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Original Research

The Risk for New-Onset Diabetes Mellitus after Kidney Transplantation in Patients with Autosomal Dominant Polycystic Kidney Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

Objectives: New-onset diabetes after kidney transplantation (NODAT) is associated with both renal allograft failure and increased rates of mortality. The objective of this meta-analysis was to evaluate the risk for NODAT in patients with autosomal dominant polycystic kidney disease (ADPKD).
Methods: A literature search was performed using MEDLINE, EMBASE and Cochrane Database of Systematic Reviews from inception through July 2015. Studies that reported relative risks, odd ratios or hazard ratios comparing the risk for NODAT in patients with ADPKD were included. Pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using a random-effect, generic inverse variance method.
Results: Included in the analysis were 12 cohort studies, which comprised 1379 patients with ADPKD of a total of 9849 patients who had undergone kidney transplants. The pooled RRs of NODAT in patients with ADPKD were 1.92 (95% CI, 1.36 to 2.70). When meta-analysis was limited only to studies with confounder-adjusted analysis, the pooled RRs for NODAT were 1.98 (95% CI, 1.33 to 2.94). However, the association between NODAT requiring insulin treatment was insignificant, with pooled RRs of 1.57 (95% CI, 0.75 to 3.27).
Conclusions: Our meta-analysis demonstrates a significant association between ADPKD and NODAT in recipients of kidney transplants. The findings of this study may impact clinical management and follow up for patients with ADPKD after kidney transplantation.

Mots clés :
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transplantation

RÉSUMÉ

Objectifs : Le diabète de novo après transplantation (NODAT pour *new-onset diabetes after transplantation*) rénale est associé à l'insuffisance rénale post-allogreffe et à l'augmentation des taux de mortalité.
Méthodes : Nous avons réalisé une recherche de littérature à l'aide des bases de données MEDLINE, EMBASE et des revues systématiques Cochrane de la création à juillet 2015. Nous avons inclus les études qui rapportaient les risques relatifs, les ratios d'incidence approché ou les rapports de risque comparant le risque de NODAT chez les patients atteints de PRAD. Nous avons calculé les risques relatifs (RR) pondérés et les intervalles de confiance (IC) à 95 % à l'aide de la méthode inverse de la variance générique utilisant des modèles à effets aléatoires.
Résultats : L'analyse comprenait 12 études de cohorte, qui regroupaient 1379 patients atteints de PRAD sur un total de 9849 patients qui avaient subi des greffes de reins. L'objectif de l'étude était d'évaluer le risque de NODAT chez les patients atteints de PRAD. Les RR pondérés de NODAT chez les patients atteints

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de PRAD étaient de 1,92 (IC à 95 %, 1,36 à 2,70). Lorsque la méta-analyse était seulement limitée aux études utilisant l'analyse ajustée en fonction d'une variable confusionnelle, les RR pondérés de NODAT étaient de 1,98 (IC à 95 %, 1,33 à 2,94). Cependant, l'association avec le NODAT nécessitant le traitement par insuline était négligeable, soit des RR pondérés de 1,57 (IC à 95 %, 0,75 à 3,27).
Conclusions : Notre méta-analyse démontre une association importante entre la PRAD et le NODAT chez les receveurs de greffes de reins. Les résultats de cette étude peuvent avoir des répercussions sur la prise en charge clinique et le suivi des patients atteints de PRAD après transplantation rénale.

Introduction

New-onset diabetes after transplantation (NODAT) is a common complication following kidney transplantation and is independently associated with mortality (1–3) and renal allograft failure (3,4). The cost for associated treatment exceeds $21,500 USD per newly diagnosed patient with diabetes by 2 years post-transplant (5). Other risk factors for developing NODAT include obesity, hepatitis C virus, cytomegalovirus infection, use of corticosteroids or calcineurin inhibitors (CNIs), type of CNIs, ethnicity (African, South Asian) and impaired fasting glucose levels (6,7). Despite the effort to prevent NODAT, evidence suggests that the incidence of NODAT has been increasing; reports range from 7% to 46% (3,8–10).

Autosomal dominant polycystic kidney disease (ADPKD) is not only the leading inheritable cause of end stage renal disease (ESRD), it is also 1 of the leading causes of ESRD worldwide (11). Because of the excellent patient survival rates following kidney transplant for ESRD secondary to ADPKD (12,13), the number of kidney transplants for this patient population has increased in recent decades (14). The link between ADPKD and NODAT in post kidney transplant recipients, however, is conflicting. A number of studies have demonstrated both an increased association (15–22) and no significant association (20–24) between ADPKD and NODAT.

The objective of this meta-analysis was to evaluate the risk for NODAT in patients with ADPKD after kidney transplantation.

Methods

Search strategy

Two investigators (WC and CT) independently searched published studies indexed in MEDLINE, EMBASE and the Cochrane database from inception through July 2015 using the search strategy described in Supplement 1 in the Appendix. In addition, a manual search was performed for additional relevant studies using references from retrieved articles.

Inclusion criteria

The inclusion criteria were as follows: 1) randomized clinical trials (RCTs) or observational studies (case-control, cross-sectional or cohort studies) published as original studies or conference abstracts that evaluated the risk for NODAT in kidney transplant recipients with ADPKD; 2) studies that included data to calculate odds ratios, relative risks, hazard ratios or standardized incidence ratio with 95% confidence intervals (CIs); and 3) a reference group composed of participants who did not have ADPKD. No limits were applied for language.

Study eligibility was independently determined by the 2 investigators noted above. Differing decisions were resolved by mutual consensus. The quality of each study was independently evaluated by each investigator using the Jadad quality assessment scale (25) for RCTs and the Newcastle-Ottawa quality assessment scale (26) for observational studies.

Data extraction

A standardized data collection form was used to extract the following information: last name of the first author, study design, year of study, country of origin, year of publication, sample size, characteristics of included participants, definitions of NODAT, confounder adjustment and adjusted effect estimates with 95% CIs. The 2 investigators mentioned above performed this data extraction independently.

Statistical analysis

Review Manager 5.3 software (Cochrane Collaboration, London, UK) was used for data analysis. Per our study protocol, we conducted a meta-analysis utilizing all included studies. Point estimates and standard errors were extracted from individual studies and were combined using the generic inverse variance method of DerSimonian and Laird (27). Given the high likelihood of interstudy variances, we used a random-effect model rather than a fixed-effect model. Statistical heterogeneity was assessed using the Cochran Q test. This statistic is complemented by the I^2 statistic, which quantifies the proportion of the total variation across studies that is due to heterogeneity rather than chance. A value of I^2 of 0 to 25% represents insignificant heterogeneity, 26% to 50% low heterogeneity, 51% to 75% moderate heterogeneity, and >75% high heterogeneity (28). The presence of publication bias was assessed by funnel plots of the logarithm of odds ratios versus their standard errors (29).

Results

Our search strategy yielded 545 potentially relevant articles. Of those, 504 were excluded on the basis of title and abstract for clearly not fulfilling the inclusion criteria on the basis of the type of article, study design, population or outcome of interest. Full-length article review was performed on 41 articles, and 29 articles were excluded (20 articles did not report the outcomes of interest, and 9 articles were not observational studies or RCTs). Included in the data analysis were 12 cohort studies (15–22,24,30–32) that comprised 1379 patients with ADPKD of a total of 9849 kidney transplant patients who were identified.

Of 12 studies, 10 performed adjusted analysis for confounders (15,17–21,24,30–32). Three studies assessed the risk for NODAT requiring insulin treatment (24,30,31). Supplement 2 outlines our search methodology and selection process. The Table 1 describes the detailed characteristics and quality assessments of the included studies.

The risk for NODAT in patients with ADPKD

The pooled relative risk (RR) for NODAT in patients with ADPKD was 1.92 (95% CI, 1.36 to 2.70; I^2=59%) as compared to those who received kidney transplants from other causes.

Figure 1 shows the forest plot of the included studies. However, the association between NODAT requiring insulin treatment was insignificant, with a pooled RR of 1.57 (95% CI, 0.75 to 3.27), as shown in Figure 2. There was no significant heterogeneity, with I^2 of 0.