INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Circulating GDF-15 in relation to the progression and prognosis of chronic kidney disease: A systematic review and dose-response meta-analysis

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Review question / Objective: **During the past decades, although great progress has been achieved in the treatment of chronic kidney disease (CKD), biomarkers for the progression, and prognosis of the disease are still limited. Therefore, it is necessary to develop novel effective indicators for improving the management of CKD patient. Growth differentiation factor-15 (GDF-15) is one of the members of the transforming growth factor β (TGF-β) superfamily, which is also referred to as macrophage inhibitory cytokine-1 (MIC-1). GDF-15 is ubiquitously expressed in a variety of organs and tissues, including immune organs, nervous system, cardiovascular systems, and many others, and its high expression has been shown to be associated with inflammation, metabolic disorder, diabetes mellitus, cardiovascular disease (CVD) and cancer. Circulating GDF-15 is also increased in CKD patients and correlate well with its mRNA expression in kidney tissue, implying kidney is one of the origins of circulating GDF-15. In this study, we aimed to conduct a meta-analysis to systematically evaluate the value of circulating GDF-15 as a progressive and prognostic indicator for CKD. In the meanwhile, we particularly intended to examine whether there are dose-response relationships between GDF-15 and incident events if sufficient data are available.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 19 October 2022 and was last updated on 19 October 2022 (registration number INPLASY2022100076).

INTRODUCTION

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improving the management of CKD patient. Growth differentiation factor-15 (GDF-15) is one of the members of the transforming growth factor β (TGF-β) superfamily, which is also referred to as macrophage inhibitory cytokine-1 (MIC-1). GDF-15 is ubiquitously expressed in a variety of organs and tissues, including immune organs, nervous system, cardiovascular systems, and many others, and its high expression has been shown to be associated with inflammation, metabolic disorder, diabetes mellitus, cardiovascular disease (CVD) and cancer. Circulating GDF-15 is also increased in CKD patients and correlate well with its mRNA expression in kidney tissue, implying kidney is one of the origins of circulating GDF-15. In this study, we aimed to conduct a meta-analysis to systematically evaluate the value of circulating GDF-15 as a progressive and prognostic indicator for CKD. In the meanwhile, we particularly intended to examine whether there are dose-response relationships between GDF-15 and incident events if sufficient data are available.

Condition being studied: Higher circulating GDF-15 levels have been suggested to be associated with CKD progression and have better predictive values for adverse clinical events, such as cardiovascular events, cardiovascular and all-cause mortality, although there were inconsistent reports. However, published data were scattered, and did not give a comprehensive evaluation of the relationship between circulating GDF-15 and the progression and prognosis of CKD.

METHODS

Participant or population: We will include CKD patients who had a minimum follow-up time of 1 year.

Intervention: Circulating GDF-15 levels will be main Exposure/Interventions.

Comparator: Comparing the highest versus lowest, or per unit change in GDF-15 at baseline.

Study designs to be included: prospective cohort, retrospective cohort, or nested case-control design.

Eligibility criteria: Studies would be deemed as eligible if they met the following criteria: (1) studies were prospective cohort, retrospective cohort, or nested case-control design; (2) circulating GDF-15 was designed as an exposure; (3) the study subjects were CKD patients regardless of dialysis; (4) mean follow-up time was more than 1 year; (5) the outcomes were CKD progression (incident ESRD or the decline of eGFR >30%), or the prognosis of CKD patients (all-cause mortality, cardiovascular mortality, or cardiovascular events); (6) multivariable-adjusted hazard ratio (HR) and the 95% confidence interval (CI) were provided; (7) studies were published in English.

Information sources: The electronic databases including Pubmed, EMBASE, and Web of Science will be searched for the information sources.

Main outcome(s): The multivariable-adjusted hazard ratio (HR) and the corresponding 95% confidence interval (CI) will be pooled to estimate the associations of GDF-15 with the risk of the progression and prognosis of CKD. Additionally, dose-response curves will be plotted for some of the included studies that provided adequate information.

Quality assessment / Risk of bias analysis: Study quality of the included studies will be assessed using the Newcastle-Ottawa Scale (NOS) for the included studies.

Strategy of data synthesis: Fixed- or random-effects models were applied to estimate the pooled effect size according to heterogeneity among studies.

Subgroup analysis: Subgroup analysis will be conducted based on study region, patient types, sample size, sample types, follow-up duration, mean age, the percentage of males, and GDF-15 detection method.

Sensitivity analysis: **Sensitivity analyses were performed to confirm the stability of overall pooled HR by removing one study at a time.**

Country(ies) involved: **China.**

Keywords: **Chronic kidney disease; growth differentiation factor-15; progression; prognosis; meta-analysis.**

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