THE LIGHT CUPULA PHENOMENON

A SYSTEMATIC REVIEW

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19AUD002

This Dissertation is submitted as part

fulfilment for the Degree of Master of Science in Audiology

University of Mysore, Mysuru

ALL INDIA INSTITUTE OF SPEECH AND HEARING

Manasagangothri, Mysuru 570 006

September 2021

CERTIFICATE

This is to certify that this dissertation entitled **'The Light Cupula Phenomenon - A Systematic Review'** is a bonafide work submitted as a part for the fulfilment for the degree of Master of Science (Audiology) of the student Registration Number: 19AUD002. This has been carried out under the guidance of the faculty of this institute and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

Mysuru
September 2021

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DECLARATION

This is to certify that this dissertation entitled **'The Light Cupula Phenomenon - A Systematic Review'** is the result of my own study under the guidance of Dr. Animesh Barman, Department of Audiology, All India Institute of Speech and Hearing, Mysore and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

Mysuru **Registration Number: 19AUD002**

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I dedicate my dissertation, to

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Chapter 1

INTRODUCTION

Dizziness refers to the abnormal sensations relating to the body's perception of space. Drachman and colleagues in 1972 classified dizziness into five types: vertigo, presyncope, light headedness, disequilibrium, and other dizziness. Within dizziness, vertigo is the abnormal sensation relating to the body's perception of space due to a sudden internal or external spinning sensation during a head movement (Wipperman, 2014). Vertigo can be due to a peripheral lesion or a central lesion. Some peripheral vestibular disorders include Benign Paroxysmal Positional Vertigo (BPPV), Meniere's disease, vestibular neuronitis, labyrinthitis, Vestibular Schwannoma, Perilymphatic Fistula, and Superior Semi-circular Canal Dehiscence. The central vestibular disorders which commonly cause vertigo include cerebellopontine angle tumours, migraine-associated vertigo, vertebrobasilar ischemic stroke, vertebrobasilar insufficiency, fistula neoplasms of higher structures, etc. (Hanley et al., 2001).

Vertigo can often be diagnosed with a detailed case history, objective tests, and subjective tests. The case history includes, obtaining the patient's symptoms where a clinician could use the traditional SO-STONED method, which means Symptoms, Often (Frequency), Since, Trigger, Otology, Neurology, Evolution, and Duration. Some of the subjective tests which are commonly used to asses vestibular function include the head impulse test, head shake nystagmus test, dynamic visual acuity test, ocular tilt test, past pointing test, Fukuda stepping test, subjective visual acuity test, hyperventilation induced nystagmus test, Valsalva induced nystagmus test, finger to nose test, diadokinesis test, and other diagnostic maneuvers for BPPV. The objective tests used to assess vestibular functions by an audiologist includes

Vestibular Evoked Myogenic Potential (VEMP), caloric test, videonystagmography (VNG), and Video Head Impulse Test (vHIT) (Parker et al., 2019; Welgampola et al., 2019).

Amongst peripheral and central forms of vertigo, peripheral vertigo is the most common type of vertigo (Omron, 2019). The most common cause of vertigo due to peripheral pathology is BPPV (Kim et al., 2021). The cardinal symptoms of a client with BPPV include sudden vertigo induced by a change in head position during several head turn activities like turning over in the bed, lying down, looking up, stooping, or any other sudden change in head position (Kim & Zee, 2014). The severity of the BPPV is broad in a spectrum, ranging from mild to severe. The mild symptoms are, positional vertigo with inconsistency, and the moderate symptoms are positional vertigo with more frequent attacks and disequilibrium. Severe vertigo gives an impression of continuous vertigo provoked by most head movements (Imai et al., 2017a; Instrum & Parnes, 2019). These vertiginous symptoms may last for a few days, weeks, months, or years or can be recurrent over many years (Imai et al., 2017a).

The pathophysiology of BPPV involves the disruption in the normal biomechanics of endolymph flow in the semicircular canals. In a BPPV condition, the Otoconia crystals from the utricle dislodge and fall into either one of the three semicircular canals or fall into two or all semicircular canals due to multiple causes (Nuti et al., 2016; Vaduva et al., 2018). The otoconia crystals in the semicircular canals become a free-floating debris that hampers the normal movement of the endolymph. In a typically normal condition, the three semicircular canals in the inner ear help to detect the angular acceleration by being positioned at nearly right angles to each other. Each of the canals is filled with potassium-rich endolymph

with a swelling at the base termed the “ampulla.” The ampulla contains the gelatinous mass “cupula,” with the same density as the endolymph. This cupula is further attached to its polarized hair cells, making it the sensory organ (Bhattacharyya et al., 2017; Kim & Zee, 2014; Vaduva et al., 2018). During a head movement, the direction of the endolymph flows in the opposite direction of the head movement, causing it to deflect the gelatinous cupula housed in the ampulla. Depending on which canals get stimulated, the responses may be an excitatory response or an inhibitory response. There are two types of movements; an Ampullofugal movement which refers to the endolymph movement of semicircular canals away from the ampulla, and an Ampullopetal movement which refers to the endolymph movement towards the ampulla. The Ampullofugal movement causes a stimulatory response in the ampulla of the superior and posterior canals. The Ampullopetal movement causes an excitatory response in the ampulla of the lateral canal (Argaet et al., 2019; Yetiser, 2019). The cupula forms an impermeable barrier across the lumen of the ampulla, and therefore if any particles are present in the lumen, the particles cannot enter through the cupula. The Otoconia crystals are not permeable through the cupula. They can only enter/exit through the non-ampullary end. In very rare cases, otoconia crystals enter through the ampullary end and get attached to the cupula proximal to the utricle (Rabbitt, 2019).

The presence of a free-floating debris in the endolymph causes a faster movement of the endolymph that creates a mismatch with the head movement due to the gravitational push made by the free-floating debris (Yu et al., 2021). BPPV caused by free-floating debris within the membranous semicircular canals is called Canalolithiasis. On the other hand, the debris gets stuck to the cupula, causing a continuous deflection of the cupula during a head movement, resulting in a

mismatch between the cupula movement and the head movement which is due to the weight of the debris on the cupula. BPPV caused by attached debris to the cupula is called Cupulolithiasis. Both Canalolithiasis and Cupulolithiasis cause nystagmus, which is the repeated and rhythmic oscillation of the eyes (Balatsouras et al., 2018; Imai et al., 2017b). Posterior canal BPPV is the most common type of BPPV, followed by the lateral canal and anterior canal BPPV being the least common. The commonality of BPPV in the posterior canal is due to the higher gravitate in the posterior canal, making it easier for the debris to have a gravity-dependent fall and the anterior is not a gravity framed structure for the debris to fall, thus making it the least common BPPV (Martens et al., 2019). BPPV can be diagnosed with the help of diagnostic maneuvers such as Dix Hallpike, modified Dix Hallpike, and side-lying test for posterior canal BPPV, roll test, bow and lean test for lateral canal BPPV, and rose test for anterior canal BPPV (Lou et al., 2020). Two types of nystagmus can be observed in clients with BPPV. One is geotropic nystagmus, and the other is apogeotropic nystagmus. Geotropic nystagmus is where the nystagmus is towards the ground during the diagnostic tests, and apogeotropic nystagmus is where the nystagmus beats away from the ground. The BPPV can be diagnosed either as canalolithiasis and cupulolithiasis (geotropic or apogeotropic) based on the latency, adaptation, fatigability of the nystagmus, and severity of vertigo. Individuals with canalolithiasis get geotropic nystagmus due to the free-flowing movement of the otoconia crystals in the endolymph in the same direction of the head movement, and individuals with cupulolithiasis get apogeotropic nystagmus due to the weight of the otoconia crystals acting upon the cupula opposite to the direction of the head movement. Many possible forms of BPPV can occur in patients. A typical form of BPPV would be transient geotropic nystagmus in the

case of Canalolithiasis and persistent apogeotropic nystagmus in the case of Cupulolithiasis. However, in very rare cases of canalolithiasis, the free-flowing debris is present in the non-ampullary arm of the Semicircular Canals, and transient apogeotropic nystagmus is seen. In rare cases where the debris is stuck to the utricular side of the cupula, a persistent geotropic nystagmus is seen in the case of Cupololithiasis (Hiruma et al., 2018; Wang & Yu, 2018).

Direction-changing positional nystagmus (DCPN) is thought to be of a central origin. In very rare cases, a peripheral origin of vertigo can also show symptoms of DCPN where there is a spontaneous reversal of initial positional nystagmus while maintaining the head position, which is also defined as reverse nystagmus of the DCPN (Shin et al., 2015; Maia et al., 2020).

Clinicians over the years have found out a very rare form of presentation of a persistent geotropic direction-changing positional nystagmus that is not caused due to a dislodged otoconia crystals but due to the change in relative density between the cupula and the endolymph. They called this phenomenon as the light cupula (Choi et al., 2017).

The light cupula is a very rare phenomenon wherein the cupula's specific gravity is comparatively lower than the surrounding endolymph. According to Ewald's law, there will be a persistent geotropic Nystagmus in these individuals due to the lightweight of the cupula. With the change in the head position, the hair cells in the semicircular canals are either activated or inhibited (Shin & Kim, 2015), and this phenomenon resembles the Canalolithiasis type of BPPV. However, similar to the cupulolithiasis (heavy Cupula phenomenon), individuals with light cupula also have a null plane with an angle approximately 15 to 20 degrees from the supine

position. The null plane or the null point is a point that corresponds to the head position where the semicircular canals are aligned horizontally/vertically. There is no influence of gravity at this particular null point, and the cupula does not get displaced due to heavy debris, light debris, or even the endolymph movement, thereby resulting in no nystagmus at this angle (Kim et al., 2018). The intake of alcohol leads to nystagmus, and the mechanism was known as the Positional alcohol nystagmus (PAN). The PAN was the first nystagmus type identified by Aschan et al. in 1956 to resemble the light Cupula hypothesis concerning the relative density between the Cupula and Endolymph (Han et al., 2020). The mechanism behind it was that the alcohol might cause an imbalance between the cupula and endolymph as ethanol with a specific gravity of 0.79 causes an accelerated diffusion of blood capillaries into the cupula lowering its density which results in hypersensitive deflection of the cupula and thereby creating an imbalance of specific gravity between endolymph and cupula (Zhang et al., 2020). The name light cupula was first coined in 2002 by Shigeno et al. In 2004, Hiruma et al. reported persistent nystagmus in some of his patients implying that symptoms were similar to cupulolithiasis and that the cupula was lighter than the surrounding endolymph (Hiruma et al., 2018; Wang & Yu, 2018; Zhang et al., 2020). Concerning the possible mechanisms of the light cupula, there have been five major hypotheses put forward to explain the phenomenon. The first hypothesis is the “lighter cupula” hypothesis which explains the reduction in the absolute density of the cupula, similar to the mechanism of positional alcohol nystagmus. The positional alcohol nystagmus has two phases. Phase one of the positional alcoholic nystagmus (PAN 1) happens in the light cupula as accelerated diffusion in the blood capillaries to the cupula may make it lighter. Another explanation for light cupula is the “heavier endolymph” hypothesis. Heavy

endolymph could result from inflammation to the inner ear in cases of meningitis or labyrinthitis. These inflammations cause a rise in the Cerebrospinal Fluid (CSF) protein at the endolymph level, making it denser. Heavy endolymph can also be seen in cases with sudden sensorineural hearing loss (SSNHL) with a vertigo symptom. In SSNHL patients, possible damage in the blood-brain barrier due to a minor hemorrhage in the inner ear results in plasma protein leakage from the inner ear vessels to the endolymph. Heavy endolymph can cause an additional force to the cupula due to its density, thereby creating hyper-sensitive deflection in the cupula. The third mechanism is the "light debris" hypothesis, which is the opposite of the heavy debris seen in cupulolithiasis. Otoconia crystals in cupulolithiasis increase the cupula's mass, and deflection seen in the cupula is due to the weight of otoconia crystals on the cupula during head movement. But light debris, which could be in the form of plasma or leukocytes during head movement, creates a buoyant force that is acted upon the cupula, making it lighter. The fourth mechanism is the "utricular macular" hypothesis proposed by Hiruma and colleagues in 2018, where they stated that a dysfunctioning utricular macular could result in persistent geotropic nystagmus (Zhang et al., 2020). The fifth mechanism is the "density" hypothesis, which is a more recent hypothesis by Kim et al. in 2018 where they proposed that if the density of the perilymph increases and is relatively more than the endolymph, a constant gravitational force is acted upon the endolymph (Kim et al., 2018). This gravitational force causes an excessive endolymph push that results in a high deflection of the cupula and causing a symptom of persistent geotropic nystagmus. The other possible causes of light cupula include vestibular migraine, meningitis, labyrinthitis, SSNH, CNS disorders, such as brainstem stroke, cerebellar tumors, and HIV encephalopathy, which may also present with persistent symptoms geotropic

Direction Changing Positional Nystagmus. Treatment methods such as intratympanic steroid injections, repositioning maneuvers have been tried but found to be partially successful. However, habituation exercises can be tried to reduce the symptoms of nystagmus (Park et al., 2018; Tang et al., 2019).

1.1 Need for the study

The concept of the light cupula, although described in 2002, has only been widely discussed recently with the presence of more previously published literature within the decade ranging from original articles to case reports (Kim.,2014 Kim, et al., 2014). Individuals with canalolithiasis present with the characteristics of geotropic nystagmus, whereas individuals with cupulolithiasis present with persistent apogeotropic nystagmus, and individuals with vertigo of a central origin present with nystagmus that can be persistent and geotropic. The light cupula is often misdiagnosed with these conditions as characteristics of these conditions are similar to that of the light cupula. Audiologists must be aware of the light cupula phenomenon and must be able to differentially diagnose between central Nystagmus, Canalolithiasis, and heavy Cupula. Two literature review studies have been documented recently, but no systematic review studies were done (Wang et al., 2017; Zhang et al., 2020). The current article is the first known systematic review article to shed light on the concept of the light cupula, its symptoms, possible causes, and documentation of various experiments from other literature.

1.2 Aim of the study

To analyze various experiments done on light cupula based on a Systematic review research design.

1.3 Objectives of the study

1. To identify published articles related to light cupula and the type of nystagmus associated with a light cupula and highlight the distinguished phenomena associated with any specific cause of light cupula.
2. To understand the diagnostic criteria for light cupula phenomena
3. To understand the Pathophysiological and possible treatment measures underlying the Light Cupula Phenomena.

Chapter 2

METHODS

Based on the objectives mentioned above, an attempt was made to extract information from the published articles as a part of the systematic review process. Information was gathered from several sources, and articles were shortlisted. Each relevant article was critically evaluated to arrive at the objectives. A flowchart of how the methodology was carried out has been depicted below:

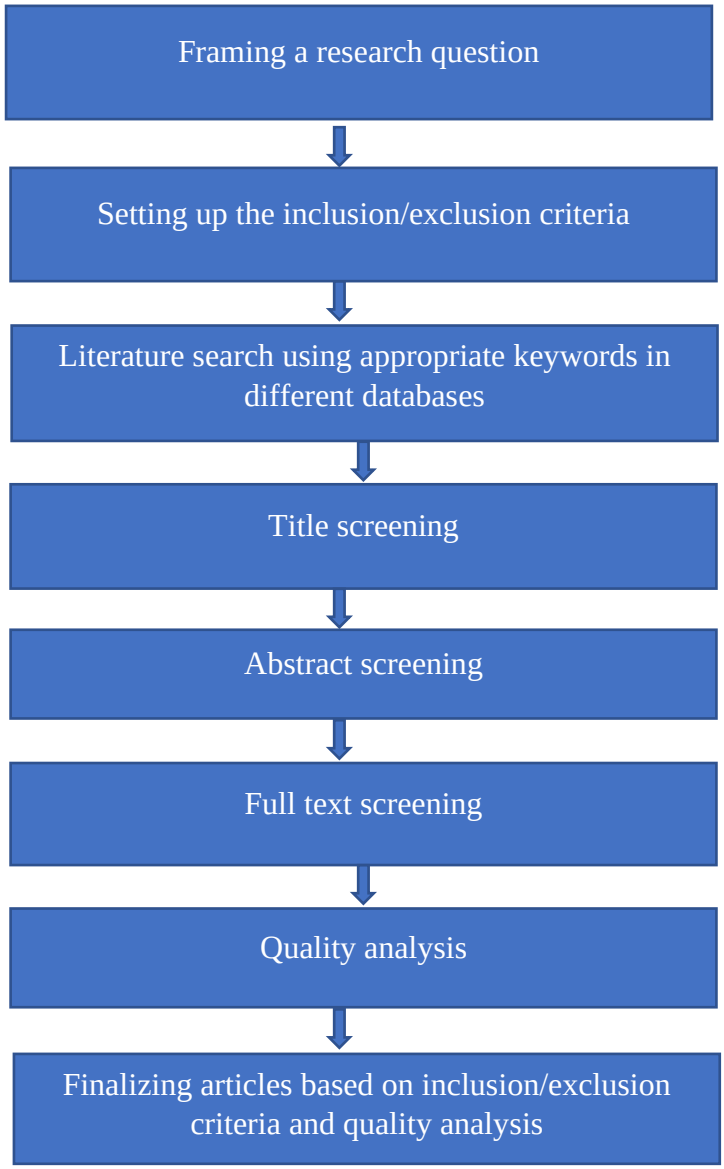

Figure 2.1: Flowchart on the way the methodology has been carried out.

2.1 Research design

The current study incorporated a Systematic Review research design.

2.2 Eligibility criteria

Eligibility criteria was defined as inclusion and exclusion criteria based on which articles were included and excluded in the systematic review. The inclusion and exclusion criteria for this systematic review is as follows

2.3.1 Inclusion Criteria

- The publications were from the peer-reviewed journals
- The articles were included but were not restricted to the topic of the light cupula.
- The articles included were original articles containing human subjects with appropriate sample size, appropriate usage of test battery utilized to diagnose light cupula, and appropriate usage of relevant statistical analysis
- The time limit for article selection was not considered, considering the rarity of the pathology, and articles from any year of publication were included.

2.3.2 Exclusion Criteria

- Articles of a single case study, short communications, letter to the editor, systematic review, and metanalysis were not included.
- Articles with language apart from English were excluded.
- Articles focussing on concepts other than light cupula were excluded.

Scientific articles from different sources focusing on light cupula or related articles were gathered from the different sources to archives the objectives of the systematic review. Articles collected from the various sources have been screened based on several criteria

before considering it for systematic review. The detailed procedure for selection of the articles is given below.

2.3 Literature search

Articles published from various peer-reviewed journals were searched in different databases like Pubmed, Pubmed Central, Science direct, Web of Science, Shodh Ganga, Google Scholar, and J-GATE. For search strategy in PubMed and PubMed central, the BOOLEAN operations such as AND, OR, and NOT were used, and for other databases, its respective keyword extraction was used. The keywords used were light cupula, heavy endolymph, persistent geotropic nystagmus, directional changing positional nystagmus, DCPN, and positional alcoholic nystagmus.

The search was based on PICOS(P- Population, I- Intervention, C-Comparison, O-Outcome, S-Study Design). The articles were filtered based on the inclusion and exclusion criteria recommended by Methley et al., 2014 where according to them the PICO framework is an endorsed framework by the Cochrane library that can be utilized to identify components related to clinical evidence for systematic review. The PICO alone could be used to extract quantitative data but PICOS can be used to extract qualitative data as well. Considering the presence of adequate medical evidence and the possibility for consideration of qualitative data in the current study, a PICOS framework was adopted rather than other frame works like SPIDER (sample, phenomenon of interest, design, evaluation, research type) and PICO.

2.4 Selection process

The selection of the articles included in the review was based on whether they met the inclusion criteria mentioned in the eligibility criteria. Each article was screened, keeping in mind the keywords for the review and inclusion and exclusion criteria. The articles that did not fulfil the inclusion criteria or which came under the exclusion criteria mentioned earlier were excluded from the study. Two authors independently carried out the selection process independently, followed by a third author if any conflict of interest was encountered. For the data selection procedure, the articles were title screened in the first stage, followed by abstract screening, and then full-text screening was done. Duplicate detection was done before title screening with the help of the same software. After duplicate detection, the remaining articles were title screened, where relevant articles were shortlisted based on the title, followed by the abstract screening. Articles were shortlisted based on the abstract where articles fulfilling the inclusion criteria were selected for the full-text screening. In contrast, the articles which didn't fulfil the inclusion criteria or which came under the exclusion criteria were excluded from the systematic review process. The study selection followed the latest PRISMA guidelines from title screening to abstract screening to finalizing the articles based on the inclusion/exclusion criteria (Moher et al., 2009). The search was carried out using the Rayyan intelligent system software (Ouzzani et al., 2016) where the databases of Pubmed, Pubmed Central, Scopus, Web of Science, Shodh Ganga, Google Scholar, and J-GATE containing the articles were imported into the Rayyan intelligent system software.

Articles were searched for in each of the above, using a set of keywords. Due to the differences in the search and indexing algorithm in place in each of the databases, the keywords mentioned were extracted separately from each database after the search and the keywords extracted from each databases have been depicted in table 2.1.

Table 2.1

Different search options used across databases

DATABASE	SEARCH
PubMed	(((((light cupula) OR (heavy endolymph)) OR (persistent geotropic nystagmus)) OR (direction changing positional nystagmus)) OR (dcpn)) OR (positional alcohol nystagmus)
PubMed central	((((((“light”[MeSH Terms] OR “light”[All Fields]) AND cupula[All Fields]) OR (heavy[All Fields] AND (“endolymph”[MeSH Terms] OR “endolymph”[All Fields]))) OR (persistent[All Fields] AND geotropic[All Fields] AND (“nystagmus, pathologic”[MeSH Terms] OR (“nystagmus”[All Fields] AND “pathologic”[All Fields]) OR “pathologic nystagmus”[All Fields] OR “nystagmus”[All Fields]))) OR (directional[All Fields] AND changing[All Fields] AND (“nystagmus, physiologic”[MeSH Terms] OR (“nystagmus”[All Fields] AND “physiologic”[All Fields]) OR “physiologic nystagmus”[All Fields] OR (“positional”[All Fields] AND “nystagmus”[All Fields]) OR “positional nystagmus”[All Fields]))) OR dcpn[All Fields]) OR (positional[All Fields] AND (“ethanol”[MeSH Terms] OR “ethanol”[All Fields] OR “alcohol”[All Fields] OR “alcohols”[MeSH Terms] OR “alcohols”[All Fields]) AND (“nystagmus, pathologic”[MeSH Terms] OR (“nystagmus”[All Fields] AND “pathologic”[All Fields]) OR “pathologic nystagmus”[All Fields] OR “nystagmus”[All Fields]))
Science direct	(“light cupula” OR “heavy endolymph” OR “persistent geotropic nystagmus” OR “direction changing positional nystagmus” OR “dcpn” OR “positional alcohol nystagmus”)
Web of science	light cupula OR heavy endolymph OR persistent geotropic nystagmus OR direction changing positional nystagmus OR dcpn OR positional alcohol nystagmus

Shodh Ganga	light cupula, heavy endolymph, persistent geotropic nystagmus, directional changing positional nystagmus, DCPN, and positional alcoholic nystagmus.
Google scholar	light cupula OR heavy endolymph OR persistent geotropic nystagmus OR direction changing positional nystagmus OR dcpn OR positional alcohol nystagmus
J-GATE	light cupula OR heavy endolymph OR persistent geotropic nystagmus OR direction changing positional nystagmus OR dcpn OR positional alcohol nystagmus

2.5 Data collection process (extraction of articles; Title screening to finalizing articles)

The preliminary search was executed independently across all the electronic databases using Boolean operators and keywords by two authors. The results that came from various databases were compiled together using a reference management system i.e., "Rayyan- intelligent, systematic review." The Rayyan intelligent system software has options of inclusion (i), exclusion I, and maybe (?). The 'inclusion' option enables insertion of the articles, the 'exclusion' option excludes/deletes the articles, and the 'maybe' option allows the reviewer to view it at a later stage. The authors had the option to use these features and segregate the articles. These features were used in all title screening, abstract screening, and full-text screening procedures before finalizing the articles for systematic review. The total number of articles combining all the databases was noted, the number of selected articles after title screening, the number of selected articles after the abstract screening, and the number of articles after full-text screening were also noted down. The articles from different databases were converted into different formats. The articles from the PubMed database were selected and downloaded in the form of a text document, while the data from the science direct and J- gate databases were downloaded in the form of RIS file format, which is developed by the research information systems. For the science direct

database and web of science, the format was extracted as BIB, and for google scholar the format was extracted as XML. The finalized articles were also imported to the MENDELEY reference managing software for citation purposes.

2.6 Quality analysis

2.6.1 Assessment of Risk of bias and reference standard using QUADAS 2

Risk of bias assessment was carried for selected studies using the Quality Assessment for Diagnostic Accuracy Studies (QUADAS-2) tool given by Whiting et al., 2011 to avoid the risk of bias. The QUADAS 2 tool helps in the assessment of the quality of the articles. The tool is completed in four phases.

Phase 1: reporting the systematic review question based on patients, index test, reference standards, and target condition.

Phase 2: review specific tailoring

Phase 3: reviewing the published flow diagram.

Phase 4: judgement on bias and applicability. The assessment of risk of bias and applicability in phase 4 consists of four domains which are patient selection, index test, reference standard, flow and timing.

Articles were assessed based on these four domains to find out the risk of bias, and applicability. All 4 domains in the tool of phase 4 assesses risk of bias and the first three domains of phase 4 assesses applicability. The scores were marked as ‘low’, ‘high’, and ‘unclear’ in both the risk of bias and applicability. The tool consists of several signaling questions under each domain (given in annexure 1), which can be answered as ‘yes ‘ with 50% or more of yes response meaning low risk of bias and if the signaling questions are answered as ‘no’ with 50% or more with no response it means there is a high risk of bias.

The same with unclear response. The applicability section does not have signaling questions and is just assessed as ‘low’, ‘high’, and ‘unclear’. However, if there are conflicts or uncertainty following inadequate information, it was answered as ‘unclear.’ The test was analyzed by two independent reviewers to avoid risk bias, where a third reviewer was considered to avoid any discrepancy between the two reviewers.

2.6.2 Level of evidence

Based on the type and methodology of the study design, the level of evidence was assessed using the Oxford Centre of Evidence Based Medicine (OCEBM) scale. The OCEBM scale has five levels. Level 1 means it is a randomized control trial, level 2 mens it is a cohort study, level 3 means it is a case control, level 4 means it is a series, and level 5 means it is a single case study. Level 1 and level 2 have subscales of ‘a’ and ‘b’, a level 1a indicates a systematic review, a level 1b means it is a randomized control trial, level 2a level 2b with cohort studies and low quality randomized control trial respectively. There was an option of rejecting articles based on the level of evidence. However, in our study, we chose to reject only level 5 type of articles (case study) and preserve the rest of the articles documenting its level of evidence (Oxford Centre for Evidence-Based Medicine: Levels of Evidence (March 2009) — Centre for Evidence-Based Medicine (CEBM), University of Oxford,).

Based on the search strategy, articles were screened from different databases and were selected based on the inclusion and exclusion criteria. All the selected articles underwent quality analysis and level of evidence testing. The objective, methodology, results, implications were discussed in detail and were critically evaluated. The objectives of the current study were discussed in detail based on the outcome of the systematically reviewed selected articles. The study selection and article informations have been explained in detail in a flowchart, table, and written in the results section.

Chapter 3

RESULTS

The articles were finalized based on the PICOS/PECOS framework with appropriate search strategies utilized in the above-mentioned databases. Out of the seven databases searched, a total of 2894 articles were obtained (Pubmed – 470, Pubmed Central – 861, Web of science - 28, Science direct – 1072, Shodh Ganga – 0, Google Scholar – 400, and J-GATE – 63) out of which 1122 articles were removed as duplicates. A total of 1772 articles underwent title screening, and post title screening, 1676 articles were removed as none of these articles either had light cupula or heavy endolymph or persistent geotropic nystagmus in their title. Around 96 articles underwent abstract screening, 29 articles that mentioned about case studies and topics other than light cupula were removed based on abstract screening with 67 articles undergoing a full text screening. The articles selected for full text screening also included articles related to BPPV that may discuss light cupula as an objective. However, only 16 articles were finalized for review after full text screening as the 51 articles removed after full text screening only dealt with BPPV and other disorder apart from light cupula. Around four articles were close to being finalized but had to be removed on specific reasons. One article mentioned persistent geotropic nystagmus to be a cupulolithiasis on the utricular side of the cupula but did not consider light cupula as a possibility. The article by Imai et al. (2011) considered treatment options for both geotropic and apogeotropic nystagmus but failed to mention about light cupula. Articles by Hong et al. (2018) does acknowledge the presence of light cupula in the background information but oriented the article completely towards pseudo spontaneous nystagmus and its pathology. The last article by Choi et al. (2018) had 32 individuals with light cupula

in their study but did not mention the mechanism, diagnostic criteria, and treatment of light cupula as the objectives and discussion of the article was only focussed towards BPPV. The rest 16 articles underwent quality analysis and level of evidence assessment by two independent reviewers.

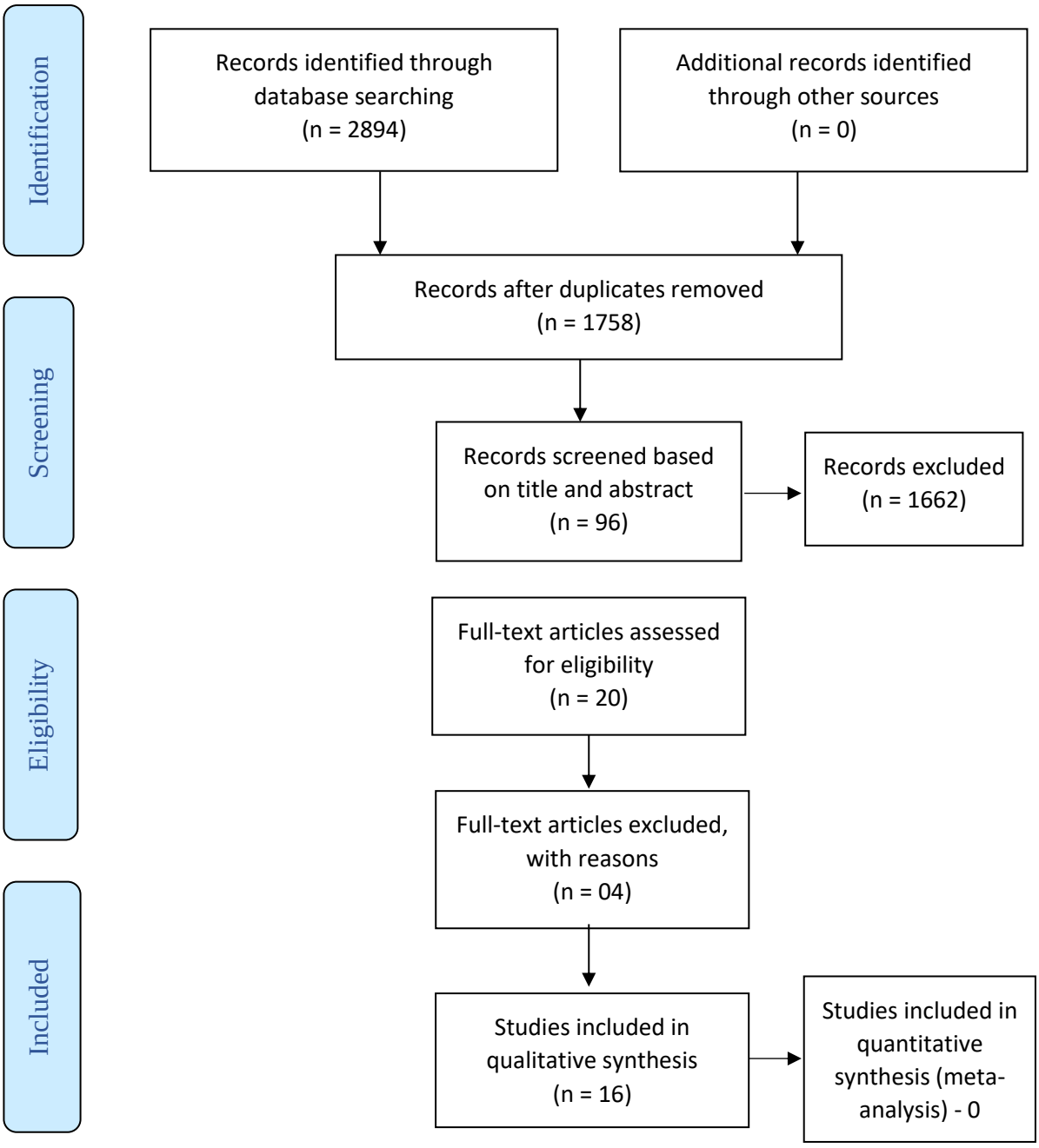

Figure 3.1 PRISMA flow diagram for representation of the items that were screened, included and excluded in the systematic review process.

Out of the 20 articles that were included for eligibility assessment, four articles were removed and 16 articles were finalized. The reason for exclusion of the four articles is given below in table 3.1.

TABLE 3.1

Reasons for the exclusion of four articles that were considered after full-text screening.

SNO	AUTHOR AND YEAR	TOPIC	REASON FOR OMMISSION
1	Imai et al. (2011)	Natural course of positional vertigo in patients with apogeotropic variant of horizontal canal benign paroxysmal positional vertigo	Although the article discussed the treatment time for both the geotropic and apogeotropic variant, it did not mention the light cupula phenomena.
2	Hong et al. (2018)	Pseudo-spontaneous nystagmus in patients with geotropic direction-changing positional nystagmus	Although the article considered light cupula one of the pathophysiological mechanisms for persistent geotropic nystagmus in the background, it abstained to elaborate on the light cupula phenomena. It only highlighted the presence of pseudo-spontaneous nystagmus and its pathophysiology.
3	S. K. Kim et al. (2019)	Differences in the Head Roll Test, Bow, and Lean Test, and Null Plane between Persistent and Transient Geotropic Direction-Changing Positional Nystagmus	This article mentions persistent geotropic nystagmus to have characteristics of long duration nystagmus and null plane. However, the article only attributes the cupulopathy/heavy cupula phenomenon to have characteristics of persistent geotropic nystagmus and not light cupula.

4	S. Choi et al. (2018)	Utility of the bow and lean test in predicting subtype of benign paroxysmal positional vertigo	The article aimed to assess the efficacy of the bow and lean test in the assessment of BPPV. Although there were 32 patients with light cupula, the complete focus of the article was to oriented to the diagnosis and management of BPPV with characteristics, assessment, and treatment of the light cupula not being discussed.

Amongst the 16 articles finalized for the review process, around 10 articles have case series type of design (level 4 evidence), three studies with a case control study design (level 3 evidence), one study with a retrospective design (level 3 evidence), one study with a retrospective cohort design (level 2 evidence), and one study with a prospective observational study (level 2 evidence). The details of the level of evidence assessment based on the OCEBM scale has been mentioned in the methods section. The number of patients with light cupula ranged from 9 to 47 patients in these articles. The type of study, number of patients, level of evidence using the OCEBM scale, and the risk bias using the QUADAS 2 quality analysis tool has been briefly mentioned in table 3.2.

TABLE 3.2

Study design and the level of evidence of the articles selected for systematic review.

S.No.	Author Name and Year	Country	Type of study	No of patients	OCEBM Scale	Quality Analysis (Risk of bias).
1	Seo et al. (2016)	Japan	Case series study design	27 (13 men and 14 women)	4	Low
2	Tomanovic and Bergenius (2014)	Sweden	Case series study design	20 (mean age of 53 years with DCPN)	4	Low
3	Imai et al. (2015)	Japan	Case control study	107 (22 men and 85 women) with horizontal canal BPPV	3a	Low
4	Hiruma et al. (2011)	Japan	Retrospective case review study	16 patients with DCPN and neutral points	4	Low
5	C. H. Kim and Hong (2018)	South Korea	Retrospective case review study	65 patients with persistent geotropic nystagmus	4	Low
6	Ichijo (2016a)	Japan	Prospective case series study design	31 heavy cupula (mean age 64.3 years) and 33 light cupula (mean age 60.9 years)	4	Low
7	C. H. Kim, Choi, et al. (2014)	Korea	Prospective case series study	19 individuals with light cupula	4	Low
8	Ichijo, (2020)	Japan	Case control study	140 patients (47 light cupula, 48 heavy cupula, and 45 canalolithiasis) with mean age of 57.4, 58.7, and 53.1 years respectively	3a	Low
9	Ban et al. (2016)	Korea	Prospective case series study	30 individuals with persistent DCPN.	4	Low

10	C. H. Kim, Kim, et al., (2014)	Korea	Retrospective case review study	47 individuals with light cupula out of the total 129	4	Low
11	Tang et al. (2019)	China	Retrospective cohort study design	25 individuals with 9 light cupula and 16 heavy cupula.	2b	Low
12	Park et al. (2018)	Korea	Prospective observational study	47 individuals (15 ITS, 16 Vestibular suppressant, and 16 CRP groups)	2b	Low
13	C. Kim et al. (2014)	Korea	Retrospective case series design	17 SSNHL (9 males and 8 females)	4	Low
14	Wang et al. (2019)	China	Case control study	52 patients (22 males, 30 females; mean age, 49.6 years) presenting with geotropic or apogeotropic DCPN.	3b	Low
15	Ichijo, (2016b)	Japan	Prospective case series study	19 patients with heavy cupula (mean age 62.8 years) and 14 patients with light cupula (mean age 63 years)	4	Low
16	Ichijo, (2012)	Japan	Retrospective study design	18 patients (16 females and 2 males with mean age of 55 years)	3b	Low

All 16 articles have incorporated specific methodology with a specific diagnostic criteria for light cupula with subjective/objective tests administered, and also some articles discussed the treatment outcomes of certain procedures in individuals with light cupula. The details of each article from the aim and objectives until discussion and implications along with author's critical evaluation has been mentioned in detail in the summary table below (table 3.3).

TABLE 3.3

Summary of the finalized articles.

Author name and year	Objectives	Methods	Results	Discussion	Pathophysiology mentioned	Critical evaluation
Tang et al. (2019)	The paper intended to explore the possibility in exacting the angle of null plane in precise diagnosis of the two types of DCPN thereby suggesting a standardized diagnosis and treatment option	***Diagnostic criteria:*** Persistent geotropic DCPN for light cupula and persistent apogeotropic DCPN for heavy cupula ***Participants:*** After undergoing the supine roll test 359 individuals were considered and only 25 patients with persistent DCPN were enrolled and followed up. According to the direction of nystagmus, the patients were further classified as light cupula and heavy	***Test findings:*** Nine patients with persistent horizontal geotropic DCPN were confirmed as "light cupula," other 16 patients with persistent horizontal ageotropic DCPN were confirmed as heavy cupula.	The null plane is crucial in determining the lesion side for light or heavy cupula. Although the short-term therapeutic effect of the light cupula is not as promising as the effect seen in heavy cupula, the long-term prognosis in both groups is comparable;	Decrease in density of cupula. Increase in specific gravity of endolymph Attachment of light debris	***Advantages:*** The need for the study, aim and objectives were well displayed in the introduction. Methods were clear and appropriately written with more of pictorial representation. A clear cut differential diagnosis between heavy

	for both heavy and light cupula.	cupula based on the direction of nystagmus. The incidence, characteristics of nystagmus and the efficacy of repositioning maneuver in the two groups were compared ***Tests administered:*** Supine roll test with videonystagmography and rotatory chair test using the Vesticon system 2000 infrared video ophthalmogram and caloric test.. ***Treatment:*** Brabecue and Guffoni maneuver with a follow up every week until one month.	All 25 patients had null plane; the mean value and standard deviation of the null plane in light cupula and heavy cupula was 25.67 and 27.06 respectively. The mean value and standard deviation of the termination plane in light cupula was 28.78 , and 30.25 in heavy cupula.	with all patients recovered after 30 days of treatment. Authors imply that individuals with light cupula must undergo VRT exercises and intratympanic steroid treatment for better prognosis.	cupula, light cupula and canalolithiasis was provided. ***Limitations:*** Use of bow and lean test was unclear as it was mentioned only in the discussion The progress of light Cupula at day 30 was not justified. The discussion was more generalized as the results were not properly mentioned and justified in the discussion section.

	There was no statistical significance between the two groups. 20% of light cupula cases had canal paresis . ***Treatment outcomes:*** All patients recovered after 30 days of treatment. The repositioning maneuvers to treat the patients with light cupula was done using the	Caloric test was not done in all subjects.

			Barbecue method. A long term prognosis could be seen in light cupula with canalith repositioning maneuvers			
C.-H. Kim et al. (2016)	The study aimed to compare the results of a Bow and lean test with those of a head roll test for lateralization of HSCC-canalolithiasis and cupulopathy (heavy cupula and	***Diagnostic criteria:*** Persistent geotropic DCPN with null plane. ***Participants:*** Total individuals enrolled were 129 (41 men and 88 women; age 19–86 years) diagnosed with either canalolithiasis (n = 66) or cupulopathy (n = 63; 47 with heavy cupula and 16 with light cupula) where all underwent the same maneuvers.	***Test findings:*** Upon the bow and lean test, the affected side was identified as the direction of bowing nystagmus 55 % (36 of 66) of patients with canalolithiasis , which was concordant with the HRT	Bow and lean test maybe of minimal use in aiding lateralization, hence the null plane direction must be noted to decide the side of lesion. In individuals with light cupula, Bow and Lean has found to be useful to identify the side	None mentioned	***Advantages:*** The need for the study, aim and objectives were well displayed in the introduction. Methods were clear and appropriately written with more of pictorial representation. A clear cut differential

	light cupula), and measure the treatment outcomes in patients with HSCC-canalolithiasis	***Tests administered:*** Head roll test, bow and lean test, and Dix-Hallpike test using Videonystagmograpy with the eye movements examined at various head positions and recorded using goggles equipped with an infrared camera.	result in 67 % (24 of 36) of cases. Both bowing and leaning nystagmus were observed in all patients with cupulopathy and light cupula, and the side of the null plane was identified as the affected side. In 16 patients with light cupula, 10 showed greater intensity of nystagmus to	of lesion along with the head roll test.	diagnosis between heavy cupula, light cupula and canalolithiasis was provided. ***Limitations:*** The pathophysiology behind light cupula was not mentioned. The possible treatment options for light cupula was not mentioned. More focus was given to canalolithiasis and cupulolithiasis than light cupula.

			the right side and 6 showed towards the left side			
Ban et al. (2016)	The study investigates the short term and immediate therapeutic benefits in individuals with persistent DCPN using canalith repositioning maneuvers (CRM).	***Diagnostic criteria:*** Presence of a geotropic DCPN for over 2 minutes duration with a null plane ***Participants:*** The authors compared the therapeutic efficacy of a canalith-repositioning procedure (CRP) in short- and long-duration geotropic DCPN on 30 individuals ***Tests administered:*** Supine head roll test visualized using videonystagmography ***Treatment:*** Barbecue maneuver for lateral canal and modified epleys maneuver for posterior canal	***Test findings:*** Individuals with long-duration DCPN had no, immediate therapeutic effect and less number of patients showed short term effects. ***Treatment outcomes:*** The barbecue roll, head shaking, and modified epleys maneuvers were given	CRP is not efficient in individuals with light cupula. The reason for no positive treatment outcomes in long duration nystagmus (light cupula) is due to the cupula deflection and not light debris.	Lighter cupula during positional alcoholic nystagmus Inner ear hypoperfusion increasing the density of the endolymph.	***Advantages:*** The treatment options and its outcomes have been mentioned. Clear cut differential diagnosis between light cupula and canalolithiasis was present. Possible pathophysiologic al mechanism has been mentioned. Ruling out the presence of light debris as a

		but no short term and immediate effect were noticed.	possible cause for light cupula. ***Limitations:*** Poor study design used. Reason why treatment outcomes were poor has not been mentioned clearly. Differential diagnosis between light cupula and central pathology has not been clearly mentioned

Wang et al. (2019)	The study aimed to compare the direction-changing horizontal positional nystagmus (DCPN) characteristics between canalolithiasis and light cupula of horizontal canal	***Diagnostic criteria:*** Horizontal canal (HC) Canalolithiasis: Transient nystagmus (<30 sec) Light cupula: Persistent geotropic nystagmus Heavy Cupula: Persistent apogeotropic nystagmus ***Participants:*** 52 patients (22 males, 30 females; mean age, 49.6 years) presenting with geotropic or apogeotropic DCPN were enrolled, and they were divided into HC-canalolithiasis, HC-Heavy cupula, or HC-Light cupula groups according their nystagmus characteristics. ***Tests administered:*** Dix-Hallpike maneuver and supine roll test using infrared illuminated, vision denied VNG system.	***Test findings:*** Time to reach slow phase velocity was longer for light and heavy cupula than canalolithiasis Other parameters showed no significant difference. The direction, duration, latency, etc were similar between light and heavy cupula except the time constant.	Characteristics between heavy and light cupula are similar and different from canalolithiais. The pathophysiology between light and heavy cupula are the same (cupulopathy)	Attachment of light debris.	***Advantages:*** Clear cut differential diagnosis was given between canalolithiasis, heavy cupula, and light cupula. Detailed test battery was carried out and multiple parameters were studied to establish the difference. The possible mechanism behind light cupula was explained.

		Peak slow phase velocity, time to reach slow phase velocity, time to reach peak slow phase velocity, time to decay to half peak intensity, latency, and time constant were the parameters administered.				***Limitations:*** Less sample size Central lesions have not been ruled out in these individuals. The light debris and possibility of cupulopathy in light cupula individuals cannot be explained without exploring the treatment outcomes in them.
Ichijo (2020)	The aim was to determine the recurrence rate and number of times of recurrence in light cupula, heavy cupula,	***Diagnostic criteria:*** Persistent nystagmus (> 1 min) in the direction of ear with a null plane for light cupula individuals, opposite to the direction of ear with a null plane for heavy cupula individuals, and brief nystagmus (<1	***Test findings:*** The recurrence rate of light cupula group was 72.3%, that of heavy cupula group was 20.8%,	The recurrence rate and number of times of recurrence is high in light cupula than heavy cupula and canalolithiasis	Light debris in the form of monocytes and lymphocytes	***Advantages:*** This was the only article that measured the recurrence rate in light cupula which is of clinical significance.

	and canalolithiasis.	min) in the direction of ear for individuals with canalolithiasis. ***Participants:*** The study included patients with light cupula (*n* = 47; males, 5; females, 42; mean age, 57.4 years), patients with heavy cupula (*n* = 48; males, 13; females, 35; mean age, 58.7 years) and patients with canalolithiasis (*n* = 45; males, 15; females, 30; mean age, 53.1 years) who complained of positional vertigo and all underwent vertigo test with evaluation of recurrence rate. ***Tests administered:*** Supine roll test with the number of times of recurrence and determined the subtypes of a recurrent vertigo attack for 5 years. Using an infrared charge-	and that of canalolithiasis group was 28.9%. Some patients experienced recurrence more than once. The mean value and standard deviation of the number of times of recurrence in light cupula group was 2.5 ±1.3 times, than that in heavy cupula group was 1.5 ±0.7 times, and that in canalolithiasis group was 1.5 ±0.7 times.	which could be due to the laterality of the sleeping postions. During a constant sleeping position the light debris may fixedly attach to the cupula.	Although many articles claim the pathophysiology to be unknown and in need of research, the current article mentions the attachment of light debris especially during sleeping positions to cause light cupula. The self remediating treatment has been mentioned. ***Limitations:*** The treatment outcomes measure using specific treatment

	coupled device camera (videonystagmography).	Results indicate more recurrence rate and high chances of recurrences in light cupula ***Treatment outcomes:*** The authors mention a self remediating mechanism within the body stating that small debris is completely absorbed as it is not foreign material which could be the reason for prognosis after two years.	method has not been carried out. Less number of subjects. A clear cut differential diagnosis and appropriate usage of test battery has not been mentioned in the article.

Park et al. (2018)	The study aims to assess the effects of intratympanic steroid injection (ITS) in light cupula.	***Diagnostic criteria:*** Criteria for light cupula included a persistent geotropic nystagmus and the presence of a null plane when the head is placed in the horizontal axis during the supine roll test. ***Participants:*** A total of 47 patients showing persistent geotropic direction-changing positional nystagmus with null point (light cupula) were randomly classified into three groups based on the treatment: ITS (n=15), vestibular suppressant (VS, n=16) and canalith repositioning procedure (CRP, n=16). ***Tests administered:*** Dizziness Handicap Inventory (DHI) and Visual Analogue Scale (VAS) were conducted	***Test findings:*** The DHI and VAS showed no significant difference between the three groups. However, a complete resolution was found in 6 patients who underwent intratympanic steroid injection. ***Treatment outcomes:*** The barbecue maneuver was used in the CRP group depending on the involved side.	Even though there were no significant differences between the three groups on DHI and VAS, it was only ITS that made a complete resolution for six individuals and reversal of stronger side of nystagmus for the others indicating good progression for ITS and the need for more animal studies.	Lighter cupula theory due to positional alcoholic nystagmus. Heavy endolymph theory due to inner ear hypoperfusion. Attachment of light debris.	***Advantages;*** The Efficacy of each treatment procedures has been well studied giving the readers a comparision of each treatment procedure. The first article to use intratympanic steroid injection. The treatment was selected in accordance with an appropriate understanding of the mechanism ***Limitations:*** The study failed to answer the challenges of diagnosing light

		before, 3 days and 1 week after the first treatment to compare the effect of each treatment. Eye movement was examined and recorded using goggles fitted to an infrared camera (VNG). ***Treatment method:*** Utility of three treatment methods; intratympanic steroid injection, vestibular suppressants, and canalith repositioning procedure	Dexamethasone disodium phosphate (5 mg/ml) was used in this study as the intratympanic steroid injection along with vestibular suppressants.			cupula by differentially diagnosing between light cupula, BPPV, and heavy cupula. Possible presence of central pathology has not been ruled out in patients with light cupula. Future directions on the utility of intratympanic steroid injection has not been clearly mentioned.
C. H. Kim and Hong, (2018)	The study investigated the efficacy of a modified	***Diagnostic criteria:*** Presence of geotropic DCPN for more than 2 min after the supine head-roll	***Test findings:*** Initially the presence of nystagmus did not resolve for	No therapeutic benefit of mCuRM for patients	Heavy endolymph theory due to inner ear hypoperfusion. Density hypothesis	***Advantages:*** The article carried out treatment manevers for light

	cupulopathy repositioning maneuver (mCuRM) on individuals with light cupula	test, and the presence of a null plan. ***Participants:*** Participants included 65 patients with a persistent geotropic DCPN: 35 underwent treatment (mCuRM group), and 30 were followed-up but received no treatment (No CuRM group). Therapeutic and survival rate of persistent geotropic DCPN were compared between the two groups. ***Tests administered:*** Supine head roll test along with audiological evaluation. Caloric test was also done. ***Treatment methods:*** utility of modified canalith repositioning maneuver (mCuRM)	both groups and later follow up days, no statistical significance was obtained between mCuRM and non mCuRM groups ***Treatment outcomes*** No benefit on modified cupulopathy repositioning maneuver on 35 patients were seen.	suggesting that the light cupula or heavy endolymph theories can be considered rather than light debris theory.	cupula individuals. Even though there was no effect of mCuRM on light cupula, the article managed to successfully eliminate the light debris theory. Appropriate diagnostic, treatment, and pathophysiology of light cupula was mentioned. ***Limitations:*** Even though the article rejected the light debris hypothesis and accepted the heavy endolymph hypothesis, it did

						not mention alternative treatment method as a future direction. Differential diagnosis between light cupula, BPPV, and heavy cupula was not mentioned. Possible presence of central pathology in individuals with light cupula was not ruled out.
C. H. Kim, Choi, et al. (2014)	The study aimed to characterize the presence of directional changing positional	***Diagnostic criteria:*** SSNHL- sensorineural hearing loss of 30 dB or more over at least three contiguous frequencies developing within	***Test findings:*** PTA threshold from initial (93.2 dB) improved to three months	SSNHL can cause light cupula as during SSNHL a haemorrhage or an extravasation of blood plasma	Higher density of endolymph due to inner ear hypoperfusion with water soluble macromolecules such as proteoglycans increasing	***Advantages:*** The article was able to successfully associate sudden sensorineural

	nystagmus post sudden sensorineural hearing loss and to explain the possible pathophysiology behind it.	3 days. Light Cupula - Long duration of DCPN with null plane ***Participants:*** Total of 17 patients (nine men and eight women; mean Age of years; range between 22 years – 72 years) with ipsilateral SSNHL and simultaneous BPPV showing geotropic DCPN were evaluated with variety of battery of tests ***Tests administered:*** The pure-tone average (PTA) was measured as the average threshold at 500, 1,000, 2,000, and 3,000 Hz. All 17 patients underwent the positioning sequence using supine head roll test using videonystagmography	post treatment (76.5 dB) with statistical significance. 15 out of 17 patients had persistent geotropic nystagmus (light cupula) Canal paresis was observed in 11 out of 17 patients. SVV was abnormal for 5 patients. ***Treatment outcomes:*** No effect of canalith repositioning maneuver on light cupula.	is caused in the inner ear creating increased protein concentration resulting in the light cupula	the density of endolymph.	hearing loss and light cupula. The pathophysiology behind SSNHL and light cupula has been properly explained. Treatment outcomes even though not effective have been carried out and mentioned. Detailed test battery has been carried out to understand the pathophysiology. ***Limitations:*** Even though treatment

	Caloric test was administered to check out possible presence of canal paresis. Subjective visual vertical test (SVV) was also administered. ***Treatment:*** A canalith repositioning maneuver was performed once daily for eight days in these individuals		measures have been carried out, it is not properly mentioned on the type of maneuver used and the time at which it was done. Alternative treatment measures have not been mentioned. Reason for abnormality in caloric test and SVV in the few subjects have not been clearly stated.

Hiruma et al. (2011)	The study aimed to examine the DCPN with neutral points as well as the pathomechani-sm of the condition of heavy and light cupula.	***Diagnostic criteria:*** Persistent geotropic DCPN with null plane-light cupula Persistent apogeotropic DCPN with null plane-heavy cupula ***Participants:*** Sixteen patients who exhibited DCPN with null plane were examined Vestibular function and the affected side were determined. In addition, the angle between the supine position and neutral point was measured in each patient. Other positional nystagmus occurring at other times were also examined. ***Tests administered:*** Supine roll test, caloric test, Magnetic Resonance Imaging (MRI), and Magnetic Resonance.	***Test findings:*** The angle of null plane was approximately 24.5 for heavy cupula and 28.5 for light cupula. For both individuals 180 degrees from the first null plane, a second null plane could be visualized. On MRI one individual with light cupula had infarction in occipital lobe. No abnormality in magnetic resonance	Repositioning maneuvers such as Epleys, Lemperts and the Brandt-Daroff exercise for a month with better efficacy in the heavy cupula group than in the light cupula	High density in endolymph due to positional alcohol nystagmus. Less density in cupula due to reduced blood flow.	***Advantages:*** A clear-cut differentiation between heavy and light cupula was provided. MRI and MRA were performed to rule out central pathology or cardiovascular pathology Appropriate test battery was administered with treatment methods tried. ***Limitations:*** Introduction and methods were brief with no proper mention of test battery used.

	Treatment: Epleys maneuver for posterior canal BPPV, Lempert maneuver for horizontal canal BPPV, Brand Daroff exercise for 2 patients with BPPV	angiography, 5 individuals with light cupula had deteriorated function on caloric test. ***Treatment outcomes;*** Treatment outcomes were better for heavy cupula individuals for all patients and treatment measures for light cupula was not discussed.		Less sample size. Treatment outcomes for light cupula were not mentioned properly and alternative treatment methods were also not mentioned for light cupula.

Ichijo (2012)	The aims of the study were to clarify whether persistent direction-changing geotropic positional nystagmus contains vertical and torsional components, and to quantify the asymmetry.	***Diagnostic criteria:*** 1.Persistent Geotropic nystagmus (1 minute) 2. In the left ear or right ear down position, horizontal nystagmus toward the left or right respectively occurs 3. In the supine position, weak horizontal nystagmus continues, and it ceases when the head is turned to the affected ear by 20–40_ (neutral position). 4. No nystagmus in the sitting position. ***Participants:*** The subjects were 18 patients (16 females and 2 males, with a mean age of 55 years, age range 28–80 years) with light cupula who underwent supine roll test with the	***Test findings:*** No significant difference between mean value of the MSV in healthy ear down and affected ear down position but significance was present between supine and nose down position. Positional nystagmus was not purely horizontal. Eight (44%) patients revealed a	The presence of vertical and torsional components can also occur from the horizontal semicircular canals as the semicircular canals are not exactly in the sagittal plane. The eye movements in the supine position and the nose-down position were not mirror images indicating that the horizontal canal ocular reflex is influenced by	The presence of light debris in the form of monocytes and lymphocytes in the semicircular canal.	***Advantages:*** The article was successfully able to postulate the presence of a vertical and torsional component in horizontal semicircular canals. The utility of maximum slow phase velocity as a parameter to differentiate the nystagmus between ears. The study eliminated the presence of central pathology.

	utility of video nystagmography ***Tests administered:*** Supine head roll test using the three-dimensional videooculography with maximum slow-phase velocity (MSV) measured.	vertical component (upward) and 15 (83%) patients had a torsional component in the healthy-ear-down position. Seven (39%) patients revealed a vertical component (downward) and 10 (56%) patients showed a torsional component in the nosed own position.	input from the otolithic organs.	**Limitations:** There was no clear cut differentiation if the participants had heavy or light cupula. Treatment methods were not explained for the participants. The study did not highlight the background, mechanism of light cupula in detail.

			Treatment outcomes: None			
Ichijo (2016a)	To measure the neutral position of apogeotropic direction-changing positional nystagmus (heavy cupula) and persistent direction-changing geotropic positional nystagmus (light cupula) of the horizontal canals.	***Diagnostic criteria:*** 1.Persistent Geotropic nystagmus (1 minute) 2. In the left ear or right ear down position, horizontal nystagmus toward the left or right respectively occurs 3. In the supine position, weak horizontal nystagmus continues, and it ceases when the head is turned to the affected ear by 20–40_ (neutral position). 4. No nystagmus in the sitting position. ***Participants:*** The nystagmus testing and analysis was done with the measurement of neutral position (null plane) for both individuals considered	***Test findings:*** The mean neutral position value and standard deviation of heavy cupula individuals was 31.6 ± 22.4 degree (5-89 degree range). The mean value and standard deviation of light cupula was 44.4 ± 20.5 degree (5-85 degree range). Both were statistically significant	As the neutral position varies widely with even. Some patients exhibiting a large angle of the neutral position (more than 40 degree); the examiners should make patients adopt a completely lateral position in the supine head roll test, and should confirm the direction of nystagmus in order to avoid mistaking	The presence of light debris in the form of monocytes and lymphocytes in the semicircular canal. Greater density of endolymph increasing the specific gravity of light cupula.	***Advantages:*** The paper was able to differentiate heavy and light cupula The paper also discussed the possibility for a persistent apogeotropic nystagmus in individuals with light cupula thus proving that not only we need to look in the direction but also the angle of null plane as based on the angle of null plane, the light

	using a large protractor on 31 individuals with heavy cupula (12 males and 19 females with average age range of 64.3 years) and 33 individuals with light cupula (10 males and 23 females with average range of 60.9 years) ***Tests administered:*** Supine head roll test using video nystagmography	***Treatment outcomes:*** None	positional nystagmus for spontaneous nystagmus.	cupula always has a greater angle than heavy cupula. The findings were appropriately correlated with the possible pathophysiologic-al mechanism. Possible presence of central pathology was ruled out ***Limitations:*** The study did not mention the treatment mode for these individuals. Weak study design

						As large protractors may not available in all clinics to measure the angle of null plane, the authors did not mention any alternatives to measure the null plane.
Seo et al. (2016)	To study the clinical features of positional nystagmus of light cupula (PNLC).	***Diagnostic criteria:*** Diagnostic criteria for PNLC were persistent geotropic positional direction-changing nystagmus, presence of nystagmus in supine position and absence of nystagmus in a position deviation from supine position and in upright position and with no evidence of cerebellar or	***Test findings:*** Null plane was found in all patients opposite to that of nystagmus in the supine position. For 22 patients the nystagmus was in the ear down position with 18	The results showed similarity in PNLC and cupulolithiasis of the lateral semicircular canal not only with respect to the nystagmus, but also in terms of the clinical course	Decrease in density of cupula. Increase in specific gravity of endolymph Attachment of light debris	***Advantages:*** The study managed to explore the clinical features of light cupula. Follow up on patients to see how the nystagmus fading away was studied.

	central nervous system pathology. ***Participants:*** 27 participants with PNLC comprising 13 men and 14 women, aged 36-80 years were included. ***Tests administered:*** Supine head roll test was done and disappearance of nystagmus was observed in all patients	having the dominant same side and 4 having the dominant side in the opposite direction. ***Treatment outcomes*** The nystagmus disappeared with in 7 days in 19 cases, within 1 month for 24 cases, and 1 patient had until 6 months. Recurrence was observed in nine cases	Ruling out the possibility of central lesion. ***Limitations:*** There was no clear cut differentiation if the participants had heavy or light cupula. The study did not mention the treatment mode for these individuals. The study did not mention the reason for disappearance of nystagmus in these individuals

C. H. Kim, Kim, et al. (2014)	The aim of this study was to characterize the clinical features and typical positional nystagmus in patients with persistent geotropic direction-changing positional nystagmus (DCPN) and address the possible pathophysiology of the disease.	***Diagnostic criteria:*** Long duration DCPN in the supine head roll along with the presence of null plane ***Participants:***19 patients with persistent geotropic DCPN. Positional nystagmus with subjective and objective test analysed ***Tests administered:*** Supine head roll test and bow and lean test using videonystagmography	***Test findings:*** All 19 patients had long duration DCPN with null plane, and the intensity of nystagmus was stronger on one side in13 patients (68%) on supine head roll test. Overall, the affected side could be identified in 18 patients (95%). ***Treatment outcomes:*** None mentioned	The presence of persistent DCPN differentiates light cupula from horizontal canal canalolithiasis. A horizontal canal BPPV with canalolithaisis presents with latency and rarely a null plane unlike the features in a light cupula.	Lighter cupula theory due to positional alcoholic nystagmus. Increase in density of endolymph due to inner ear hypoperfusion, inner ear ischemia, and inflammation or injury to the inner ear that causes debris to float in the endolymph.	***Advantages:*** Clear cut differentiation between light cupula and canalolithiasis was provided. Appropriate pathophysiology has been mentioned Clear cut clinical characteristics and diagnostic criteria has been mentioned. ***Limitations:*** Background and methods were very brief not explaining the detail protocol.

						Treatment for light cupula was not attempted and mentioned. Possible presence of central pathology has not been ruled out in patients with light cupula. Weak study design.
Imai et al. (2015)	The study aimed to classify the pathophysiolo-gical basis of nystagmus based on time constant, angle of head rotation, and slow phase velocity	***Diagnostic criteria:*** Persistent geotropic DCPN for light cupula diagnosis ***Participants:***107 patients with horizontal canal BPPV (36-88 years) who underwent subjective and objective vestibular tests. ***Tests administered:*** Supine roll test using Videonystagmography where time constant and	***Test findings:*** A time constant value of 35 seconds and less was seen in transient geotropic nystagmus and time constant of 35 seconds and	The time constant of 35 s and above is due to the deviation of the cupula in response to gravity at each head position. It is also suggested that the direction of	Decrease in density of cupula. Increase in specific gravity of endolymph Attachment of light debris	***Advantages:*** A clear-cut differentiation between light cupula and heavy cupula has been mentioned. Utility of detailed test battery and concluding the exact time

	slow phase velocity were calculated.	more was seen in persistent geotropic nystagmus with the slow phase velocity and angle of head rotation in persistent geotropic nystagmus linearly symmetrical against apogeotropic nystagmus ***Treatment outcomes***: None mentioned	cupula deviation in patients with PGN is opposite to that of patients with Apogeotropic Nystagmus across the neutral head positional range with no nystagmus where the long axis of cupula is in alignment with the axis of gravity. Apogeotropic Nystagmus is considered as heavy cupula and persistent geotropic nystagmus is	constant (35 s), more than which light cupula can be declared. Appropriate pathophysiology has been mentioned ***Limitations:*** Possible presence of central pathology has not been ruled out in patients with light cupula. Treatment for light cupula was not attempted and mentioned.

				considered as light cupula.		
Ichijo (2016b)	The study aims to clarify whether the dysfunction of the lateral semicircular canal remain or not in patients with heavy or light cupula using caloric test.	***Diagnostic criteria:*** 1. Persistent Geotropic nystagmus (1 minute) 2. In the left ear or right ear down position, horizontal nystagmus toward the left or right respectively occurs 3. In the supine position, weak horizontal nystagmus continues, and it ceases when the head is turned to the affected ear by 20–40_ (neutral position). 4. No nystagmus in the sitting position. 5. Horizontal nystagmus occurs in the nose-down position, and the direction is opposite to that in the supine position.	***Test findings:*** In heavy cupula group, no one revealed canal paresis (CP) and 4 patients (21%) showed inverse CP (affected ear response is greater than healthy ear response). In light cupula group, 3 patients (21%) revealed CP. The MSV for light cupula and heavy cupula were	Individuals with heavy or light cupula do not always have a lateral canal dysfunction. The caloric response increases in the 4 cases with heavy cupula could be explained by the hydrostatic pressure theory involved in ossicles.	Attachment of light debris.	***Advantages:*** Exploring whether light cupula and heavy cupula have canal paresis or not has been explored. Differentiating between heavy and light cupula has been mentioned Appropriate sample size is available. ***Limitations*** Treatment for light cupula was not attempted and mentioned.

		6. No cochlear symptoms related to vertigo, and no central nervous system disorder ***Participants:***The subjects were 19 patients with heavy cupula (3 males, 16 females; mean age, 62.8 years) and 14 patients with light cupula (5 males, 9 females; mean age, 63 years) ***Tests administered:*** Head roll test, Caloric test using ice cold water. The maximum slow-phase velocity and calculated asymmetry were measured.	29.2 and 24.9 respectively. ***Treatment outcomes***: None mentioned			Possible presence of central pathology has not been ruled out in patients with light cupula. Background methodology and explanation of pathophysiology of light cupula was very brief.
Tomano-vic and Bergenis (2014)	The aim of the study was to examine and correlate between the nystagmus	***Diagnostic criteria:*** Velocity of DCPN of atleast 1 degree per second exceeding 60 seconds with patients not consuming	***Test findings:*** In 72% of patients, nystagmus in the Prone position was	As there were more common dysfunctions in the vestibular test battery (caloric and	Increase in specific gravity of endolymph Attachment of light debris	***Advantages:*** Presence of central pathology was ruled out.

	patterns and vestibular impairment in an extended group of patients with geotropic positional DCPN	alcohol or having history of CNS lesions. ***Participants:*** The study included 20 patients with the mean age of 53 years with the history of position- induced horizontal nystagmus. ***Tests administered:*** Subjective visual Horizontal test, Cervical VEMP, and Videonystagmography	opposite to that in the Supine position. The vestibular tests were pathologic in about 60% of patients. At FU position (sitting, head in normal and straight forward) geotropic nystagmus was found in 40% of patients, but was significantly less intense. The vestibular test results remained at	utricular test), it can be implied that the persistent geotropic nystagmus in these individuals were purely of inner ear disorder hence concluding the presence of light cupula.	A sophisticated test battery was carried out which could explain the characteristics of light cupula better. The test was properly correlated with the possible pathophysiologic-al mechanism and the mechanism behind light cupula was explained in detail. ***Limitations:*** There was no clear cut differentiation if the participants

	the same level at FU. Recurrent vertigo was reported in 78% of the patients. In all, 40% of the patients suffered from migraine. Caloric showed abnormality for 7 patients. ***Treatment outcomes***: None mentioned	had heavy or light cupula. The study did not mention the treatment mode for these individuals. The significance of the intensity of nystagmus at different positions has not been mentioned.

The quality analysis was carried out using the QUADAS 2 questionnaire for all the articles to avoid risk of bias. The QUADAS 2 was chosen as it is the most accepted quality analysis tool for diagnostic research with the tool meeting with the objectives of the current study. The details on the QUADAS 2 tool and how the risk of bias was carried out is given in the methods section. Based on the quality analysis administered using the QUADAS 2 questionnaire, amongst the four domains at risk of bias, around 14 articles had a high risk of bias in patient selection, low risk of bias in other three domains of index test, reference standard, and flow & timing and 2 articles had low risk of bias in all the four domains of patient selection, index test, reference standard, and flow & timing. For applicability concern, around 16 articles under patient selection had low concern for applicability, and all 16 articles had low concern for applicability under index test and reference standard. Based on the level of evidence, ten articles were rated level 4, four articles as level 3, and two articles as level 2, with level 5 being a case study design and level 4 being a weak design. Even though around 14 articles had a high risk of bias in patient selection, it was due to the poor methodological quality that contributed in having a high risk of bias. The risk of bias in patient selection got directly correlated with the level of evidence. Based on the type and methodology of the study design, the level of evidence was assessed using the Oxford Centre of Evidence Based Medicine (OCEBM) scale. Articles of high risk of bias in patient selection had a level 4/3 evidence and articles of low risk of bias in patient selection and other domains had atleast level 2 evidence. However, none of the articles were rejected based on the level of evidence and quality analysis as there was a low risk of bias and also conisdering rarity of the disorder of the light cupula. Results of the level of evidence and quality analysis have been summarized in table 3.2 and table 3.4

TABLE 3.4

Quality analysis for the articles depicting the results for the four domains

Study	Risk of bias				Applicability concern		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Seo et al. (2016)	2	1	1	1	1	1	1
Tomanovic and Bergenius (2014)	2	1	1	2	1	1	1
Hiruma et al. (2011)	2	1	1	1	1	1	1
C. H. Kim and Hong (2018)	2	1	1	1	1	1	1
Ichijo (2016a)	2	1	1	1	1	1	1
C. H. Kim, Choi, et al (2014)	2	1	1	1	1	1	1
Ichijo (2020)	2	1	1	1	1	1	1
Ban et al (2016)	2	1	1	1	1	1	1
C. H. Kim, Kim, et al., (2014)	2	1	1	1	1	1	1
Tang et al., (2019)	1	1	1	1	1	1	1
Park et al., 2018	1	1	2	1	1	1	1
C. Kim et al., (2014)	2	1	1	2	1	1	1
Wang et al., (2019)	2	1	1	2	1	1	1
Ichijo, (2016b)	2	1	1	2	1	1	1
Ichijo, (2012)	2	1	1	2	1	1	1
Imai et al. (2015)	2	1	1	2	1	1	1

Note: *Low -1, High -2, Unclear -3

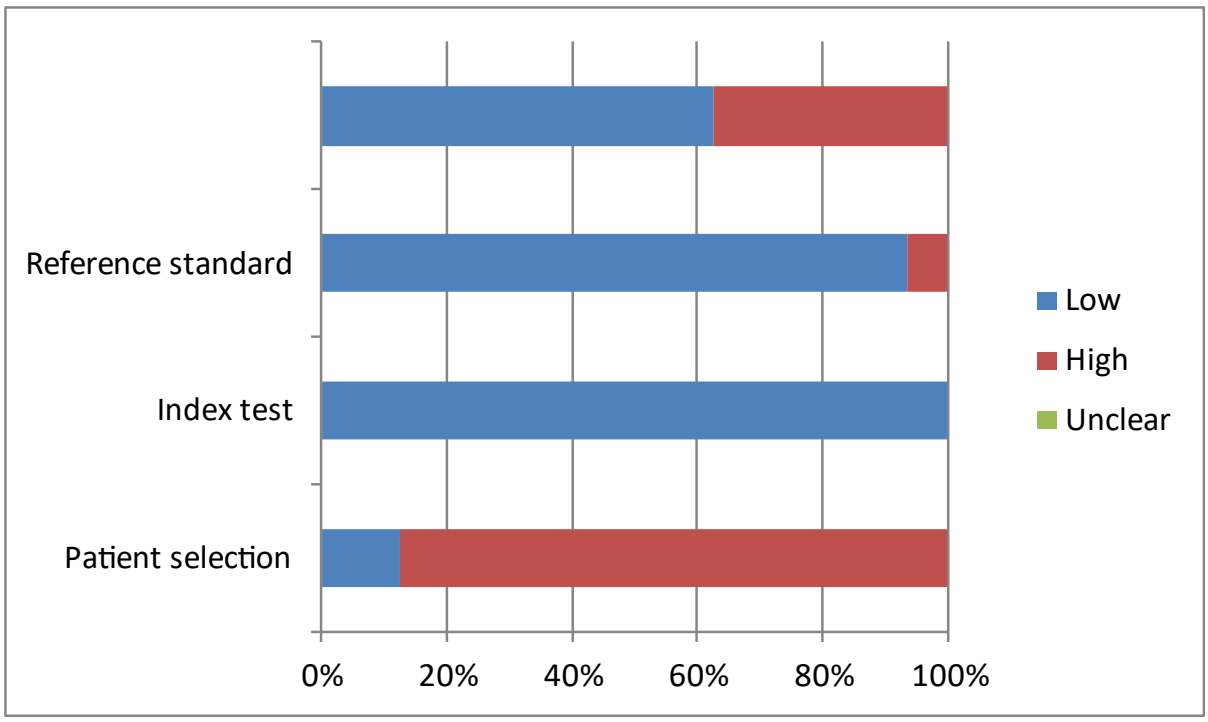

Figure 3.2 Graphical representation of QUADAS 2 results depicting proportion of studies depicting low, high, and unclear for risk of bias assessment

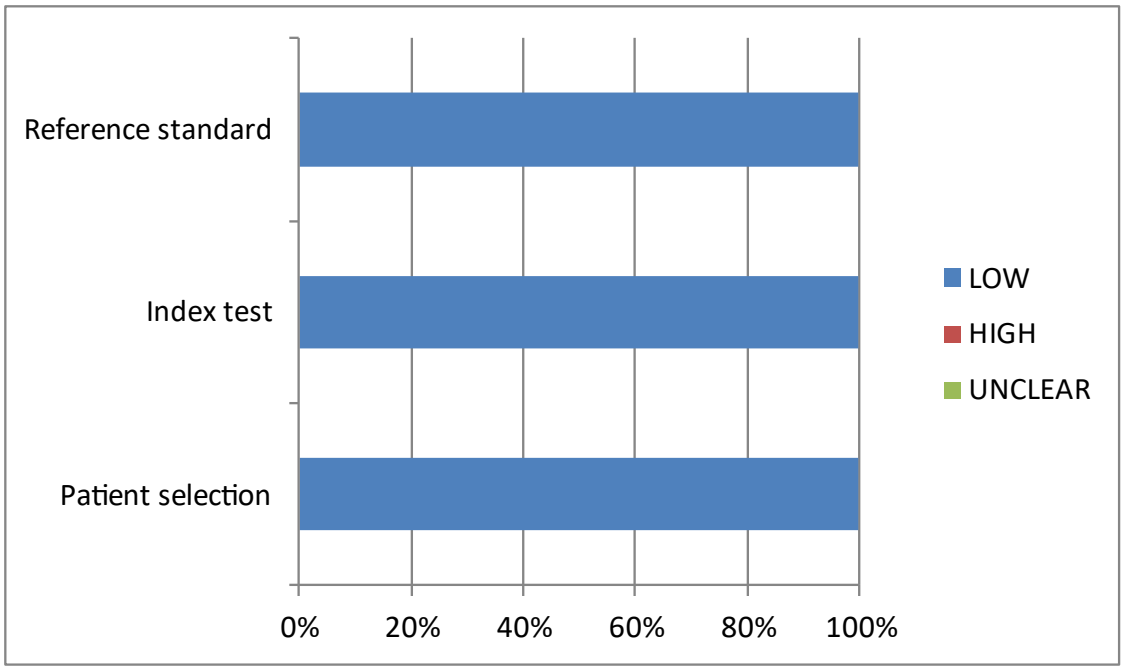

Figure 3.3 Graphical representation of QUADAS 2 results depicting proportion of studies depicting low, high, and unclear for concerns regarding applicability.

3.1 Tests administered

Around 14 articles discussed the utility of the supine head roll test along with videonystagmography for the diagnosis of light cupula. As the light cupula has features of persistent geotropic nystagmus with null plane, all these characteristics can be seen primarily on the supine head roll test. However, many authors have explored the utility of other tests that can aid in differential diagnosis as characteristics of light cupula may be similar to that of canalolithiasis and cupulolithiasis. Articles by Tang et al.,(2019), Kim etal.,(2018), Kim et al.,(2014), Hiruma et al., (2010), Ichijo et al.,(2016) utilized the caloric test in individuals with light cupula and for all them the caloric were deteriorated in either some or more individuals with light cupula thus indicating the presence of canal paresis in individuals with light cupula. Articles by Kim et al., (2015), Kim et al., (2014) carried out the Bow and Lean test and implied that individuals with

light cupula require the bow and lean test along with the supine roll test to identify the side of lesion. Articles by Kim et al.,(2015) and Wang et al.,(2019) carried out the Dix-Hallpike test in individuals with BPPV and felt the need for carrying out this test to exclude a posterior canal BPPV or to even identify the possible presence of light cupula in the posterior canal. Couple of authors utilized the peak slow phase velocity in individuals with light cupula (Wang et al.,2019; Ichijo.,2019; Ichijo.,2015; Kim et al.,2014) and established that the slow phase velocity was longer and abnormal for individuals with light cupula thus making it as an additional test battery to consider. Apart from the presence of null plane in light cupula, some authors felt the need to consider the angle of null plane for diagnosis of light cupula. For both heavy and light cupula, the null plane is present. Apart from the features of geotropic or apogeotropic nystagmus, the angle of null plane could also be considered for differential diagnosis. From the articles by Tang et al. (2019), Hiruma et al. (2010), Ichijo (2015), Ichijo (2016), all have implied that the null plane angle of the light cupula is more than that of the heavy cupula and it can be used as differential diagnosis parameter. The subjective visual vertical test has also been done by authors to check for utricular involvement in light cupula and also explore the mechanism and pathophysiology behind the light cupula mechanism. Articles by Tomanovic et al. (2014), Imai et al.,(2015), Kim et al.,(2014), have found out that the subjective visual vertical test is only affected in few patients and thus no conclusion can be drawn from it.

3.2 Treatment

Around eight articles discuss the possible treatment measures and efficacy of treatment on individuals with light cupula. Hiruma et al.,(2010) compared the effectiveness of therapeutic maneuvers between heavy and light cupula. It implied that

the treatment is effective in heavy cupula than in light cupula even after one month as heavy cupula individuals have heavy debris and light cupula have heavier endolymph. Based on his results, Kim et al., (2018), implied that there is no benefit on modified cupulopathy maneuvers on the light cupula, thus ruling out the presence of light debris. A similar finding by Ban et al., (2015) and Kim et al., (2014) was documented with no effect of canalith repositioning maneuvers on light cupula. Tang et al., (2019) also documented canalith repositioning maneuvers' effectiveness and discussed that although short-term benefits are not visualized in individuals with light cupula, the long-term benefits can be seen through vestibular retraining therapy. Park et al., (2018) tried to document the effectiveness of an intratympanic steroid injection (Dexamethasone disodium phosphate) for light cupula individuals. They found out that intratympanic steroid injection showed complete resolution to only six patients with light cupula. Ichijo (2019) mentioned a self-cleansing mechanism in individuals with light cupula where the light debris gets absorbed over time, normalizing their vestibular function.

3.3 Pathophysiology of light cupula mentioned in the articles

Except Kim etal.,(2015), all the other articles have mentioned the possible mechanism behind light cupula either correlating with their test and findings or from supporting literatures. The two most widely discusses pathophysiological mechanisms were the attachment of light debris in the form of monocytes and lymphocytes to the cupula and the increase in density of the endolymph due to inner ear hypoperfusion. The other possible mechanism mentioned by Tang et al.,(2019), Park et al.,(2018), Hiruma et al.,(2010), and Ban et al.,(2015) is the reduction in the density of the cupula resulting in reduced specific gravity due to the positional alcoholic nystagmus phase 1

that causes the alcohol to travel faster than blood through the capillaries thus making the cupula light. The article by Kim et al.,(2018) carried out the effect of modified CuRM on individuals with cupula and found out that there was no effect of canalith repositioning maneuvers on the light cupula thus successfully rejecting the light debris hypothesis as if there was a light debris, the debris must displace from the cupula during a canalith repositioning maneuver. Considering the rejection of light debris hypothesis, the overall accepted theory is the heavy endolymph theory.

3.4 Diagnostic criteria and Implications

All 16 authors have mentioned that the diagnostic criteria for a light cupula to be a persistent directional changing positional nystagmus with the presence of a null plane. The supine head roll test and the bow and lean test can help reach this diagnosis. But apart from that, there is a need to differentiate between heavy and light cupula. One way to differentiate the heavy cupula and light cupula is the direction of the nystagmus and the efficacy of treatment. Heavy cupula individuals may have persistent nystagmus which is apogeotropic, and during canalith repositioning maneuvers, the heavy cupula showed better and immediate short time progress while the light cupula, on the other hand, light cupula does not show a short term progress. Another way to differentiate is the angle of null plane, the light cupula individuals have a null plane angle that is comparatively more than the heavy cupula individual. With respect to the treatment efficacy, none of the authors of the seven articles were able to provide effective treatment measures for light cupula. Park et al., was able to show some efficacy with intratympanic steroid injections on some patients, but however there was no statistical significance between intratympanic steroid injection, vestibular suppressants and canalith repositioning maneuver as all showed poor outcomes in light cupula. Only

Tang et al.,(2019) mentioned the long-term utility of vestibular rehabilitation therapy as a possible treatment method to improvise the balance function. However, none of the documented articles performed the maneuver as such. The table 3.5 depicts the diagnostic criteria, pathophysiology, diagnostic tests, and treatment for light cupula.

Table 3.5

Characteristics, pathophysiology, test to be administered, treatment for light cupula based on critical evaluation of reviewed articles.

DIAGNOSTIC CRITERIA	**PATHOPHYSIOLOGY**	**TEST TO BE ADMINISTERED**	**TREATMENT**
1. Persistent Nystagmus 2. Geotropic in nature 3. Presence of null plane	1. Light debris due to lymphocytes and monocytes. 2. Increase in specific gravity of endolymph due to inner ear hypoperfusion. 3. Reduction of density of cupula due to reduced blood supply.	1. Supine head roll test 2. Bow and lean test 3. Caloric test	1. Brandt-Daroff exercise 2. Intra tympanic steroid injection

Chapter 4

DISCUSSION

Clinical characteristics of the light cupula is very much similar to BPPV and vertigo of a central origin. Understanding the light cupula phenomenon is very much essential to avoid misdiagnosis and for successfully differentially diagnosing between BPPV and vertigo of a central origin. The current study has successfully systematically reviewed original articles pertaining to the light cupula phenomena. In order to have detail understanding, the pathophysiology, characteristics, diagnosis, and possible treatment options of light cupula must be understood.

4.1 Pathophysiology of light cupula:

The articles reviewed had discussed three common mechanisms for light cupula that is the lighter cupula hypothesis, heavy endolymph hypothesis, and the light debris hypothesis. In normal circumstances the specific gravity of the endolymph and the specific gravity of the cupula must be equal, but in cases where the relative density of the cupula is lower than that of endolymph or relative density of the endolymph is higher than of the cupula, it may result in the light cupula. There are totally five hypothesis that have been put forward to explain the light cupula phenomenon (Zhang et al., 2020).

4.1.1 Lighter Cupula Hypothesis:

The lighter cupula is caused when the density of the cupula reduces thereby causing a reduction in the relative density between cupula and endolymph. There is hyper deflection of the cupula in this case. The reduced density of cupula can be seen in the phase 1 of positional alcohol nystagmus (Tang et al., 2019). Increased alcohol content increases ethanol in the cupula. As the density of ethanol is less than that of the density of the perilymph, a light cupula

develops (buoyancy hypothesis). The alcohol diffuses into the cupula faster than the surrounding endolymph owing to the proximity to capillaries, thus reducing the density of the cupula (Ban et al., 2016). The other cause could be if the flow from the vertebrobasilar artery may be disturbed, thus reducing the peripheral flow of the vestibular artery resulting in peripheral hypoperfusion, which could thereby affect the density or the viscosity of the endolymph (Zhang et al., 2020).

4.1.2 Heavier endolymph hypothesis:

In the heavier endolymph theory, an alteration of chemical composition of the endolymph caused by labyrinthine haemorrhage, inner ear hypoperfusion, inflammation, or hormonal imbalance may increase the density of the endolymph (C. H. Kim & Hong, 2018). In cases of SSNHL with or without vertigo, there are high chances to have pathological alterations within the inner ear fluid. A minor haemorrhage is caused due to SSNHL increases inner ear concentrations on proteins (C. H. Kim, Choi, et al., 2014). Another hypothesis mentioned is that there is a disruption of the blood labyrinth barrier that causes leakage of plasma protein to the inner ear thereby increasing the density of the endolymph. An increased protein content in the ear which also could be due to no reason may increase the density of the endolymph (Ban et al., 2016). However, this particular theory is difficult to explain why horizontal canal is more involved apart from the other two semicircular canals (C. H. Kim, Choi, et al., 2014).

4.1.3 Light debris theory:

In cupulolithiasis, the otoconia debris makes the cupula heavier due to the weight attached to the cupula. On the other hand, a light debris attached to the cupula may increase the buoyancy and make the cupula lighter. Head trauma in

the utricular macula may generate this free floating debris (Ichijo, 2012, 2016a). The light debris may be in the form of degenerative, swollen and inflammatory cells in the endolymph. Researchers have found the presence of monocytes and lymphocytes on dissecting squirrel monkeys as contributing factor to the light debris (Ichijo, 2012, 2016a, 2016b). The Light debris gets attached to the light cupula during the sleeping position if a person lies down in that particular position for a longer duration of time (Ichijo, 2020). The article by Kim et al.,2018 carried out the effect of modified CuRM on individuals with cupula and found out that there was no effect of canalith repositioning maneuvers on the light cupula thus successfully rejecting the light debris hypothesis and if there was a light debris, the debris must displace from the cupula during a canalith repositioning maneuver.

4.1.4 Utricular macular hypothesis:

Hiruma and colleagues proposed that in individuals with audio-vestibular dysfunctions, a utricular macula dysfunction may contribute to the persistent geotropic nystagmus. The utricular macular dysfunction may generate some proteins to increase the density of the endolymph thus increasing its specific gravity (Zhang et al., 2020).

4.1.5 Density hypothesis:

A more recent hypothesis by Kim et al. in 2018 where they proposed that if the density of the perilymph increases and is relatively more than the endolymph, a constant gravitational force is acted upon the endolymph (Kim et al., 2018). This gravitational force causes an excessive endolymph push that results in a high deflection of the cupula and causing a symptom of persistent geotropic nystagmus (C. H. Kim, Choi, et al., 2014).

4.2 Clinical manifestation of light cupula:

Based on the review carried out on the 16 articles, individuals with light cupula will present with the following; (1) persistent nystagmus with a duration of more than a minute, (2) direction-changing positional nystagmus, (3) horizontal nystagmus in the direction of the affected side in the bow test and the opposite direction in the lean test, and (4) presence of a null plane occurring at an approximate angle of 20 degrees upon the supine roll test (Ichijo, 2016b; Imai et al., 2015; C. H. Kim, Choi, et al., 2014; C. H. Kim, Kim, et al., 2014; C. H. Kim & Hong, 2018; Seo et al., 2016; Tomanovic & Bergenius, 2014). The null plane or zero plane, or neutral plane, is the exact horizontal axis where there will be no effect of gravity and movement of the endolymph fluid. This non-movement of endolymph creates no deflection of the cupula, and nystagmus is not visualized (Zhang et al., 2020). The absence of nystagmus at a particular angle is not seen in individuals with Canalolithiasis. The free-floating debris still causes a viscous drag to the endolymph fluid even without the influence of an extra gravitational force resulting in vertigo at the null plane (Ban et al., 2016). The following clinical presentation of the light cupula can be helpful in the differential diagnosis between a light cupula, central vertigo, and peripheral vertigo. The following figures (figure4.1-4.5) illustrate the activity of cupula in individuals with normal balance system and in individuals with light cupula.

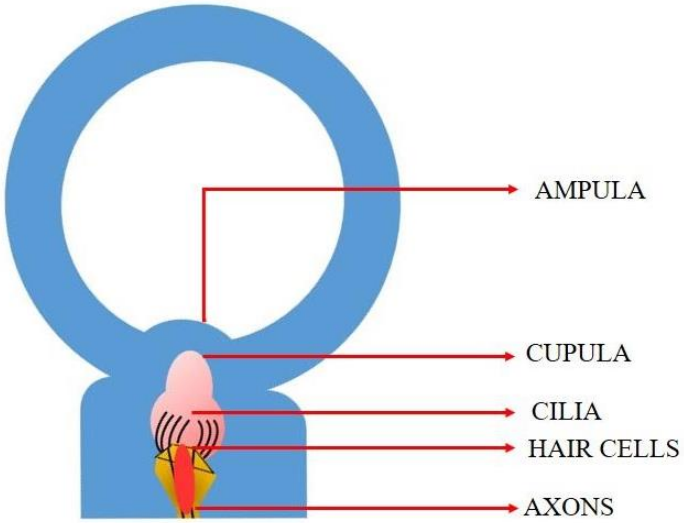

Figure 4.1 Activity of cupula during rest position in individuals with normal vestibular functions

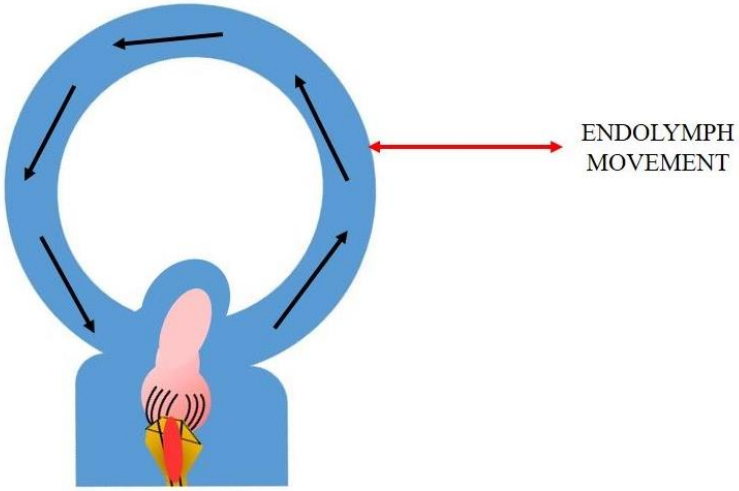

Figure 4.2 Cupula deflection in the right ear at rest position in individuals with light cupula due to reduced density in cupula or increased density in endolymph.

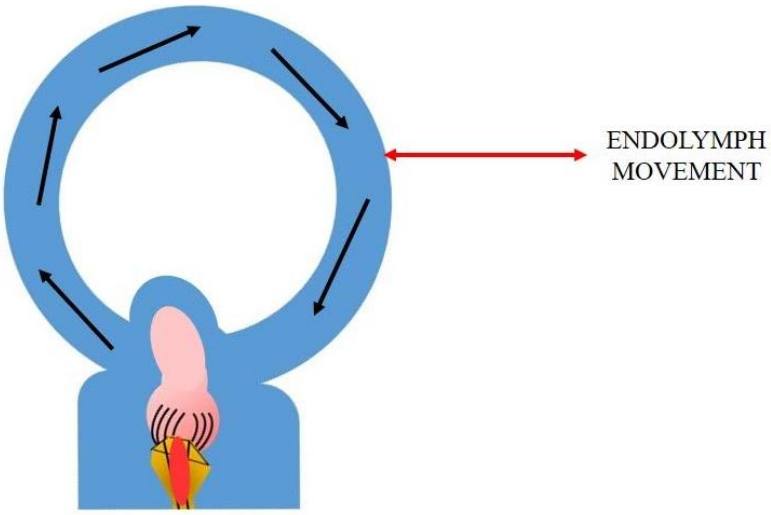

Figure 4.3 Cupula deflection in the left ear at rest position in individuals with light cupula due to reduced density in cupula or increased density in endolymph.

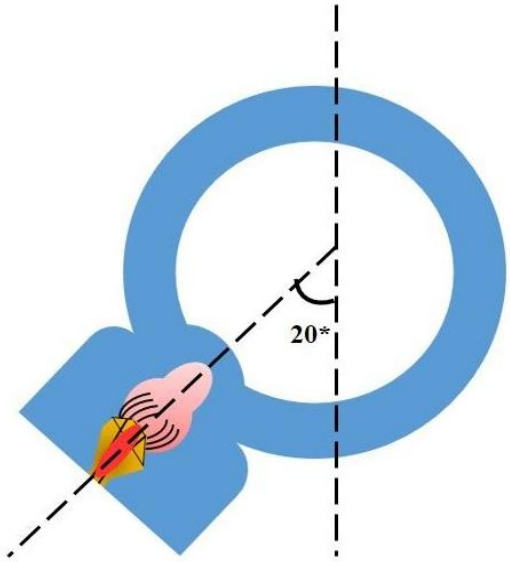

Figure 4.4 Head movement towards the right with an approximate null plane angle of 20 degree where Cupula is seen to have no activity.

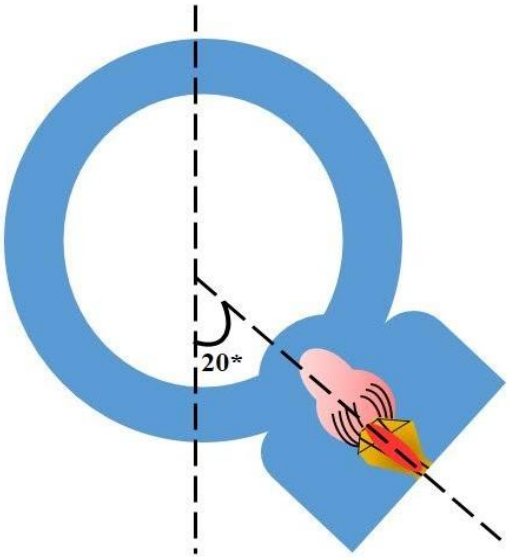

Figure 4.5 Head movement towards the left with an approximate null plane angle of 20 degree where Cupula is seen to have no activity.

4.3 Challenges in diagnosing light cupula:

Based on the systematically reviewing the 16 articles, the supine roll test is the most common subjective test used. The caloric test and videonystagmography tests are the common objective tests used in diagnosing light cupula. Based on the unique presentation of the light cupula, at times it may be challenging for clinicians to arrive at a diagnosis/impression of the light cupula based on its presentation, one such presentation is geotropic nystagmus (Ban et al., 2016; Ichijo, 2016a; Imai et al., 2015; C. Kim et al., 2014). Geotropic nystagmus is typically seen in canalolithiasis BPPV, and a presentation with geotropic nystagmus may be confused with canalolithiasis BPPV. Another challenge is persistent nystagmus of a duration of more than one minute, which can be confused with vertigo of a central origin (Tang et al., 2019). In these two conditions, it may be relatively easier to differentially diagnose BPPV, and central pathology with light cupula as all the features of light cupula are not seen in BPPV or a central lesion with vestibular involvement. However, one clinical

presentation matches the characteristics of the light cupula, and that is cupulopathy on the utricular side of the cupula. A patient with cupulolithiasis presents with persistent apogeotropic nystagmus with the presence of null plane and duration of nystagmus over one minute. In this case, the debris will be on the cupula of the non-utricular side, But if the same debris is on the cupula of the utricular side, the direction of nystagmus changes to a persistent geotropic nystagmus with a null plane which is typically seen in light cupula. The only way to differentiate between the two is during the treatment process. Suppose it's a heavy cupula, regardless of whether the debris is on the utricular or non-utricular side of the cupula, in that case, the nystagmus subsides with canalith repositioning maneuvers, and on the other hand, treatment maneuvers are not effective in individuals with light cupula (Ichijo, 2012a; C. Kim et al., 2014; Tang et al., 2019; Zhang et al., 2020). In some cases, the light cupula may present as a persistent apogeotropic nystagmus too that is similar to that of heavy cupula. According to Ichijo (2014), the presence of a light debris in the lateral side of the canal may cause a persistent geotropic nystagmus, but the same debris if present in the utricular side of the canal may cause a persistent apogeotropic nystagmus. To differentiate between these two, the angle of null plane can be considered. Regardless of whether the nystagmus is geotropic or apogeotropic in nature, the angle of null plane of light cupula is always greater than that of heavy cupula. In very rare situations, there may be a presentation of the light cupula in all three semicircular canals. Even though light cupula is most predominantly seen in the lateral canal, the concept of change in specific gravity can affect the entire endolymph and thus affecting all three semicircular canals. The null plane in such cases will be present during the supine roll test and Dix-Hallpike test too (C. H. Kim, Shin, et al., 2014). According to the case study by Kim et al., 2014, the light cupula in three semicircular canals may often be misdiagnosed as posterior

canal BPPV due to the presence of torsional component, and in this case, light cupula can be diagnosed by looking out for the presence of the null plane on both supine roll test and Dix-Hallpike test. Clinicians must consider these challenges and be well aware of the light cupula characteristics to differentially diagnose light cupula from other pathologies with similar characteristics.

4.4 Challenges in treating the light cupula:

Out of the eight articles that have discussed the possible treatment of light cupula, around four different possible treatment options have been discussed. The first is canalith repositioning maneuvers, second is vestibular rehabilitation therapy like the Brandt-Daroff exercises, third is the use of intratympanic steroid injection, and fourth is a self cleansing mechanism (Ban et al., 2016; Ichijo, 2016a, 2020; C.-H. Kim et al., 2016; C. H. Kim & Hong, 2018; Park et al., 2018; Seo et al., 2016; Tang et al., 2019). One of the challenges for treatment is that all the articles do not portray effectiveness of these treatment techniques for light cupula. Concerning the treatment of the light cupula, it has not been proven to be of much effect which can be challenging for the audiologists and otorhinolaryngologists. Out of the treatment options discussed in the seven articles, the self cleansing mechanism of light debris theory can be ruled out as a treatment option as it is proven that any debris regardless of whether it is light or heavy can be treated with repositioning maneuvers. (C. H. Kim & Hong, 2018). Even though there is no self cleansing mechanism in light debris, the self cleansing mechanism may be present in cases of heavy endolymph which is why reduction of nystagmus is seen in individuals with light cupula one month after onset (C. Kim et al., 2014). But in terms of the presence of light debris, articles state that the canalith repositioning maneuvers have not been effective thus ruling out the presence of light debris as regardless of

heavy or light debris, the canalith repositioning maneuvers have an effect in displacing the debris from the cupula and channel it back to the utricle (C. H. Kim & Hong, 2018). Some case studies and articles have documented the utility of semicircular canal plugging for reducing the symptoms of vertigo in individuals with light cupula post sudden sensorineural hearing loss. The mechanism behind semicircular canal plugging is that it hampers the flow of the endolymph leading to minimal movement of the kinocilium during a positional change (Zhang et al., 2020). The other documentation is the utility of the vagus nerve stimulation. Individuals with light cupula rapidly recovered from their symptoms after transcutaneous vagus nerve stimulation; however, the symptoms reappeared later. The study was unable to document the mechanism behind the improvement of symptoms, but more experiments can be carried out in the future (Zhang et al., 2020). The two treatment modalities that may show some positive effects are the utility of intratympanic steroid and vestibular retraining therapy that can suppress the symptoms of the light cupula. Clinicians with expertise in VRT can carry out exercises like the Brandt-Daroff exercises to suppress the light cupula symptoms.

4.5 Critical evaluation of the articles systematically reviewed:

Based on the inclusion and exclusion criteria, a total of 16 articles were finalized for the review (Ban et al., 2016; Hiruma et al., 2011; Ichijo, 2012a, 2016a, 2016b, 2020; Imai et al., 2015; C.-H. Kim et al., 2016; C. H. Kim, Choi, et al., 2014; C. H. Kim, Kim, et al., 2014; C. H. Kim & Hong, 2018; Park et al., 2018; Seo et al., 2016; Tang et al., 2019; Tomanovic & Bergenius, 2014; Wang et al., 2019). Unlike many articles that have documented only single case studies (level 5 evidence), these 16 articles had participants with light cupula of more than one that enabled to run statistical analysis and arrive at a hypothesis. Another positive outcome from these articles is the

establishment of an appropriate test battery considering the challenges of diagnosing light cupula. It can be established from the majority of articles that the supine roll test is sufficient to diagnose the light cupula based on the direction, latency, persistency, fatigability, and the presence of a null plane. Table 4.1 illustrates the differential diagnosis between light cupula, canalolithiasis, cupulolithiasis, and vertigo of central origin. As an objective test, 11 articles have used the VNG, and from this, we can infer that the utility of VNG can aid in the diagnosis of the light cupula. Around seven articles mentioned the possible treatment options for the light cupula that could guide clinicians and researchers when dealing with these patients. Park et al. (2018) indicated slight progress on intratympanic steroid injection, which is a positive sign as clinicians can use it as a treatment method. One of the advantages of all the articles is that every author managed to document at least more than nine individuals with a light cupula due to which better description of the light cupula could be given. The figure 4.6 depicts the number of subjects in each article.

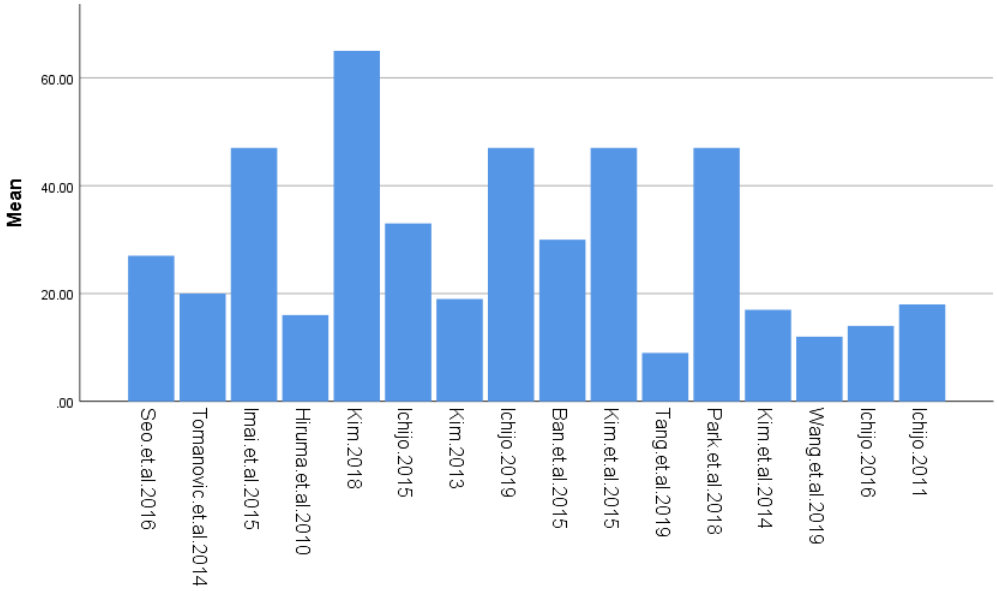

Figure 4.6 Number of individuals with light cupula in each article (ranges from 9 to 47).

Table 4.1

Differential diagnosis between light cupula. Canalolithiasis, Cupulolithiasis, and central pathology based on the direction, latency, persistency, and fatigability of nystagmus with null plane being either present or absent.

	Light Cupula	**Horizontal Canal Canalolithiasis**	**Central pathology**	**Cupulolithiasis (Heavy Cupula)**
Geotropic DCPN	+	+	+	-
Latency	-	+	-	-
Persistency	+	-	+	+
Fatigability	-	+	-	-
Null plane	+	-	-	+

On the contrary there are some limitations with these articles which can be rectified as a future direction. The first limitation is that although all articles were able to successfully document atleast more than one individual with light cupula, most of the articles (11) had a very weak study design, thus statistically limiting themselves. The other limitation is the inability to successfully come up with a treatment method as individuals with light cupula cannot only be diagnosed but must also be treated as the symptoms do not fade over time. Most of the articles (8) did not rule out the presence of central pathology that may also mimic the symptoms of light cupula. In some articles (6) a clear cut differentiation between heavy cupula, canalolithiasis, and heavy endolymph were not given. The other limitation was the mention of a self-cleansing mechanism within the body to light debris by Ichijo in 2019 as the theory of self cleansing mechanism within the light debris was ruled out by Kim et al.,(2018) and Ichijo failed to oppose the theory by Kim and colleagues. The possibility of light debris in light cupula can be ruled out as individuals with light debris can show significant progress on canalith repositioning maneuvers similar to heavy cupula as the debris,

regardless of whether it is heavy or light, can be channelled back to the utricle on CRM (C. H. Kim & Hong, 2018).

Thus, from the above systematic review it can be implied that the symptoms presented in individuals with light cupula is still a dilemma to confirm the presence of it and an effective diagnostic tool must be established to identify the light cupula to enable differential diagnosis from other disorders of BPPV and vertigo of a central origin. Overall, there has been no definitive effective treatment that is available for individuals with light cupula. The existing canalith repositioning maneuvers and other treatment options cannot completely cure the disease, although some treatment modalities have been shown to have minimal progress. The treatment discussed in the articles cannot remove the presence of any potential pathogenic factors that causes this light cupula. Even after thorough discussion, the pathophysiology of light cupula still remains unclear with further research warranted on the pathophysiology and treatment. Studies with temporal bone enable researchers to have a better understanding of the cupula and the molecular basis of the light cupula phenomena. These studies help clinicians better understand direction-changing positional nystagmus and come up with better treatment options.

Chapter 5

SUMMARY AND CONCLUSION:

BPPV is the most common vestibular pathology found in individuals with symptoms of vertigo and it has two forms which is canalolithiasis and cupulolithiasis. However, there is one condition where the condition seems to mimic the symptoms of BPPV, but actually is not a BPPV and that condition happens to be the light cupula. The light cupula is a condition wherein the specific gravity of the cupula is comparatively lesser than the endolymph of the semicircular canals. Possible reasons for the cupula to have reduced specific gravity may include vestibular migraine, meningitis, labyrinthitis, SSNH, CNS disorders, such as brainstem stroke, cerebellar tumors, and HIV encephalopathy. The pathophysiology behind light cupula includes five possible theories; light debris theory, heavy endolymph theory, lighter cupula theory, density theory and utricular macular theory. The concept of the light cupula, although described in 2002, has only been widely discussed recently with the presence of more previously published literature within the decade ranging from original articles to case reports. Individuals with canalolithiasis present with characteristics of geotropic nystagmus, individuals with cupulolithiasis present with persistent nystagmus, and individuals with vertigo of a central origin present with nystagmus that can be persistent and geotropic. The light cupula is often misdiagnosed with these conditions as characteristics of these conditions are similar to that of the light cupula. Audiologists must be aware of the light cupula phenomenon and must be able to differentially diagnose central Nystagmus, Canalolithiasis, and heavy Cupula. Considering the challenges in diagnosis, treatment, and differential diagnosis, there is a need to carry out a systematic review of articles and document the diagnosis and treatment of light cupula that can aid clinicians in differential diagnosis and treatment. The following

study is a systematic review that utilized the latest PRISMA guidelines for systematically reviewing the articles and PICOS framework for determining the inclusion criteria for the study. Articles published from various peer-reviewed journals were searched in different databases like Pubmed, Pubmed Central, Science direct, Web of Science, Shodh Ganga, Google Scholar, and J-GATE. For search strategy in PubMed and PubMed central, the BOOLEAN operations such as AND, OR, and NOT were used, and for other databases, its respective keyword extraction was used. The keywords used were light cupula, heavy endolymph, persistent geotropic nystagmus, directional changing positional nystagmus, DCPN, and positional alcoholic nystagmus. Out of 2886 articles that have been screened, 16 articles were finalized based on the inclusion and exclusion criteria. All 16 articles underwent quality analysis and level of evidence testing with no articles rejected based on the level of evidence and quality analysis. Out of the 16 articles, 14 articles discusses that the supine roll test being appropriate for diagnosing light cupula with the help of an objective videonystagmography, and eight articles discussed about the possible treatment options for light cupula. Overall, the supine roll test is the accepted test to diagnose the light cupula and the vestibular retraining therapy such as the Brandt-Daroff exercise must be tried as a possible treatment option. The symptom of light cupula is persistent geotropic nystagmus with a null plane and the knowledge of this symptom can be useful to differentially diagnose between canalolithiasis, cupulolithiais, and vertigo of central origin. As a future direction, systematic review of case reports must be carried out to get more details and knowledge of the light cupula phenomena.

5.1 Implications

- The study has given us the knowledge of the symptoms and pathophysiology of the light Cupula.
- Emphasis on the possible diagnostic tests to assess light cupula has been provided and the differential diagnosis between light cupula and other disorders has been highlighted.
- The study has also discussed the possible treatment procedures for light cupula which are useful for audiologists and otorhinolaryngologists.

5.2 Limitations

- Based on the systematic review of articles, a definitive treatment procedure for light cupula has not been established.
- The study design for most of the articles were weak with level 4 evidence and were not rejected considering the rarity of the articles.
- A meta-analysis could not be carried out.

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ANNEXURE

QUADAS 2 questionnaire template used as quality analysis in the current systematic review study.

QUADAS-2 tool: Risk of bias and applicability judgments

Domain 1: Patient selection	
A. Risk of bias	
Describe methods of patient selection:	
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear
• **Was a case-control design avoided?**	Yes/No/Unclear
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	
Describe included patients (prior testing, presentation, intended use of index test and setting):	
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 2: Index test(s) ***(if more than 1 index test was used, please complete for each test)***	
A. Risk of bias	
Describe the index test and how it was conducted and interpreted:	
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	

Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 3: Reference standard	
A. Risk of bias	
Describe the reference standard and how it was conducted and interpreted:	
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 4: Flow and timing	
A. Risk of bias	
Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram):	
Describe the time interval and any interventions between index test(s) and reference standard:	
• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear
• **Did all patients receive a reference standard?**	Yes/No/Unclear
• **Did patients receive the same reference standard?**	Yes/No/Unclear
• **Were all patients included in the analysis?**	Yes/No/Unclear
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR