Effect of pre-transplant vitamin D level on liver transplantation outcome

Citation

Shalika Kurukulaarachchi, Kausala Sithamparapillai, Dileepa Ediriweera, Madunil Niriella. Effect of pre-transplant vitamin D level on liver transplantation outcome. PROSPERO 2023 CRD42023489304 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023489304

Review question

What is the effect of pre-transplant vitamin D level on the outcome of

patients following liver transplantation?

Searches

We have followed the guidance in PRISMA-S to plan and describe the search process for the review in order to minimise bias in our search results. We will adapt the literature search strategy to suit each database. We will use both text words and medical subject heading terms.

Electronic searches: We will conduct a literature search to identify all the published randomized controlled trials, quasi-randomized trials, case control studies and cohort studies with a comparator arm. We will identify all the potential studies published in English as full text. We will search the following electronic databases to identify potential studies:

- MEDLINE through PubMed (1994 to present)
- Cochrane Central Register of Controlled Trials (CENTRAL)

Searching other resources: We will search the reference lists of all included studies and reference lists of published review articles as well

Search strategy

https://www.crd.york.ac.uk/PROSPEROFILES/489304_STRATEGY_20231205.pdf

Types of study to be included

We will include the Randomized Controlled trials (RCTs), quasi-randomized trials, case-control studies, and cohort studies with a comparator arm. We will include studies published as full text and in English only. We will not apply any restriction to our search based on year of publication or outcomes assessed.

Condition or domain being studied

Liver transplantation (LT) is the definitive treatment for many liver diseases. Advancement in the immunosuppressive therapy has resulted in a reduction in the incidence of graft rejection. However acute cellular rejection following LT still occurs in about 15-25% of LT recipients and the reported incidence widely vary among studies. Rejection is immune mediated.

There is evolving evidence that Vitamin D plays an important role in anti- inflammatory and immuno modulatory functions. Vitamin D is believed to play a role in immune tolerance. Therefore, vitamin D deficiency may contribute to rejection following transplantation through its immuno-modulatory properties. In addition, vitamin D deficiency may increase the incidence of infections following LT which in turn will lead to increased duration of hospital stay and mortality.

Vitamin D deficiency is highly prevalent in patients with end stage liver disease and patients listed for LT The evidence on the association between pre-transplant vitamin D level and LT outcome is unclear.

This systematic review and meta-analysis aims to systematically collect and combine all the evidence evaluating the pre-transplant vitamin D level and its association with liver transplantation outcome in order to provide the best evidence at present.

Participants/population

Types of participants: We will include all patients underwent liver transplantation irrespective of age and regardless of aetiology.

Intervention(s), exposure(s)

Exposure of interest: Pre-transplant serum vitamin D level and any interventions to correct any deficiency

Comparator(s)/control

The group with normal vitamin D levels will be compared to the group with vitamin D deficiency/insufficiency

Context

We will not exclude a study meeting the eligibility criteria if it does not report any one of the predefined outcomes.

Main outcome(s)

Outcome measures will be:

● Primary outcome: Graft rejection – early rejection episodes (<1 year) and late rejection episodes (after 1 year)

● Secondary outcomes: Mortality, dose of immunosuppressant required during first three months and incidence of infections

Measures of effect

Data on rejection (number of patients with rejection and no rejection in both groups) will be analysed as odds ratio. We

will do meta-analyses only if the participants and the clinical question are similar enough for pooling so that it is meaningful. If a trial includes multiple arms, we will include only the relevant arms.

Dealing with missing data: We will contact original authors to verify key study characteristics and obtain missing numerical outcome data where possible.

Additional outcome(s)

● Secondary outcomes: Mortality, dose of immunosuppressant required during first three months and incidence of infections

Measures of effect

Data on rejection (number of patients with rejection and no rejection in both groups) will be analysed as odds ratio. We will do meta-analyses only if the participants and the clinical question are similar enough for pooling so that it is meaningful. If a trial includes multiple arms, we will include only the relevant arms.

Dealing with missing data: We will contact original authors to verify key study characteristics and obtain missing numerical outcome data where possible.

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Data extraction (selection and coding)

Two reviewers (SK and KS) will independently screen the titles and abstracts for inclusion of all potential studies. The reviewers will label the eligible, potentially eligible, and unclear studies as 'retrieve' and other studies as 'do not retrieve'. Any disagreements between two reviewers will be resolved by another reviewer (MN). Two reviewers (will independently screen the full texts of the studies labelled as 'retrieve' and identify the 'studies for inclusion' and 'ineligible studies'. These reviewers will record the reason for ineligibility. Any disagreements between two reviewers will be resolved by another reviewer . Multiple reports of the same study will be identified as a single study and will record the selection process in sufficient detail to complete a PRISMA flow diagram.

Two reviewers (KS, SK) will extract the following study characteristics of the included studies.

1. General information: Name of the journal, year of publication, and author's name

2. Methods: Study design, date of study, total duration of study, and location.

In RCTs: random sequence generation, allocation concealment, type of blinding, withdrawals and follow-up;

In cohort studies: representativeness of the exposed cohort, selection of the non-exposed cohort, comparability of the cohorts, adequacy of duration of follow-up, and adequacy of follow-up of cohorts.

3. Participants: Number of participants, mean age, gender and aetiology

4. Exposure of interest: Pre-transplant vitamin D level and any interventions to correct any deficiency

5. Outcomes: Number of patients with rejection in both the groups, timing of rejection (<1 year or >1year), mortality, dose of immunosuppressant required during first three months, occurrence of any infections.

6. Notes: Funding for trial, conflicts of interests of trial authors

One of the review authors will copy the data from the data collection form into the Review Manager 5.4.1. The entries will be double-checked by another author.

Risk of bias (quality) assessment

Two review authors (SK, KS) will independently assess the risk of bias for each randomised controlled trial and quasi randomised trial using criteria outlined in the Cochrane Handbook for Systematic Review of Interventions [8]. Any disagreement will be resolved by involving another trial author (MN) as the assessor.

We will assess the risk of bias according to the following domains: random sequence generation; allocation concealment; blinding of participants and personnel; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other biases.

Each potential source of bias will be graded as high, low or unclear. The risk of bias judgement across different studies will be summarised for each of the domains listed. The assessment of the risk of bias will be presented as a 'Risk of bias graph' figure and 'Risk of bias summary' figure.

Two review authors (KS, SK) will independently assess the methodological quality of each cohort study included in the review using Newcastle-Ottawa Scale [9]. Any disagreement will be resolved by involving another trial author (MN) as the assessor.

Strategy for data synthesis

Summary of findings table: We will create a summary of findings table using the following outcomes:

1. Graft rejection

2. Mortality

3. Incidence of infection

ASSESSMENT OF HETEROGENEITY

We will inspect the forest plots to see if the CIs of individual studies are overlapping. We will use the I^2 statistic as well to measure heterogeneity among the studies in each analysis. The interpretation will be roughly as follows: 0% to 40%: might be unimportant; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; and75% to 100%: may represent considerable heterogeneity.

ASSESSMENT OF REPORTING BIASES

We will attempt to contact study authors requesting them to provide missing outcome data. If the missing outcome data cannot be collected, we will do a sensitivity analysis to explore the impact of including such studies in the overall assessment of results.

We will create and examine a funnel plot to explore the possible publication biases if we are able to pool more than 10 studies.

Analysis of subgroups or subsets

We plan to carry out the following subgroup analyses:

1. Children vs. adults

2. Males vs. females

3. Vitamin D correction was done vs. not done

Sensitivity analysis:

We will perform a sensitivity analysis to assess the robustness of our conclusions. This will include restricting the analysis to studies with low risk of bias.

Reaching conclusions:

We will base our conclusions only on findings from quantitative or narrative synthesis of studies included in this review. We will give the reader a clear sense of where the uncertainties in this area are and what the focus of any future research should be.

Contact details for further information

Shalika Kurukulaarachchi

2712sha@gmail.com

Organisational affiliation of the review

None

Review team members and their organisational affiliations

Dr Shalika Kurukulaarachchi. National Hospital of Sri Lanka

Dr Kausala Sithamparapillai. Department of Physiology, University of Jaffna, Sri Lanka

Professor Dileepa Ediriweera. Health Data Science Unit, Faculty of Medicine, University of Kelaniya, Sri Lanka

Professor Madunil Niriella. Department of Medicine, Faculty of Medicine, University of Kelaniya, Sri Lanka

Type and method of review

Meta-analysis, Systematic review

Anticipated or actual start date

14 December 2023

Anticipated completion date

07 March 2024

Funding sources/sponsors

None

Grant number(s)

State the funder, grant or award number and the date of award

None

Conflicts of interest

Language

English

Country

Sri Lanka

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Humans

Date of registration in PROSPERO

23 December 2023

Date of first submission

12 December 2023

Details of any existing review of the same topic by the same authors

None

Stage of review at time of this submission

The review has not started

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication

details in due course.

Versions

23 December 2023

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