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Restriction of salt intake and other dietary modifications for the treatment of Ménière's disease or syndrome (Protocol)

Hussain K, Murdin L, Schilder AGM

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[Intervention Protocol]

Restriction of salt intake and other dietary modifications for the treatment of Ménière's disease or syndrome

Kiran Hussain[1], Louisa Murdin[1], Anne GM Schilder[2]

[1]Ear Institute, Faculty of Brain Sciences, University College London, London, UK. [2]evidENT, Ear Institute, Faculty of Brain Sciences, University College London, London, UK

Contact address: Kiran Hussain, Ear Institute, Faculty of Brain Sciences, University College London, London, UK. kiranh@doctors.org.uk.

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine the effectiveness of dietary modifications, specifically restriction of salt, alcohol and caffeine intake, in patients suffering from Ménière's disease or syndrome. We will also review other dietary modifications but we will limit analysis of these studies to a narrative review.

BACKGROUND

Description of the condition

Ménière's disease or syndrome is a chronic inner ear disorder that results in sporadic attacks of vertigo, sensorineural hearing loss, aural fullness and tinnitus. The term 'Ménière's disease' refers to an idiopathic disorder, but a clinically identical presentation can occur secondary to other conditions, such as infections, genetic disorders or trauma, and this is referred to as 'Ménière's syndrome'. In a large US study the prevalence of Ménière's disease was estimated at 200 per 100,000 people (Alexander 2010). It most commonly affects people between the ages of 40 and 60 years, with a slight female preponderance (da Costa 2002). Acute attacks usually occur in clusters, with those affected often being symptom-free for months in between. There is a higher frequency of attacks in the initial period after presentation with an eventual reduction but sustained deterioration in hearing (Moffat 1997). The number of vertiginous episodes has been noted to cease eventually (Silverstein 1989).

At present no 'gold standard' diagnostic test for Ménière's disease exists and the diagnosis is frequently based on the practitioner's assessment of the patient's history and neurotologic evaluation. The American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS) has produced diagnostic guidelines (Alford 1972), which have since been revised twice (Ménière's Guide 1995; Pearson 1985). The guidelines state that a diagnosis can be made if the following criteria are met:

- at least two spontaneous episodes of rotational vertigo lasting at least 20 minutes;
- audiometric confirmation of a sensorineural hearing loss;
- tinnitus and/or a perception of aural fullness.

When patients meet the AAO-HNS criteria and the symptoms are attributed to a specific cause they are classified as having Ménière's syndrome.

Although the pathophysiology of Ménière's disease is unknown, there is thought to be an association with endolymphatic hydrops, which is distortion of the membranous labyrinth due to the over accumulation of endolymph (Hallpike 1938).

At present there is no definitive treatment for Ménière's disease and treatment options range from dietary modification through medication to surgery. Two medications that have been used are betahistine and diuretics. A Cochrane review, which was last updated in 2010, concluded that there was no evidence of a benefit from the use of betahistine in Ménière's (James 2001). Another Cochrane review looked at the use of diuretics and concluded that there was insufficient evidence for or against the use of diuretics in the treatment of Ménière's disease or syndrome, due to the fact that there were no studies that met the review inclusion criteria (Burgess 2006). Other treatment modalities include intratympanic injections of gentamicin or dexamethasone. A Cochrane review on the use of gentamicin found two studies that met the criteria for inclusion and concluded that there was evidence for its use in the treatment of Ménière's disease or syndrome, although it carries a risk of hearing loss (Pullens 2011). Surgical intervention includes a vast number of procedures, which can be classified as destructive and non-destructive. Destructive procedures aim to control the individual's vestibular symptoms by destroying their vestibular function (e.g. labyrinthectomy or vestibular nerve section). Non-destructive procedures are less invasive and aim to alter the natural course of the disease (e.g. endolymphatic sac decompression or insertion of ventilation tubes (grommets)). A relatively recent Cochrane review has looked at surgery for Ménière's disease but identified only two randomised controlled trials, both of endolymphatic sac decompression, neither of which showed a benefit of this surgical procedure (Pullens 2013).

Description of the intervention

It is suggested that high sodium levels may induce endolymphatic hydrops. The observation that water retention can exacerbate the symptoms of Ménière's disease was first documented in 1929 (Dederding 1929). Subsequent uncontrolled studies suggested that the manipulation of salt intake influences the symptoms experienced by those suffering with Ménière's (Furstenberg 1934; Furstenberg 1941). More recent studies of restricted salt intake, usually together with other treatment modalities, such as the use of diuretics, have also suggested better symptom control in patients with Ménière's disease (Klockhoff 1974; Santos 1993). As such, dietary salt restriction is recommended by many clinicians. Excessive reduction in salt intake may, however, in extreme and rare cases result in hyponatraemia, although this is more commonly due to specific diseases. Hyponatraemia is associated with conditions ranging from mood disturbance to cerebral oedema and possible death in extreme cases (Thompson 2010.)

Other dietary modifications include limiting the intake of alcohol and caffeine (Luxford 2013). Both alcohol and caffeine can result in vasoconstriction and a reduction in the blood supply to the inner ear, which may make patients' symptoms worse. Although no recognised adverse effects of reducing alcohol consumption in normal individuals have been documented, reduction in people who have a dependency on alcohol can result in withdrawal symptoms such as psychotic episodes and delirium tremens (Stern 2010). Caffeine is a commonly ingested substance found in liquid form in beverages such as tea and coffee, and it is also found in food such as chocolate. Caffeine is a recognised ergogenic aid even at physiological levels and enhances concentration and alertness whilst reducing fatigue. A reduction in the intake of caffeine may lead to withdrawal effects in individuals who are accustomed to its effects, which can result in symptoms ranging from mood disturbance to headaches (Pesta 2013).

How the intervention might work

Disturbance of the volume and/or electrolyte composition of the endolymph is considered to be the cause of the symptoms experienced by patients with Ménière's disease. High dietary intake of salt can affect the concentrations of electrolytes in the blood, which in turn affects the composition of the endolymph. It has been reported that high salt intake can contribute to attacks and it therefore follows that dietary modification can be used to control both the volume and composition of the endolymph (Stahle 1984). Fluctuation in the composition and volume of the endolymph is considered to contribute to the fluctuating nature of the symptoms experienced by sufferers of Ménière's.

Why it is important to do this review

Dietary modifications, including restriction of salt, caffeine and alcohol intake, are widely recommended to those suffering with Ménière's. It is therefore important to conduct a systematic review of randomised controlled trials of these dietary modifications in patients suffering with Ménière's disease.

OBJECTIVES

To determine the effectiveness of dietary modifications, specifically restriction of salt, alcohol and caffeine intake, in patients suffering from Ménière's disease or syndrome. We will also review other dietary modifications but we will limit analysis of these studies to a narrative review.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled trials. We will also include cluster-randomised and cross-over trials.

Types of participants

Adult patients, aged 18 and over, with a diagnosis of Ménière's disease or syndrome.

We will classify studies according to the diagnostic criteria used to diagnose Ménière's disease or syndrome. We will grade those using the AAO-HNS criteria, or equivalent, to define probable, definite or certain Ménière's as grade 'I' studies and the remaining studies as grade 'II'.

Settings will include both the community and hospital.

Types of interventions

The experimental intervention of interest is dietary modification, specifically, salt, caffeine and alcohol restriction or substitution (or both). The control intervention will be no modification of these agents or the use of a placebo. We will also identify studies where other dietary modifications are investigated but we will limit analysis of these studies to a narrative review.

The main comparators will be placebo or no alteration in diet.

The main comparison pairs are:

- dietary restriction of salt *versus* no restriction or placebo;
- dietary restriction of caffeine *versus* no restriction or placebo;
- dietary restriction of alcohol *versus* no restriction or placebo.

Other possible comparison pairs include:

- dietary restriction of salt *versus* dietary restriction of caffeine;
- dietary restriction of salt *versus* dietary restriction of alcohol;
- dietary restriction of alcohol *versus* dietary restriction of caffeine;
- dietary restriction of salt + caffeine *versus* no restriction or placebo;
- dietary restriction of salt + alcohol *versus* no restriction or placebo;
- dietary restriction of alcohol + caffeine *versus* no restriction or placebo.

We will exclude studies where dietary modification plus another treatment modality (e.g. a pharmacological agent) is used due to the potential for interactive effects. We will include studies where multiple dietary restrictions are used in conjunction but we will note this note in the analysis. We expect that there will be variability as to the level and duration of dietary modification, but we will note this in the analysis.

Types of outcome measures

We will analyse the following outcomes in the review, but they will not be used as a basis for including or excluding studies.

Primary outcomes

- Control of vertigo or decrease in vertigo attacks, as suggested by the AAO-HNS* (Ménière's Guide 1995), using the results of the various questionnaire-based assessment tools including the Vertigo Symptom Scale, the Vertigo Dizziness Imbalance Questionnaire and the Dizziness Handicap Inventory amongst others.
- Adverse effects, based on patient-reported symptoms as well as the results of the specific questionnaires including the Vertigo Symptom Scale, the Vertigo Dizziness Imbalance Questionnaire and the Dizziness Handicap Inventory amongst others.

Secondary outcomes

- Hearing: progression of hearing loss, as measured by a pure-tone audiogram.
- Severity of tinnitus, as measured by using patient-reported questionnaire scores such as the Vertigo Dizziness Imbalance Questionnaire.
- Perception of aural fullness, as measured by using patient-reported questionnaire scores such as the Vertigo Dizziness Imbalance Questionnaire.
- Functional impairment and disability, using the results of the various questionnaires, particularly the Dizziness Handicap Inventory.
- Overall changes in well-being and quality of life, as reported in the Dizziness Handicap Inventory Questionnaire.

*The AAO-HNS Committee on Hearing and Equilibrium proposed the "control of vertigo" as a main objective outcome measure when assessing therapy in Ménière's disease. The number of attacks six months prior to treatment are compared to the number in the period between 18 and 24 months following treatment. The resulting number indicates the extent of "control of vertigo". The AAO-HNS further divides the control of vertigo into classes, where Class A (CoV = 0) is complete control and class B (CoV 1 to 40) is substantial control. They recommend a period of at least two years of follow-up in order to assess fully the effect of the intervention. We will also consider studies with shorter periods of follow-up for this review.

We also anticipate various questionnaire-based assessment tools being used in the different studies, including the Vertigo Symptom Scale (VSS), the Vertigo Dizziness Imbalance Questionnaire

and the Dizziness Handicap Inventory amongst others. We will include all forms of questionnaire that address the patient's perception of their symptoms if used consistently. These questionnaires will enable us to assess the impact on the patients' quality of life, functional impairment and disability.

The instruments to assess the outcomes of interest are therefore pure-tone audiograms, which will address any change in hearing loss or its progression (or both), and various questionnaires that will address the remaining primary and secondary outcome measures.

Search methods for identification of studies

The Cochrane ENT Information Specialist will conduct systematic searches for randomised controlled trials and controlled clinical trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

Electronic searches

Published, unpublished and ongoing studies will be identified by searching the following databases from their inception:

- Cochrane Register of Studies ENT Trials Register (search to date);
- Cochrane Central Register of Controlled Trials (CENTRAL, current issue);
- PubMed (1946 to date);
- Ovid EMBASE (1974 to date);
- EBSCO CINAHL (1982 to date);
- Ovid AMED (1985 to date);
- Ovid CAB abstracts (1910 to date);
- LILACS (search to date);
- KoreaMed (search to date);
- IndMed (search to date);
- PakMediNet (search to date);
- Web of Knowledge, Web of Science (1945 to date);
- CNKI (searched via Google Scholar to date);
- ClinicalTrials.gov (www.clinicaltrials.gov) (search via the Cochrane Register of Studies to date);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (search to date);
- ISRCTN (www.isrctn.com) (search to date);
- Google Scholar (search to date);
- Google (search to date).

The subject strategies for databases will be modelled on the search strategy designed for CENTRAL (Appendix 1). Where appropriate, these will be combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. (Handbook 2011)).

Searching other resources

We will scan the reference lists of identified publications for additional trials and contact trial authors if necessary. In addition, the Information Specialist will search PubMed, TRIPdatabase, *The Cochrane Library* and Google to retrieve existing systematic reviews relevant to this systematic review, so that we can scan their reference lists for additional trials. We will search for conference abstracts using the Cochrane ENT Trials Register and EMBASE.

Data collection and analysis

Selection of studies

Two authors (KH and LM) will independently scan the initial search results to identify trials that appear to meet the inclusion criteria. They will use abstract review to eliminate any trials that are clearly ineligible. If either author identifies the paper as potentially suitable, we will review the full text of the article. We will resolve disagreements by discussion or, failing that, with the input of the third author (AS).

Data extraction and management

Two authors (KH and LM) will extract data independently. We will use standardised data extraction forms. There will be no blinding of journal, author names or affiliations.

For each study, we will extract the following information:

- study design;
- duration of study;
- randomisation;
- allocation concealment;
- number of participants;
- setting of study;
- diagnostic criteria;
- exclusion criteria;
- age and sex distribution of participants;
- country of recruitment;
- co-morbidity;
- date of study;
- number of intervention groups;
- type of dietary modification;
- outcomes measured and definition of outcomes;
- missing data and final sample size.

Assessment of risk of bias in included studies

KH and LM will undertake assessment of the risk of bias of the included trials independently, with the following taken into consideration, as guided by the*Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We will use the Cochrane 'Risk of bias' tool in RevMan 5.3 (RevMan 2014), which involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias.
We will also judge two extra domains: the certainty of the diagnosis of Ménière's (see also Types of participants) and the quality of outcome assessment (see Types of outcome measures). However, we will report and address these domains in the 'Characteristics of included studies' table rather than consider them as a risk of bias domain.

Measures of treatment effect

We will use appropriate statistical tests based on the data. For dichotomous data we will calculate an odds ratio (OR), risk ratio (RR) and risk difference (RD, also called absolute risk reduction), as well as the number of participants needed to treat to avoid a case of the disease (number needed to treat to benefit - NNTB) from the pooled results, based on the median risk in the control groups.
For the intervention effect measures of continuous data we plan to calculate the difference in means (mean difference, MD) between the groups, provided that different studies are using the same scale of measurement. We plan to calculate the standardised mean difference (SMD) if different scales are used.
For ordinal data we will check to see whether the scale used has been validated. Depending on the number points in these scales (and how the data were reported), we will either dichotomise these or analyse them as continuous outcomes.

Unit of analysis issues

Cluster-randomised trials

Cluster-randomised trials allocate groups instead of individuals. The participants in each group may be related in some way, therefore this needs to be taken into account in the analysis otherwise there is a unit of analysis error, which would produce an artificially smaller P value and a risk of false positive results. For this purpose we will use a special statistical method, as detailed in chapter 16.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011), with the appropriate statistical advice.

Cross-over trials

Cross-over trials may have a carry-over effect. For this reason we will use data from cross-over trials only if data from before the cross-over can be obtained.

Multi-arm studies

If we find studies with more two groups (e.g. two or more active treatments being tested against placebo), we will establish which of the comparisons are relevant to the systematic review and relevant to each of the meta-analyses that we may implement. If the study design uses independent groups, we will treat the study as independent comparisons. However, if we encounter participants that have been included in several groups, there is a risk of unit of analysis error and we will ensure that participants are only included once per meta-analysis as per chapter 16.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011).

Repeated observations on participants

In longer studies, results may be recorded at more than one time interval. In order to avoid unit of analysis error when combining these results in a single meta-analysis (and therefore counting the same participants in more than one comparison), we will aim to retrieve individual patient data and perform a time-to-event analysis using the whole follow-up for each participant.
We will also aim to establish short-term (three months), medium-term (12 months) and long-term (over 24 months) effects.

Dealing with missing data

When the required data are not available in published accounts, we will contact the principal investigator to request the data. If no useful response is obtained, we will treat missing data differently if they are judged to be 'missing at random', in which case the effect may not be important, or 'not missing at random', where missing data may affect the overall result. In the first case, the data can be ignored. If large numbers of drop-outs are found, we will conduct sensitivity analysis with different assumptions.
We will be alert to potential mislabelling or non-identification of standard errors and standard deviations. Unless missing standard deviations can be derived from confidence intervals we will not assume values for analysis purposes.

Assessment of heterogeneity

We will assess studies for clinical, statistical and methodological heterogeneity. If sufficient non-heterogeneous studies are found, we will subject the data to a meta-analysis with a fixed-effect model

where applicable. If there is statistical heterogeneity, we will use random-effects modelling. If the level of heterogeneity and the appropriate model that should be used is unclear, we will take statistical advice.

Assessment of reporting biases

If an individual meta-analysis contains at least 10 studies, we will assess publication bias using funnel plots and Egger's test.

Data synthesis

Analysis will be on an intention-to-treat basis. If the data are compatible we will combine data to give summary measures of effect. If data are missing we will use available case analysis - using all data (as reported) for all randomised patients available at the end of the trial/time point of interest, regardless of actual treatment received.

Subgroup analysis and investigation of heterogeneity

If sufficient data are available, we will undertake subgroup analysis based on:

- meeting/not meeting the AAO-HNS criteria;
- the treatment protocol (i.e. the nature of salt, caffeine or alcohol restriction and the duration of dietary modification).

Sensitivity analysis

We will conduct a sensitivity analysis by comparing the effect of the inclusion and exclusion of studies with different risk of bias. If we deem studies to have a high risk of bias, we will exclude them from the analysis.

GRADE and 'Summary of findings' table

We will use the GRADE approach to rate the overall quality of evidence. The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct and we will apply this in the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high quality of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low quality implies that any estimate of effect obtained is very uncertain.

The GRADE approach rates evidence from RCTs that do not have serious limitations as high quality. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision; and
- publication bias.

We will include a 'Summary of findings' table, constructed according to the recommendations described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). We will include the following comparisons and outcomes in our 'Summary of findings' table(s):

- proportion of patients with control of vertigo or decrease in vertigo attacks (as suggested by the AAO-HNS);
- proportion of patients with adverse effects;
- proportion of patients with loss or gain of hearing/ reduction in progression of hearing loss;
- proportion of patients with a reduction in the severity of tinnitus;
- proportion of patients with a reduction in the perception of aural fullness;
- functional impairment and disability;
- overall changes in well-being and quality of life.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Endolymphatic Hydrops] explode all trees
#2 meniere*
#3 (endolymphatic or cochlea*) and hydrops
#4 (aural or labyrinth*) and (hydrops or syndrome or vertigo)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Diet, Sodium-Restricted] explode all trees
#7 MeSH descriptor: [Food Habits] explode all trees
#8 MeSH descriptor: [Diet Therapy] this term only
#9 MeSH descriptor: [Sodium, Dietary] explode all trees
#10 MeSH descriptor: [Caffeine] explode all trees
#11 MeSH descriptor: [Drinking Behavior] explode all trees
#12 salt* or sodium*
#13 Caffein* or decaffein* or "de caffein*" or de-caffein* or coffee or tea or alcohol*
#14 (diet* or food) and (restrict* or modif* or habit* or free*)
#15 nutrition*
#16 Any MeSH descriptor with qualifier(s): [Diet therapy - DH]
#17 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 #5 and #17
#19 MeSH descriptor: [Endolymphatic Hydrops] explode all trees and with qualifier(s): [Diet therapy - DH]
#20 #18 or #19

CONTRIBUTIONS OF AUTHORS

KH will obtain studies. KH and LM will select studies, extract data and assess risk of bias. KH will enter data into RevMan, and carry out and interpret the analysis. AS will provide advice as needed throughout. KH, LM and AS will draft the final review. KH will have responsibility for updating and maintaining the review.

DECLARATIONS OF INTEREST

Kiran Hussain: Kiran Hussain is a recipient of a small grant from the Ménière's Society (charity).

Louisa Murdin: none known.

Anne GM Schilder: Professor Anne Schilder is joint Co-ordinating Editor of Cochrane ENT, but had no role in the editorial process for this protocol. Her evidENT team at UCL is supported by her NIHR Research Professorship award with the remit to develop a UK infrastructure and programme of clinical research in ENT, Hearing and Balance. Her institution has received a grant from GSK for a study on the microbiology of acute tympanostomy tube otorrhoea.

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- National Institute for Health Research, UK.

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