INPLASY PROTOCOL

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The Relationship between Early Stage of Diabetic Nephropathy and Soluble Klotho Proteins: A Systematic Review and a Network Meta-Analysis

Li, Y[1]; Chen, X[2]; Gong, X[3]; He, D[4]; Cheng, X[5]; Du, W[6].

Review question / Objective: **The present network meta-analysis investigates the relationship between soluble Klotho proteins and early-stage DN.**
Eligibility criteria: **I. Patients/population: A study would be included if it studied or participants were patients diagnosed with early-stage DN. The degree of DN was informed by the Chronic Kidney Disease-Kidney Disease Outcomes Quality Initiative (CKD-KDOQI) and the Urine Albumin-Creatinine Ratio (UACR). Participants with diabetic nephropathy were classified into three: based on UACR, we obtained the following classes;a. Normoalbuminuria: < 30 mg/g of creatinineb. Microalbuminuria: 30 to 299 mg/g of creatininec. Macroalbuminuria: ≥ 300 mg/g of creatinine.The early stage of DN will be defined as CKD stages 1 to 2 or microalbuminuria.I. Intervention: Standard or no care. However, a detailed analysis of the levels of soluble klotho proteins was performed.II. Comparison: A comparison will be made with the rest of the stages of DN.III. Outcomes: The relationship between soluble klotho proteins and the early stage DN. This included both indirect and direct relationships. IV. Randomized-controlled trials (RCTs, like double-blind, single-blind, quadruple-blind, open-label, and triple-blind). Only RCTs with large sample sizes were selected. The following exclusion criteria were implemented in this investigation:I. Study duplicates.II. Studies reporting outcomes are irrelevant to this present study.III. Studies involving a comparison between animal and human specimens. IV. Studies report the relationship between α-klotho proteins and DN. V. Studies published in languages other than English and Chinese language.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 December 2022 and was last updated on 10 December 2022 (registration number INPLASY2022120040).

INTRODUCTION

Review question / Objective: **The present network meta-analysis investigates the relationship between soluble Klotho proteins and early-stage DN.**

Condition being studied: Diabetic nephropathy(DN).

METHODS

Participant or population: Patients diagnosed with early-stage Diabetic nephropathy(DN).

Intervention: Standard or no care. However, a detailed analysis of the levels of soluble klotho proteins was performed.

Comparator: The rest of the stages of DN.

Study designs to be included: Randomized-controlled trials (RCTs, like double-blind, single-blind, quadruple-blind, open-label, and triple-blind). Only RCTs with large sample sizes were selected.

Eligibility criteria: I. Patients/population: A study would be included if it studied or participants were patients diagnosed with early-stage DN. The degree of DN was informed by the Chronic Kidney Disease-Kidney Disease Outcomes Quality Initiative (CKD-KDOQI) and the Urine Albumin-Creatinine Ratio (UACR). Participants with diabetic nephropathy were classified into three: based on UACR, we obtained the following classes;a. Normoalbuminuria: < 30 mg/g of creatinineb. Microalbuminuria: 30 to 299 mg/g of creatininec. Macroalbuminuria: ≥ 300 mg/g of creatinine.The early stage of DN will be defined as CKD stages 1 to 2 or microalbuminuria.I. Intervention: Standard or no care. However, a detailed analysis of the levels of soluble klotho proteins was performed.II. Comparison: A comparison will be made with the rest of the stages of DN.III. Outcomes: The relationship between soluble klotho proteins and the early stage DN. This included both indirect and direct relationships. IV. Randomized-controlled trials (RCTs, like double-blind, single-blind, quadruple-blind, open-label, and triple-blind). Only RCTs with large sample sizes were selected. The following exclusion criteria were implemented in this investigation:I. Study duplicates.II. Studies reporting outcomes are irrelevant to this present study.III. Studies involving a comparison between animal and human specimens. IV. Studies report the relationship between α-klotho proteins and DN. V. Studies published in languages other than English and Chinese language.

Information sources: EMBASE,the Cochrane Central Register of Controlled Trials, PubMed, CNKI, and Web of Science.

Main outcome(s): We found that sKlotho proteins are low or negligible during the early stages of DN. This suggests that sKlotho proteins could be the new biomarkers for DN in the coming years. This outcome is consistent with findings from other studies.

Quality assessment / Risk of bias analysis: We found transitivity, inconsistency, and heterogeneity across the three participant groups. The global inconsistency in the present study could have resulted from publication bias in the individual studies reporting different outcomes. Inconsistency arises from publication bias in studies reporting EDN, SDM and placebo. Likewise, heterogeneity results from the disparities in study participant groups in individual studies. As with transitivity, the outcomes of the present study are different due to dissimilar interventions.

Strategy of data synthesis: We used the Bayesian approach in this network meta-analysis to establish the relationship between sKlotho proteins and early-stage DN. The direct relationship between sKlotho proteins and early-stage DN was performed using the Liard and DerSimonian random effects to measure pooled odd ratios (OR) and 95% Confidence Intervals (CI). We used the I2 statistic to assess statistical heterogeneity, where values above 50% were considered to be substantial (that is, substantial heterogeneity) [25]. Also, we used the I2 statistic to assess global heterogeneity.
We used the Markov Chain Monte Carlo methods in the present network meta-analysis. We used the random-effects model to assess selected data for every aspect through which sKlotho proteins are

associated with the ear stage of DN with reference to the Deviance Information Criterion (DIC), using the least value, using the model.
The underlying transitivity assumption in the present network meta-analysis was assessed by comparing the levels of sKlotho proteins among the participants. The node-splitting method was employed during the assessment of local inconsistency in the analytical model through the separation of evidence linking sKlotho proteins and early-stage DN both directly and indirectly. In this approach, a $p>0.1$ would imply no significant inconsistency.
We used the mean ranks and the Surface Under the Cumulative Ranking Curve (SUCRA) to rank levels of sKlotho proteins among patients with early-stage DN. This was key to concluding the relationship between early-stage DN and sKlotho proteins. Also, we only focused on observations and relationship aspects of interest or relevant to the present study.
We used the R programming language to perform the network meta-analysis. In particular, we used G-plot and G-lay as they support rational data structures like graphs, trees, and networks, which are potent in the present network meta-analysis.

Subgroup analysis: N/A.

Sensitivity analysis: We used the multiple R interpretation approaches, where any value between -1 and 1 implied relationship strength to the to 1 implied relationship strength correlated number of participants in the SDM groups and the corresponding mean. We found a multiple regression of 0.034491, which implies a weak positive correlation between the number of participants in the SDM groups and the corresponding mean.

Country(ies) involved: China.

Keywords: Early-stage DN, diabetic nephropathy, soluble Klotho proteins, microalbuminuria.

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