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# Prevalence of Fabry Disease in Patients with Chronic Kidney Disease: A Systematic Review and Meta-analysis

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## ADMINISTRATIVE INFORMATION

**Support -** The present study has not obtained financial support from any funding source.

**Review Stage at time of this submission -** Completed but not published.

**Conflicts of interest -** Uma Ramaswami has no conflict of interest relating to this manuscript. Outside this manuscript: Uma Ramaswami has research grants from Amicus, Intrabio, JCR and Takeda; Uma Ramaswami has received honoraria for advisory boards and/or lecture fee from Amicus, Sanofi and Takeda. The remaining authors have no conflict of interest to report.

**INPLASY registration number:** INPLASY2023100030

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 October 2023 and was last updated on 07 October 2023.

## INTRODUCTION

**Review question / Objective** The objective of this study is to determine the prevalence of Fabry disease among three distinct groups: Chronic Kidney Disease patients undergoing dialysis, recipients of kidney transplants, and individuals diagnosed with Chronic Kidney Disease who are not undergoing renal replacement therapy.

**Rationale** This study is crucial because it determines the prevalence of Fabry disease in three high-risk kidney involvement groups at different disease stages. It also provides insights into research methodologies, diagnostic techniques, the impact of inclusion/exclusion criteria on prevalence rates, and the identification of prevalent pathogenic variants.

**Condition being studied** Fabry disease (FD) is a genetic metabolic disorder caused by GLA gene mutations, leading to deficient α-galactosidase A (α-GalA) enzyme activity. This deficiency results in the buildup of Gb3 and lyso-Gb3 in various cells. Although traditionally seen as an X-linked recessive condition, FD can affect heterozygous females due to random X-inactivation.
FD exhibits a spectrum of phenotypes, including a severe classic form with <1% α-Gal A enzyme activity, often presenting with skin and nerve symptoms in childhood and progressing to kidney

and heart issues later. Late-onset atypical FD, caused by residual α-Gal A enzyme activity, can remain asymptomatic until middle age, primarily affecting the kidneys and heart. Some GLA gene variants initially thought to cause FD have been reclassified as benign, while the significance of others remains uncertain.

## METHODS

**Search strategy** Three reviewers conducted a literature search of PubMed in November 2022. The following terms were used: (fabry disease OR fabry's disease OR Anderson-fabry disease OR alpha-galactosidase A deficiency) which were combined with (dialysis OR hemodialysis OR renal screening OR chronic kidney disease OR end stage renal disease OR kidney replacement therapy OR kidney transplantation). The search was not restricted to studies in English. Additional screening studies were found by crosschecking references.

**Participant or population** Chronic Kidney Disease patients on dialysis, kidney transplant recipients, and those with Chronic Kidney Disease but not on renal replacement therapy.

**Intervention** Not applicable to prevalence meta-analysis.

**Comparator** Not applicable to prevalence meta-analysis.

**Study designs to be included** Studies designed as observational cohort study or cross-sectional study. We decided to incorporate studies published in the form of abstracts and letters to the editors, provided they encompassed the requisite data. Additionally, we included studies featuring small cohorts that specifically identified a limited number of FD cases and were published as either case reports or case series, contingent upon the inclusion of essential information, such as the total population size.

**Eligibility criteria** The criteria for study inclusion were: (1) studies designed as observational cohort study or cross-sectional study, (2) prevalence data were reported as number of confirmed cases over sample size, reported on an individual basis; (3) the study population consisted of kidney patients, regardless of intervention (i.e. hemodialysis, peritoneal dialysis, transplantation, etc.); (4) the study should not have preselected cohorts.

**Information sources** The main source of information was Pubmed, an electronic database, searching for all articles published up to November 2022.

**Main outcome(s)** The main outcome is the prevalence of Fabry disease among individuals with chronic kidney disease.

**Additional outcome(s)** Additional outcomes are the GLA gene variants reported by the included studies (classical, late-onset, and of uncertain significance), and the prevalence of fabry disease by sex.

**Data management** The search for studies was carried out by 2 authors independently, the inclusion of articles was evaluated by 3 authors using a voting system.

**Quality assessment / Risk of bias analysis** The quality of all studies included was investigated using the JBI (Joanna Briggs Institute) Prevalence Critical Appraisal Tool. The tool is a nine-question questionnaire with four possible responses: yes, no, unclear or not applicable. Where disagreements among the reviewers occurred, ratings were discussed until a consensus was reached.

**Strategy of data synthesis** We calculated Fabry disease prevalence as percentages for each study and employed a random-effects meta-analysis with DerSimonian and Laird variance estimation due to the diverse range of studies. Data was transformed using the Freeman and Tukey double arcsine method to handle extreme proportions, and separate subgroup analyses were performed for patients on dialysis, kidney transplant recipients, and those with Chronic Kidney Disease but not on renal replacement therapy. Heterogeneity was assessed using Chi-squared and I-squared statistics, and publication bias was evaluated through Begg's funnel plot and Egger's weighted regression, with additional methods in the Supplementary material. Statistical analysis was conducted using R software (version 4.2.2) and relevant packages (meta, metafor, metagear) to provide comprehensive insights into Fabry disease prevalence across subgroups.

**Subgroup analysis** Subgroup analysis was performed in all three groups, regardless of heterogeneity, considering the type of population (i.e. in the case of dialysis population, hemodialysis alone or including in addition peritoneal dialysis), the inclusion criteria of each particular study (inclusion of patients already diagnosed with Fabry disease and inclusion only of patients with CKD of unknown etiology), sample size (greater or equal

vs. lesser than 1000), publication year (before vs. after 2010), presence of female gender.

**Sensitivity analysis** Sensitivity analysis was conducted excluding low quality and outlying studies, an outlying study was defined principally as one with an externally standardized residual (also called studentized residual) bigger than 3. At the same time, to prevent misleading conclusions for the Freeman-Tukey double arcsine transformation, we conducted a sensitivity analysis using logit transformation.

**Language restriction** The main language was English, but the search was not limited to this language only.

**Country(ies) involved** Bolivia, United Kingdom.

**Keywords** Fabry disease, chronic kidney disease, dialysis, kidney transplantation, screening, prevalence.

**Dissemination plans** Publication in reseach journal.

**Contributions of each author**

Author 1 - Daniel Linares - Responsible for the concept of the manuscript, search and extracted all the necessary data, designed the study, executed the meta-analysis, and prepared all figures and tables.
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