Normal	N	38	40	50		
		%	76.0%	80.0%	100.0%		
	Delayed latency	N	12	10	0	5.96	0.045*
		%	24.0%	20.0%	0.0%		
n23	Normal	N	34	38	48		
		%	68.0%	76.0%	96.0%	6.52	0.03*
	Delayed latency	N	16	12	2		
		%	32.0%	24.0%	4.0%		
Total	N	50	50	50			
	%	100.0%	100.0%	100.0%			

This table shows that Delayed peaks were significantly associated with group I and group II.

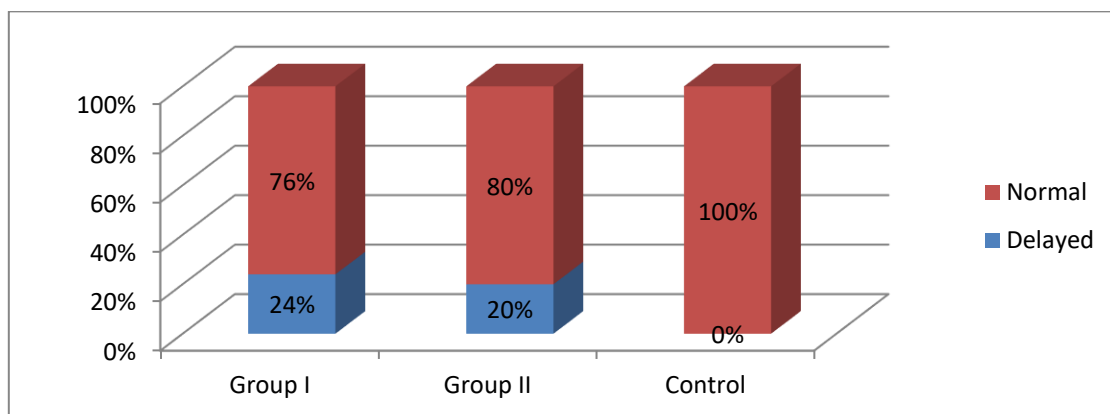


Figure (1): Distribution of p13 peak latency among studied groups

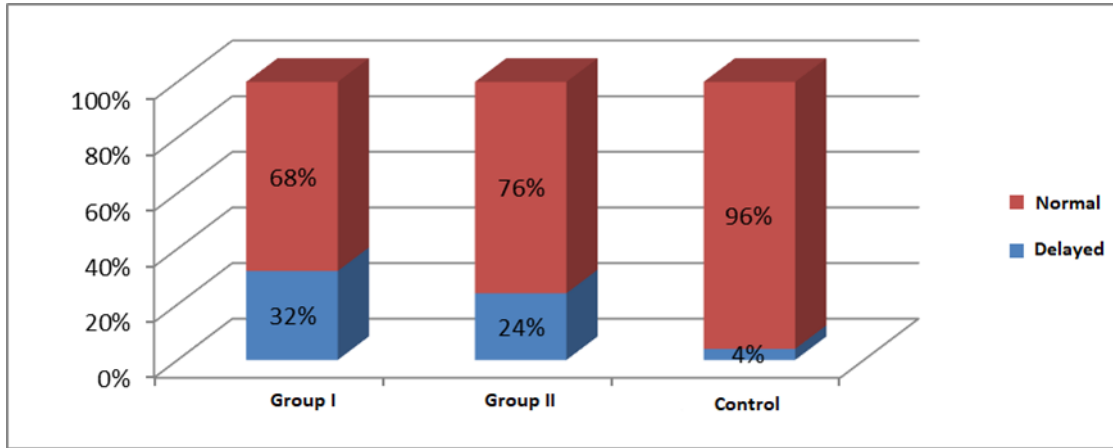


Figure (2): Distribution of n23 peak latency among studied groups.

Table (6): Correlation of cVEMPs results with Vitamin D:

		Vitamin D
P13 latency	r	-.515**
	P	.000
N23 latency	r	-.521**
	P	.000
Amplitude	r	.190
	P	.112
Asymmetry	r	.082
	P	.484

This table shows that Vit D was significantly negatively correlated with P13, N23 peak latencies of cVEMPs.

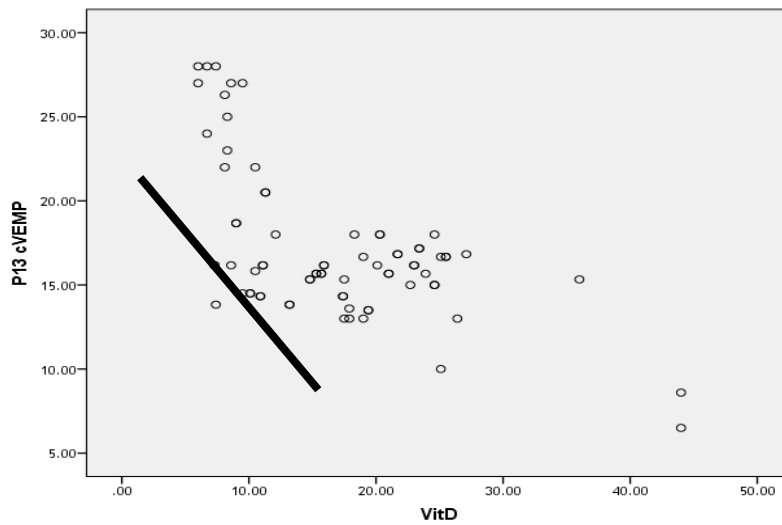


Figure (3): Scatter plot with guided line of serum hydroxy vitamin D level versus peak latencies in the study and control groups in cVEMPs.

Table (7): The oVEMP peak latencies (right and left ears) in different study groups:

		Group I	Group II	Control	F/Kruskal Walis test	P
Right ear	N10 latency (msec.)	13.61±0.34* 11-18.5	11.84±0.46 11-15.83	10.04±1.05# 11.17-12.33	4.244	0.023*
	P15 latency (msec.)	17.60±4.85* 0-20.5	15.45±0.90 15.17-18.17	13.55±1.01# 12.33-18.0	4.051	0.028*
Left ear	N10 latency (msec.)	13.81±2.0* 4.67-17.5	12.52±0.89 10.6-15.3	11.40±0.93# 11.17-13.0	6.283	0.003*
	P15 latency (msec.)	17.12±2.34* 10.3-24.17	16.51±1.49 14.3-19.5	14.85±2.20# 14.3-18.17	7.526	0.00**

* Group significantly higher by LSD (least significant difference)
 # Group significantly lower BY LSD

This table shows significant differences regarding N10 and P15 latencies (p < 0.05) at both right and left ears among studied groups.

Table (8): The oVEMP amplitude (right and left ears) in different study groups:

		Group I	Group II	Control	F/Kruskal Walis test	P
Right ear	P1-N1 Amplitude (uv)	5.16±2.5 1.3-14.2	4.86±1.54 1.5-14.8	6.26±2.15 1.5-14.6	2.940	0.085
Left ear	Amplitude (uv)	5.73±2.69 1.1-9.6	4.78±1.75 1.6-9.7	5.49±3.17 1.45-12.7	0.728	0.487

This table shows that there was no statistically significant difference between all case groups as regards amplitude among studied groups.

Table (9): The oVEMP asymmetry ratio (right and left ears) in different study groups:

	Group I	Group II	Control	F/Kruskal Walis test	P
Asymmetry (%)	12.25±4.9 0-25	14.63±4.83 0-25	15.88±5.69 0-28	1.132	0.329

This table shows no statistically significant difference between all case groups as regards asymmetry ratio.



Table (10): Distribution of oVEMPs peak latency among studied groups

			Group I	Group II	Control	X ²	P
n10	Normal	N	34	19	22		
		%	68.0%	76.0%	88.0%		
	Delayed latency	N	8	6	3	10.83	0.028*
		%	16.0%	24.0%	12.0%		
	No response	N	8	0	0		
		%	16.0%	0.0%	0.0%		
p15	Normal	N	30	42	50		
		%	60.0%	84.0%	100.0%		
	Delayed latency	N	12	8	0	16.09	0.003*
		%	24.0%	16.0%	0.0%		
	No response	N	8	0	0		
		%	16.0%	0.0%	0.0%		
Total	N	50	50	50			
	%	100.0%	100.0%	100.0%			

This table shows that Delayed peaks were significantly associated with group I and group II, and no response significantly associated with group I.

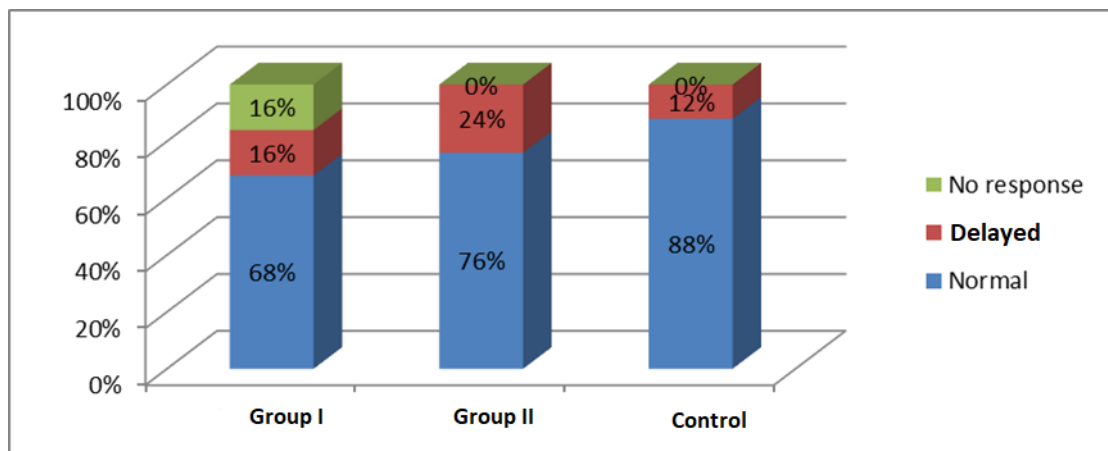


Figure (4): Distribution of n10 peak latency among studied groups.

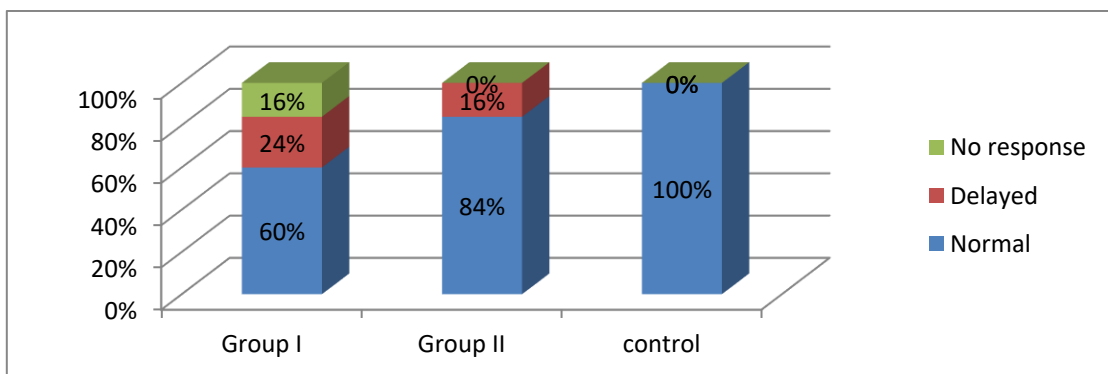


Figure (5): Distribution of p15 peak latency among studied groups.

Table (11): Correlation of oVEMP results with Vitamin D:

		Vit D
N10 latency	r	-.326**
	P	.005
P15 latency	r	-.315**
	P	.007
Amplitude	r	-.103-
	P	.393
Asymmetry	r	.055
	P	.648

This table shows that vitamin D was significantly negatively correlated with P15 & N10 peak latencies of oVEMP.

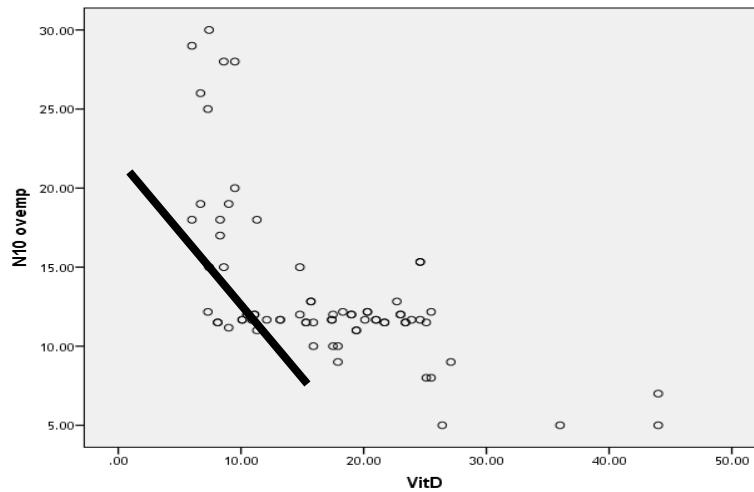


Figure (6): Scatter plot with guided line of serum hydroxy vitamin D level versus peak latencies in the study and control groups in oVEMPs.

Table (12): DHI score distribution among studied groups

	Group I	Group II	Control	Kruskal Walis	P
Total DHI	14.42±7.3* 0-44	4.18±2.58 0-26	5.60±2.36 0-30	7.535	0.001**
Functional	7.78±3.25* 0-20	3.63±1.23 0-16	3.85±1.85 0-16	7.163	0.001**
Physical	3.50±1.2* 0-12	1.01±0.52 0-4	1.14±0.74 0-6	10.776	0.00**
Emotional	3.14±2.36* 0-12	1.15±0.48 0-6	1.60±0.95 0-8	4.545	0.014*

* Group significantly higher by LSD (least significant difference test)

This table shows that group I was significantly higher as regards all parameters and total score with no sig difference between group I and group II.



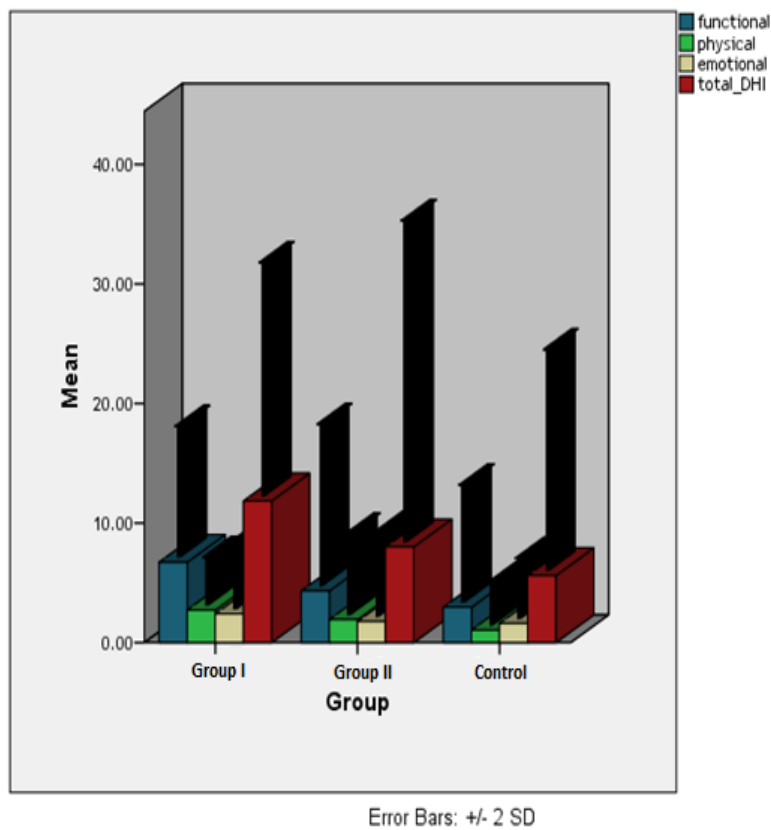


Figure (7): Distribution of functional, physical, emotional, and total DHI score among studied groups.

Table (13): Correlation of DHI results with Vitamin D:

		Vit D
Total DHI	r	-.323-^{**}
	P	.005
Functional	r	-.349-^{**}
	P	.002
Physical	r	-.352-^{**}
	P	.002
Emotional	r	-.205-
	P	.078

This table shows that vitamin D significantly negatively correlated with Total DHI, Functional and Physical.

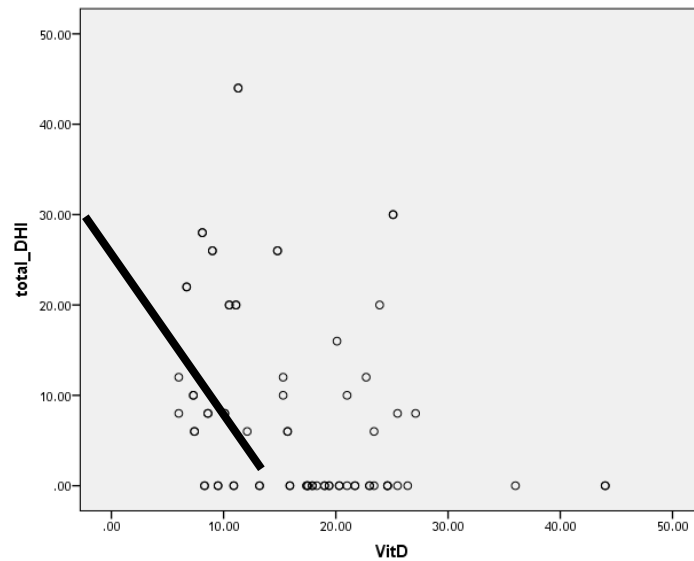


Figure (8): Scatter plot with guided line of serum hydroxy vitamin D level versus total DHI questionnaire score in the study and control groups.

4. Discussion

Several studies have reported the vital role of vitamin D for the normal vestibular and hearing functions (Kwon et Al 2016). In this work we aimed to study the audio-vestibular assessment of patients with vitamin D deficiency.

The cut-off values for defining vitamin D deficiency and sufficiency remain controversial. However, the European Calcified Tissue Society (ECTS) Working Group has defined severe vitamin D deficiency as a serum 25(OH)D lower than 12 ng/mL (Need et al., 2008). The ECTS and the Institute of Medicine (IOM) have defined vitamin D deficiency as a serum 25(OH)D concentration below 20 ng/mL, a concentration that covers the needs of nearly all healthy individuals in the population in relation to bone health similar to the European Food Safety Authority (EFSA) (Weggemans et al., 2013). Moreover, European Standing Committee of Medical Doctors and several scientists supported the conclusions of IOM on optimal 25(OH)D concentrations being ≥ 20 ng/ml (Lips et al., 2019).

Vestibular assessment:

Office tests:

In the present study all subjects showed no positive signs in both Dix-Hallbike and supine roll tests which was important to exclude cases with BPPV.

VEMPs:

Only a few studies documented VEMPs recordings in vitamin D deficiency. Depending on the fact that vitamin D is important for Ca^{2+} homeostasis in the inner ear and for the Ca^{2+} absorptive system that maintain low ca level in the vestibular endolymph and consequently it is important for development of otoconia in utricle and saccule. So, any disturbance in Ca^{2+} metabolism may generate structural and ultrastructural otoconial changes that may lead to otolith dysfunction (Yamauchi, et Al., 2010).



According to cVEMPs:

In the present study, Using ANOVA test, there was no significant difference as regards P13 and N23 latencies between study and control groups ($p>0.05$) (**table2**). Similarly, (**Taleby et Al, 2019**) did not show significant difference between vitamin D deficiency patients and the normal group. However, (**Sanyelbhaa H& Sanyelbhaa A, 2015**) reported significant difference as regards p13 peak latency between the study and the control groups as quantitative independent groups ($p<0.001$).

Using Chi square qualitative test; cVEMP abnormalities (Delayed P13, N23 peaks) were significantly associated with the study groups compared to the control group ($p>0.05$) (**Table5**) (**figures 1,2**). These findings agreed with (**Sanyelbhaa H& Sanyelbhaa A, 2015**) study which disclosed a significantly higher prevalence of cVEMP abnormalities in the study groups compared to the control group ($p<0.001$).

Amplitude depends on the muscle's contractility; it has negative correlation with age. As the range of amplitude is wide across the literature, its clinical significance is questionable (**Kumar et Al., 2021**).

In the present study, as regards P1N1 Peak amplitude of the right and the left ears in the control group, the mean value was $290.69(\pm 95.6) \mu v$ and $291.20(\pm 88.6) \mu v$ respectively (**table 3**). These results were consistent with **Ochi et Al., (2001)**. They reported that P13N23 amplitude to be $293.35(\pm 179.29) \mu V$. There was no statistically significant difference between the control and the study groups as regards peak amplitude ($p>0.05$) (**table 9**).

In the current study, the asymmetry ratio was $13.56(\pm 5.63)$ in the control group (**table 4**). This value in the current study is consistent with the most published VEMP reports that reported by **Janky and Shepard (2009)** who reported that normal asymmetry ratio was $14.22(\pm 9.42)$ and

Tourtillott et al., (2010) who reported average asymmetry ratio of $15.7(\pm 13.9) \%$. The diagnostic value of VEMP amplitude asymmetry measurement in individual patients is low, because of the large overlap of the VEMP amplitude asymmetry range for unilateral vestibular lesions with that for normal subjects (**Kingma and Wit, 2011**). There was no statistically significant difference between the control and the study groups as regards the asymmetry ratio ($p>0.05$) (**table 4**).

According to oVEMPs:

We also reported a significant difference regarding N10, P15 latencies between the study groups and the control group using ANOVA/kruskal wallis tests ($p<0.05$) (**table 7**). Also, a significantly higher prevalence of oVEMP abnormalities (delayed and absent peaks) in the study groups compared to the control group using chi square test was reported ($p<0.05$). (**Table 10**) (**figure 4,5**).

Similarly, (**Sanyelbhaa H& Sanyelbhaa A, 2015**) had reported a significant difference as regards N10 peak latency between the study and the control groups as quantitative independent groups ($p<0.001$). They also had studied the

Distribution of VEMP results (normal, delayed, or absent response) in the ears of the control and the study groups and it disclosed a significantly higher prevalence of oVEMP abnormalities in the study groups compared to the control group ($p<0.001$).

The upward gaze is one of the main factors that affect oVEMP amplitude and response rate because it is believed that an upward gaze makes the inferior oblique muscle more superficial. **Murnane et al. (2011)** reported an increased response rate of oVEMP testing after 20° gaze elevation. **Govender et al., (2009)** suggested that maximum gaze elevation should be applied before deciding that the response is absent. We used 30° upward gaze

In the present study, as regards N1P1 Peak amplitude of the right and the left ears in the control group, the mean value was $6.26(\pm 2.15)$ μv and $5.49(\pm 3.17)$ μv respectively (**table 8**). This agreed with **Biker et al., (2011)** and **wang et al., (2009)**. **Chiarovano et al., (2011)** reported that in case of oVEMPs amplitude, the mean amplitude of P13-N23 of cVEMPs was much larger than the mean amplitude N1-P1 of oVEMPs which agreed with our results.

In the current study, the asymmetry ratio was $15.88(\pm 5.69)$ in the control group (**table 9**). This agreed with **Makowiec et al., (2017)** that reported that normal asymmetry ratio was $17.59(\pm 10.76)$ in Supine position by infraorbital electrode montage.

As regards correlation with vitamin D:

While (**Sanyelbhaa H& Sanyelbhaa A, 2015**) study showed no correlation between VEMP results and Vitamin D deficiency. They detected a qualitative rather than a quantitative relationship as there was an association between vitamin D deficiency and delayed VEMP peaks, but the degree of deficiency of vitamin D not necessarily related to the degree of VEMP peaks delay. They reported a sigmoidal relationship between vitamin D level and VEMP peak latency which suggests that there is a critical level of vitamin D required to develop normal VEMP peak latencies and below that level increase in peak latencies occurs.

In the present study, there were negative correlation between VEMP peak latencies and Vitamin D deficiency; oVEMPs' N1 ($r=-0.326$), P1 ($r=-0.315$) And cVEMPs' P1 ($r=-0.515$), N1 ($r=-0.521$) which means that Vitamin D deficiency may have a role in otolith dysfunction (**table 6, 11**) (**Figures 3,6**).

Difference between our results and the previous study may be related to the sample consideration as we used 20 ng/ml serum 25 hydroxy vitamin D as a cut off, above which considered normal and below which considered

vitamin D deficient. While (**Sanyelbhaa H& Sanyelbhaa A, 2015**) considered subjects with serum level ≥ 30 ng/ml vitamin D sufficient, (20-30 ng/ml) insufficient and ≤ 20 ng/ml deficient.

DHI:

Evaluation of dizzy patients is difficult due to non-specific symptoms related to vestibular and non-vestibular dysfunction that require a multi specialist approach. Moreover, there are individual differences in central processing of vestibular stimuli as well as differences in coping mechanisms (**Donovan & McCaslin, 2021**).

Otolith optimally responds to linear and gravitational acceleration due to translational Head movements and head tilts. This could explain Why anecdotal reports of feeling like rocking, tilting, walking on pillows, being pushed, feeling drunk, and falling have been used by patients with otolith dysfunction (**Farrell & Rine, 2014**). In Addition to perceived orientation, canals and otolith organs contribute to postural control via vestibulospinal pathways. However, Pathophysiological assumptions about isolated otolith dysfunction are not always consistent with the actual clinical symptoms. That is, it may be difficult to define otolith-specific symptoms (**park et Al., 2019**).

DHI is used in assessment of dizziness related disability. In the present study we used the Arabic version of the Dizziness handicap inventory designed by **El gohary et al. (2000)**. It was conducted to all the subjects in the study and control groups for self-assessment affection of the daily life activity. Thirty-seven subjects (49%) out of 75 subjects (Nine subjects (36%) of the control group and twenty-eight subjects (56%) of the study groups) showed mild to moderate degree of handicap (**table 12**) (**figure 7**). The rest of the subjects showed no handicap.

Patients with chronic vestibular disease may manifest various degrees of behavioral and psychological adaptation resulting in variance of DHI score. (**Yip, C. W., & Strupp, M., 2018**).



Compensated chronic vestibular disease may explain the low DHI score.

As in (fig 7) subjects reported higher functional impairment scores than that of physical and emotional impairment. This is in line with Lin et al. (2002) who found that functional complaints were most prevalent, but they also found that the emotional impairment was the least. Apparently, patients perceive the functional consequences as more impairing than the emotional.

In the present study, there was a negative correlation between DHI score and level of vitamin D ($r=-0.323$) (Table 13) (figure 8). DHI was reported to be highly correlated to psychological status (Zamyslowska-Szmytke et Al., 2021). Moreover, there have been many studies reporting associations between vitamin D and psychiatric disorders, including depression and anxiety (Cheng et al., 2020). So DHI score may be not exclusively related to otolith dysfunction. Data about subjects' psychological status may be helpful.

5. Conclusion

Vitamin D deficiency may be associated with development of otolith dysfunction affecting both utricle and saccule. This was evidenced by

- Increased n10, p15 latencies in the study groups in comparison to the control group in

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oVEMPs. However, increased p13, n23 latencies of cVEMPs in the study groups in comparison to the control group wasn't enough to be significant

- High prevalence of abnormal oVEMPs (delayed latencies or even absent response) in the study groups in comparison to the control group.
- High prevalence of abnormal cVEMPs (delayed latencies) in the study groups in comparison to the control group.
- Correlation between vitamin D and cVEMPs.
- Correlation between vitamin D and oVEMPs.
- Correlation between vitamin D and DHI scores.

Recommendations:

Future research is needed to improve our knowledge. Lack of available data for certain variables of interest may be a limitation in this work such as:

- Calcium level.
- Parathyroid hormone (PTH).
- Bone mineral density (BMD).
- psychological status that may affect DHI score.

For better judgement more studies with higher sample size, more variables and different age groups are recommended.

Conflict of Interest: None

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