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New onset diabetes after kidney transplantation in patients with autosomal dominant polycystic kidney disease: systematic review protocol

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ABSTRACT

Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disorder with numerous cysts developing in bilateral kidneys. Meanwhile, ADPKD can also be regarded as a systemic disease because the cystic and non-cystic abnormalities could be identified in multiple organs in patients with ADPKD. Several lines of evidence suggest the risk of post-transplant diabetes mellitus or new-onset diabetes after transplantation (NODAT) is higher in patients with ADPKD compared with non-ADPKD renal recipients, but the available results are conflicting. We describe the protocol of a systematic review and meta-analysis for investigating the risk of NODAT in patients with ADPKD.

Methods and analysis: PubMed, EMBASE and The Cochrane Library will be searched. Cohort studies irrespective of language and publication status, comparing the incidence of NODAT in renal recipients with ADPKD and other kidney disease will be eligible. We will assess heterogeneity among studies. Along with 95% CIs, dichotomous data will be summarised as risk ratios; numbers needed to treat/harm and continuous data will be given as standard mean differences. Excluding outliers and testing small sample size studies if our results are robust, sensitivity analysis will be carried out.

Ethics and dissemination: Ethical approval is not required because this study includes no confidential personal data or patient interventions. The review findings will be helpful in designing and implementing future studies and will be of interest to a wide range of readers, including healthcare professionals, researchers, health service managers and policymakers. The systematic review will be published in a peer-reviewed journal and disseminated electronically and in print.

Trial registration number: The study protocol has been registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/) under registration number CRD42014009677.

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD), as the most common, potentially lethal monogenic inherited renal disorder, occurs in 1:400 to 1:1000 live births.[1 2] ADPKD is caused by the mutation in one of two genes: *PKD1* or *PKD2* in most cases.[3–5] Numerous fluid-filled cysts progressively grow in bilateral kidneys of the patients. Besides kidney cysts, cystic and non-cystic abnormalities can be found in multiple organs and systems in patients with ADPKD.[6 7] As a result, ADPKD can be regarded as a systemic disease. Previous observational studies suggested that the presence of ADPKD was associated with components of metabolic syndrome such as hypertension, abdominal obesity and higher fasting glycaemia.[8] Even in the early stages of ADPKD, decreased coronary flow velocity reserve, increased carotid intima media thickness and increased insulin resistance can be found,[9] which suggests that the risks of cardiovascular diseases and type 2 diabetes are elevated in patients with ADPKD. The reasons for metabolic abnormalities in patients with ADPKD are not fully elucidated. One reasonable explanation is that the function of polycystins might not be limited to the preservation of normal nephron structure but also involved in metabolic adjustment.[10] The mutations of *PKD1* or *PKD2* might cause a genetic predisposition to metabolic abnormalities.

End-stage renal disease (ESRD) occurs in more than 70% of patients with ADPKD.[11] As successful kidney transplantation can correct the disturbance of the internal environment comprehensively, it is the preferred option of renal replacement therapy. Post-transplant diabetes mellitus or new-onset diabetes after transplantation (NODAT) are important complications after organ transplantation due to the use of immunosuppressive medications such as tacrolimus, CsA, mTORi and corticosteroids.[12–15] Several

observations report that the risk of diabetes mellitus is higher in patients with ADPKD compared with non-ADPKD renal recipients. But the results from different studies are conflicting; there are also studies suggesting that ADPKD is not a risk factor for NODAT.[16 17] The relationship between ADPKD and an increased risk of NODAT is far from being clarified. This systematic review and meta-analysis aims to comprehensively summarise the available evidence about the risk of NODAT in ADPKD renal recipients compared with non-ADPKD recipients.

METHODS

The protocol of this review has been registered in PROSPERO (CRD42014009677) (http://www.crd.york.ac.uk/PROSPERO). The drafting of this protocol followed the preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) checklist.[18]

Search strategy and study selection

PubMed, EMBASE and The Cochrane Library will be searched. No language or publication period restrictions will be applied. The PubMed search strategy is shown in box 1. The search terms will be adapted for the other electronic data sources. We will also search the reference lists of the original studies, letters to the editor, case reports, guidelines, reviews and meta-analyses retrieved through the electronic searches. We will perform our search in April 2015 and update our search after finishing the full review.

Types of study to be included

Cohort studies, irrespective of language and publication status, will be included that compare the incidence of NODAT in renal recipients with ADPKD and other kidney diseases.

Types of participants

Inclusion criteria

Participants will include adult renal recipients. However, patients who have impaired glucose regulation before kidney transplantation (defined as no positive finding in fasting insulin, HbA1c or oral glucose tolerance test) and patients who have received kidney–pancreas/kidney–liver combined transplantation will be ineligible.

Type of exposure

Exposure

ESRD resulting from ADPKD. Diagnosis of ADPKD is based on the detection of multiple cysts by renal ultrasound and a positive family history; patients with renal cysts and negative family history with molecular genetic testing confirmed *PKD1* or *PKD2* mutation are also eligible.

Box 1 Search strategy for PubMed

#1 Kidney Transplantation
#2 Polycystic Kidney, Autosomal Dominant
#3 #1 and #2

Type of control

Adult renal recipients with non-ADPKD ESRD.

Outcomes

Primary outcomes

Changes in biochemical indices relevant to diabetes (such as HbA1c, GLU, fasting insulin) and changes in renal manifestations (evaluated by biochemical markers such as eGFR, creatinine clearance, serum creatinine, urine albumin-to-creatinine ratio or dichotomous outcomes such as the occurrence of urinary tract infection, acute kidney injury, and other renal and urinary disorders) will be analysed.

Secondary outcomes

Lipid metabolism, urate metabolism, survival of graft and patients will be analysed as secondary outcomes.

Data extraction (selection and coding)

After completion of the literature search and review of the titles and abstracts of all identified studies, we will determine which articles require further consideration, and then obtain the full records. Two authors will, independently, assess the eligibility of each trial to be included in the review, with the third author being consulted to resolve disagreement. Data from each identified study will be independently extracted and recorded on a standardised data extraction form by two authors. Disagreements will be resolved by discussion. When requiring additional information, we will contact the original author of the studies. Details of the study selection procedure are shown in figure 1.

The data to be extracted: first author, year, journal, study design, funding sources, study duration. Relevant participants: (1) age; (2) sex; (3) disease status before transplantation; (4) duration of kidney insufficiency; (5) living/cadaveric kidney donor; (6) concomitant disease; (7) immunosuppressive regiments. Relevant outcomes: (1) biochemical indexes relevant to glucose metabolism (HbA1c, 5FRG, fasting insulin); (2) biochemical indexes assessing renal function (evaluated by biochemical markers such as eGFR, creatinine clearance, serum creatinine, urine albumin-to-creatinine ratio or dichotomous outcomes such as the occurrence of urinary tract infection, acute kidney injury, and other renal and urinary disorders); (3) adverse events. When needed data are missing, we will attempt to contact the original investigators to obtain further information.

Risk of bias (quality) assessment

We will assess the risk of bias for each cohort study with the Newcastle-Ottawa Quality Assessment Scale,[19] according to the quality in domains of cohort selection, comparability and outcome. A consensus will be reached to

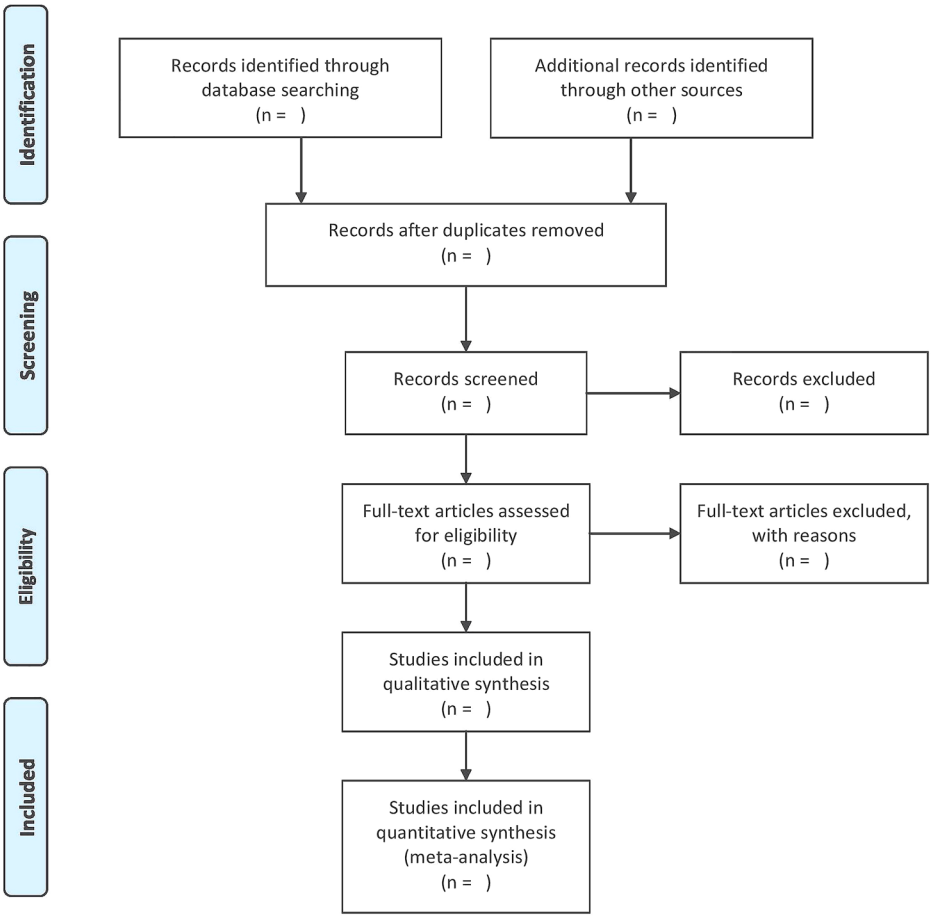

Figure 1 Flow diagram of studies included.

assess the risk of bias. With the Newcastle-Ottawa Quality Assessment Scale, studies will be scored a maximum of nine points on items including the selection of subjects, the comparability between groups, and the ascertainment of outcome of interest. Risk of bias for each domain will be rated as high (seriously weakens confidence in the results), unclear or low (unlikely to seriously alter the results).

Strategy for data synthesis

Using the I^2 statistic and χ^2 test (assessing the p value), we will assess heterogeneity among studies. Heterogeneity will be considered to be substantial among the studies in which the p value is less than 0.10 and I^2 exceeds 50%. We will combine the data with a random effects model if significant heterogeneity exists ($p<0.1$; $I^2>50\%$). Along with 95% CIs, dichotomous data will be summarised as risk ratio; however, numbers needed to treat or harm and continuous data will be given as standard mean difference. Excluding outliers and testing small sample size studies if our results are robust, a sensitivity analysis will be carried out. If the data are so sparse that quantitative synthesis is not appropriate, we will only carry out a systematic review.

Review Manager (RevMan) (computer programme), V.5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014) will be used to generate forest plots. The funnel plots will be assessed for evidence of asymmetry, and possible publication bias or other small study effects. We will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in reporting our findings.[20]

Analysis of subgroups or subsets

We plan to perform subgroup analyses according to the disease classification in control groups, immunosuppressive regimens, duration of kidney insufficiency, living/cadaveric kidney donor and concomitant disease. We will specifically analyse diseases known to be metabolism related, such as hypertensive nephropathy, obesity and mutations in HNF1 α/β.

Risk of bias across studies

The possibility of publication bias will be assessed visually using funnel plots in which non-publication of small trials with negative results could result in asymmetry, and formally with Egger's test. In funnel plots, the effect of each trial will be plotted by the inverse of its standard error.

Confidence in cumulative evidence

We will assess the quality of the body of evidence using the principles of the GRADE system.[21] We will construct

a Summary of Findings table using the GRADE software. The GRADE approach will appraise the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence assessment considers within-study risk of bias (methodological quality), the directness of the evidence, the heterogeneity of the data, the precision of effect estimates and the risk of publication bias.

DISCUSSION

In recent clinical studies and reviews, it was suggested that the incidence of glucose metabolic disorders after kidney transplantation in patients with ADPKD is higher than in those with other kidney diseases.[22] Some authors even proposed potential mechanisms[23 24] to explain this finding.

However, there is still no robust evidence supporting the association between ADPKD and NODAT, and the available data are conflicting. To further clarify this association, we present a protocol of a systematic review to determine the risk of NODAT in renal recipients with ADPKD compared with non-ADPKD recipients. The conclusions drawn from this review will benefit the design and implementation of future studies and will be of interest to a wide range of readers, including healthcare professionals, researchers, health service managers and public policy makers.

There are several strengths of this review. The review question is an important clinical issue closely correlated to further research, and our extensive search of the relevant literature will provide a comprehensive assessment of the review question. This review will be the first high-quality systematic review and meta-analysis to summarise current evidence on the occurrence of new onset diabetes after kidney transplantation in patients with ADPKD. Some potential limitations should be discussed. The poor quality and heterogeneity of the primary studies which might appear in our future analysis are the most common reasons for downgrading the quality of evidence. Challenges in optimising search terms, poor indexing of studies, limitations of databases used or the existence of grey literature will also prevent us from collecting comprehensive data.

Contributors ZM acts as guarantor for the validity of the study report. Study concept and design: ZM and AO. Acquisition of data: BY and SC. Extraction of data: BY and GY. Checking of data: CM. Analysis and interpretation of data: BY and SC. Drafting of the protocol: BY and GY.

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Competing interests None declared.

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