**PRISMA 2009 Checklist for the four meta-analyses**

1. **Insulin Receptor Knockout meta-analysis.**

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| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| **TITLE**  |
| Title  | 1 | Identify the report as a systematic review, meta-analysis, or both.  | Not applicable (NA) since meta-analyses is one of the methods used to address the question and not the only method.  |
| **ABSTRACT**  |
| Structured summary  | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.  | Main paper: Page 1 |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of what is already known.  | Main paper: Page 8, Line 223 |
| Objectives  | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | Main paper: Page 11, Line 327Supplementary information 1: Page 2, Table 2 |
| **METHODS**  |  |
| Protocol and registration  | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | PROSPERO Registration ID: CRD42019132379 |
| Eligibility criteria  | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | NA |
| Information sources  | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | Main paper: Page 11, Line 327Supplementary information 1: Page 2, Table 2 |
| Search  | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | Main paper: Page 11, Line 327Supplementary information 1: Page 2, Table 2 |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  | Main paper: Page 11, Line 327Supplementary information 1: Page 2, Table 2 |
| Data collection process  | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | Data extraction: Supplementary information 1: Pages 1 and 2No process for obtaining and confirming data from investigators, only published data used.  |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.  | Supplementary information 1: Page 1 |
| Risk of bias in individual studies  | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | NA |
| Summary measures  | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | Difference in means with the 95% Confidence Intervals of the means. (Supplementary information 1: Page 1) |
| Synthesis of results  | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.  | NA |
| Risk of bias across studies  | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | NA |
| Additional analyses  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | NA |
| **RESULTS** |
| Study selection  | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | Main paper: Page 11, Table 1 |
| Study characteristics  | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.  | Supplementary information 1: Pages 1 and 2 |
| Risk of bias within studies  | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | NA |
| Results of individual studies  | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.  | 1. Supplementary information 1: Page 2, Table 2
2. Main paper: Figures 3 to 6
3. Main paper: Table 4
 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | Main paper: Pages 16, Line 471 |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | NA |
| Additional analysis  | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | NA |
| **DISCUSSION** |
| Summary of evidence  | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).  | Main paper: Pages 26-29 |
| Limitations  | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  | Main paper: Pages 26-29 |
| Conclusions  | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | Main paper: Pages 30-32 |
| **FUNDING**  |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.  | Main paper: Page 32 |

1. **Insulin Degrading Enzyme (IDE) meta-analysis**

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| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| **TITLE**  |
| Title  | 1 | Identify the report as a systematic review, meta-analysis, or both.  | Not applicable (NA) since meta-analyses is one of the methods used to address the question and not the only method.  |
| **ABSTRACT**  |
| Structured summary  | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.  | Main paper: Page 1 |
| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of what is already known.  | Main paper: Page 8, Line 239 |
| Objectives  | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | Main paper: Page 11, Line 337Supplementary information 1: Page 4, Table 3 |
| **METHODS**  |  |
| Protocol and registration  | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | PROSPERO registration ID: CRD42019140619 |
| Eligibility criteria  | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | NA |
| Information sources  | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | Main paper: Page 11, Line 337Supplementary information 1: Page 4, Table 3 |
| Search  | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | Main paper: Page 11, Line 337Supplementary information 1: Page 4, Table 3 |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  | Main paper: Page 11, Line 337Supplementary information 1: Page 4, Table 3 |
| Data collection process  | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | Data extraction: Supplementary information 1: Pages 1 and 4No process for obtaining and confirming data from investigators, only published data used. |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.  | Supplementary information 1: Page 1 |
| Risk of bias in individual studies  | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | NA |
| Summary measures  | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | Difference in means with the 95% Confidence Intervals of the means. (Supplementary information 1: Page 1) |
| Synthesis of results  | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.  | NA |
| Risk of bias across studies  | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | NA |
| Additional analyses  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | NA |
| **RESULTS** |
| Study selection  | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | Main paper: Page 12, Table 2 |
| Study characteristics  | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.  | Supplementary information 1: Pages 1 and 4 |
| Risk of bias within studies  | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | NA |
| Results of individual studies  | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.  | 1. Supplementary information 1: Page 4
2. Main paper: Figure 7
3. Main paper: Table 5
 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | Main paper: Page 18, Line 570 |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | NA |
| Additional analysis  | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | NA |
| **DISCUSSION** |
| Summary of evidence  | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).  | Main paper: Pages 26-29 |
| Limitations  | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).  | Main paper: Pages 26-29 |
| Conclusions  | 26 | Pages 37-43 | Main paper: Pages 30-32 |
| **FUNDING**  |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.  | Main paper: Page 32 |

1. **Insulin Suppression by Diazoxide (DZX) meta-analysis.**

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| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
| **TITLE**  |
| Title  | 1 | Identify the report as a systematic review, meta-analysis, or both.  | Not applicable (NA) since meta-analyses is one of the methods used to address the question and not the only method.  |
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| **INTRODUCTION**  |  |
| Rationale  | 3 | Describe the rationale for the review in the context of what is already known.  | Main paper: Page 8, Line 239 |
| Objectives  | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | Main paper: Page 12, Line 352Supplementary information 1: Page 5, Table 4 |
| **METHODS**  |  |
| Protocol and registration  | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | PROSPERO Registration ID: CRD42020141688 |
| Eligibility criteria  | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | NA |
| Information sources  | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | Main paper: Page 12, Line 352Supplementary information 1: Page 5, Table 4 |
| Search  | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | Main paper: Page 12, Line 352Supplementary information 1: Page 5, Table 4 |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  | Main paper: Page 12, Line 352Supplementary information 1: Page 5, Table 4 |
| Data collection process  | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | Data extraction: Supplementary information 1: Pages 1 and 5No process for obtaining and confirming data from investigators, only published data used. |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.  | Supplementary information 1: Page 1 |
| Risk of bias in individual studies  | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.  | NA |
| Summary measures  | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | Difference in means with the 95% Confidence Intervals of the means. (Supplementary information 1: Page 1) |
| Synthesis of results  | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.  | NA |
| Risk of bias across studies  | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | NA |
| Additional analyses  | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.  | NA |
| **RESULTS** |
| Study selection  | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.  | Main paper: Page 12, Table 3 |
| Study characteristics  | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.  | Supplementary information 1: Pages 1 and 5 |
| Risk of bias within studies  | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | NA |
| Results of individual studies  | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.  | 1. Supplementary information 1: Page 5
2. Main paper: Figure 8
3. Main paper: Table 6
 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | Main paper: Page 19, Line 601 |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | NA |
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| Conclusions  | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | Main paper: Pages 30-32 |
| **FUNDING**  |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.  | Main paper: Page 32 |

1. **Insulin Suppression by Octreotide (OCT) meta-analysis**

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| **Section/topic**  | **#** | **Checklist item**  | **Reported on page #**  |
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| **INTRODUCTION**  |  |
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| Objectives  | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | Main paper: Page 12, Line 352Supplementary information 1: Page 6, Table 5 |
| **METHODS**  |  |
| Protocol and registration  | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | PROSPERO Registration ID for CRD42020141464 |
| Eligibility criteria  | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.  | NA |
| Information sources  | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | Main paper: Page 12, Line 352Supplementary information 1: Page 6, Table 5 |
| Search  | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.  | Main paper: Page 12, Line 352Supplementary information 1: Page 6, Table 5 |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  | Main paper: Page 12, Line 352Supplementary information 1: Page 6, Table 5 |
| Data collection process  | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.  | Data extraction: Supplementary information 1: Pages 1 and 6No process for obtaining and confirming data from investigators, only published data used. |
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| Study characteristics  | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.  | Supplementary information 1: Pages 1 and 6 |
| Risk of bias within studies  | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).  | NA |
| Results of individual studies  | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.  | 1. Supplementary information 1: Page 6
2. Main paper: Figure 8
3. Main paper: Table 6
 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency.  | Main paper: Page 19, Line 601 |
| Risk of bias across studies  | 22 | Present results of any assessment of risk of bias across studies (see Item 15).  | NA |
| Additional analysis  | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).  | NA |
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| Summary of evidence  | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).  | Main paper: Pages 26-29 |
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| Conclusions  | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research.  | Main paper: Pages 30-32 |
| **FUNDING**  |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.  | Main paper: Page 32 |

*From:*  Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097