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## Effect of sirolimus as an immunosuppressive agent on kidney transplantation in patients with diabetes mellitus; a systematic review

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### ABSTRACT

**Background:** Sirolimus is a macrolide and a type of immunosuppressant drug to prevent rejection of transplanted organs. This drug inhibits the activation of T and B lymphocytes and reduces the production of interleukin-2 (IL-2). This study aimed to review the effect of sirolimus in kidney transplantation in patients with diabetes mellitus as a systematic review.

**Materials and Methods:** International databases including PubMed, Web of Science and Scopus were considered for search of English articles by 29 June 2019. Twenty-one published articles were finally entered into the study. Keywords were sirolimus, rapamune, rapamycin, diabetes mellitus and kidney transplantation or a combination of them in the title/abstracts. Treatment using a combination of sirolimus and tacrolimus were excluded.

**Results:** There were more than 3244 research units reviewed in this systematic review of 21 published articles.

**Conclusion:** According to the results, sirolimus-based immunosuppression for preventing kidney transplantation is effective and has a low-risk in diabetic patients resulting in suitable glucose control.

### Implication for health policy/practice/research/medical education:

Sirolimus-based immunosuppression for preventing kidney transplantation is effective and has a low-risk in diabetic patients.

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### Introduction

Nowadays, chronic diseases are prevalent such as chronic kidney disease and end-stage renal disease (ESRD), with an average increase of 6% per year (1). ESRD as a form of chronic kidney failure is an irreversible decrease in kidney function that results in death without dialysis or kidney transplantation (2, 3). Diabetes, hypertension, polycystic hereditary disease and glomerulonephritis are some important risk factors associated with ESRD (4). Renal replacement therapy (RRT) is a general term used in the treatment of patients with ESRD, including hemodialysis, peritoneal dialysis, and renal allograft transplantation (5). The quality of life of patients receiving kidney

transplantation is better than others since the quality of life of hemodialysis patients was significantly lower than other groups (6). Kidney transplantation was encountered with lots of challenges during the development, in which rejection of transplantation is the most important challenging issue. In this regard, some drugs are used to prevent the rejection of the kidney transplantation (7, 8). One of the well-tolerated drugs with acceptable results in this field is sirolimus. Sirolimus is a macrolide and a type of immunosuppressant drug to prevent rejection of transplanted organs. This drug inhibits the activation of T and B lymphocytes and reduces the production of interleukin-2 (IL-2) (9-11). There are some systematic

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reviews about the effect of sirolimus in the past decades e.g. Webster et al suggested that long-term hard-endpoint data from robust randomized trials are still required to make a decision (12). It is worthy to be noted that due to the importance of sirolimus outcome on the transplanted patients, further studies are needed. Thus, this study aimed to review the effect of sirolimus on kidney transplantation in patients with diabetes mellitus as a systematic review.

## Methods

### Search strategy

International databases including PubMed, Web of Science and Scopus were considered for search of English articles by 29 June 2019. Twenty-one published articles were finally entered into the study. Keywords were sirolimus, rapamune, rapamycin, diabetes mellitus and kidney transplantation or a combination of them in the title/abstracts. Treatment using a combination of sirolimus and tacrolimus were excluded.

### Search strategy for PubMed

(Sirolimus [MeSH] and Sirolimus\* [TIAB] OR rapamycin [TIAB] OR Rapamune [TIAB]) AND (Diabetes mellitus [Mesh] OR Diabetes mellitus [TIAB]) AND (Kidney transplantation [MeSH] OR Kidney transplantation rejection [TIAB]). After collection of articles of interest, references were imported to Endnote software and removed duplicate titles. Then, after browsing titles, studies with irrelevant purposes were removed, and then the remaining studies assessed by two independent investigators. The selected studies were performed on humans and published in English.

### Data extraction

Information dealing with the selected articles (the author's last name, year of publication, study design, sample size and the results of each article) was taken by two independent investigators. The differences observed in this process were corrected by a third investigator who was independent with the two previous investigators.

## Results

There were more than 3244 individuals reviewed in this systematic review of seven published articles consisted of two retrospective, two prospective studies and seventeen clinical trial studies. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, a checklist of items that should be included in reports of interventional studies for selected articles (13,14). Figure 1 shows the selection process using PRISMA. The summary of the selected articles was shown in Table 1.

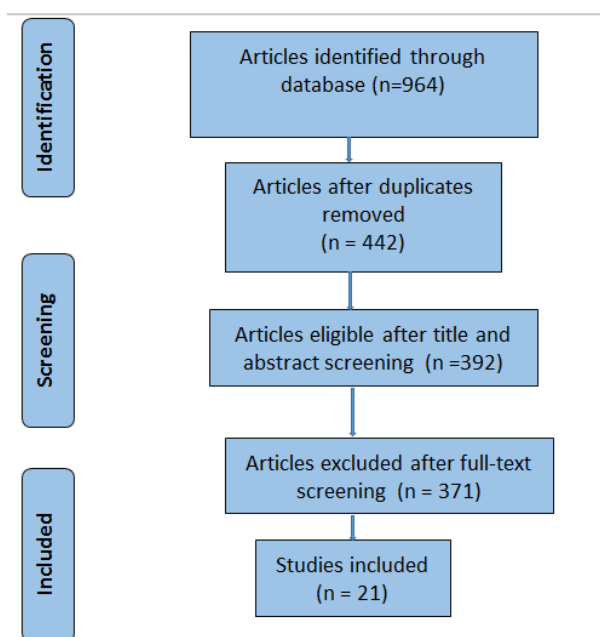


Figure 1. Flow chart of study selection based on PRISMA.

## Discussion

Kidney transplantation is the best treatment for patients with renal failure after kidney transplantation. Improved kidney function, survival and quality of life using anti-rejection drugs as suppressive agents had been observed in these patients. Immunosuppressive agents help to prevent graft rejection (36). Similar research done in other countries is largely similar to the results obtained in this review supporting the preventive effect of sirolimus following transplantation (37). A review study by Pascual et al has shown that using sirolimus can reduce the dose of calcineurin inhibitors and the combination results in better outcomes (38). Cooper et al showed sirolimus in combination with low-dose cyclosporine or tacrolimus is more effective in treating and preventing graft rejection, and improves graft transplant function (39). A systematic and meta-analysis performed by Araki et al has yielded similar results in comparison with our review (40). All studies approximately concluded the protective effect of sirolimus after kidney transplantation accompanied with the reduced dose of cyclosporine.

## Conclusion

Based on the results, sirolimus-based immunosuppression for preventing kidney transplantation is effective and has a low-risk in diabetic patients resulting in suitable glucose control.

## Conflicts of interest

The authors declare that there is no conflict of interest in this study.

**Table 1.** The detail of reviewed articles in this systematic study

First author	N	Age (y)	Design	Conclusion
Almeida et al (15)	30	41±10.5	Cross-sectional	Conversion to SRL was safe. There was no deterioration in renal function nor episodes of acute rejection. There was a significant increase in cholesterol values after conversion.
Anil Kumar et al (16)	150	49±13.7	Prospective	It needs further studies to be evaluated.
Arellano et al (17)	50	Not reported	Prospective	Sirolimus monotherapy is safe in a selected group of immunological low-risk patients without increasing the risk of rejection.
Ciancio et al (18)	150	14-78	RCT	This three-year (interim) analysis has indicated a trend towards better graft function, fewer endocrine disorders, and fewer acute rejection episodes comparing adjunctive MMF and Tacro vs. Siro.
Ferreira et al (19)	70	34.4 ± 11.6	RCT	In black recipients of primarily living renal allograft donors reduced CsA exposure and SRL concentration-controlled regimens produced low incidences of acute rejection, post-transplant diabetes mellitus and CMV disease, with no significant impairment in graft function.
Gatault et al (20)	150	18-65	RCT	Sirolimus improved renal graft function at 8 years without increased risk of donor-specific antibodies appearance.
Gyurus et al (21)	514	42.2±1.1	RCT	Our 10-year experience revealed SRL to be an etiologic agent for NODAT, displaying interactive, possibly pharmacokinetic, and pharmacodynamic effects with concomitant CsA in combination treatment.
Havrdova et al (22)	30	42.5±6.0 vs. 42.3±6.1	RCT	Recipients on sirolimus treatment had significantly lower insulinemia during the test and consequently more favorable indices of insulin action
Jaber et al (23)	84	45 ± 14 vs. 46± 16	RCT	Early steroid-withdrawal in renal transplant recipients with a sirolimus and mycophenolate mofetil-based and calcineurin inhibitor-minimization protocol can effectively reduce many of the steroid-related side effects, decrease risk factors for cardiovascular disease, and is associated with improved recipient survival without compromising graft function.
Johnston et al (24)	124	47±14.6	Cross-sectional	Sirolimus is independently associated with non-onset diabetes. Given the negative impact of NOD on post-transplantation outcomes, these findings should be confirmed in prospective studies or in meta-analyses of existing trials that involved sirolimus.
Kahan et al (25)	149	18-65	RCT	SRL in combination with CsA and steroids not only lowers the incidence of biopsy-proven acute renal allograft rejection episodes, but also may permit CsA sparing, at least among Caucasian patients, without an increased risk of rejection
Legendre et al (26)	161	Not reported	RCT	Patients receiving sirolimus experience an initial increase in lipid levels, but these effects are manageable with the use of lipid-lowering agents. Hypertension was less frequent and renal function was improved with CsA-free, sirolimus-based therapy. Based on this early experience, overall cardiovascular risk does not appear to be increased with sirolimus-based compared with CsA-based therapy
Mital et al (27)	37	2-63	RCT	This study demonstrates the exciting prospect of safe and effective sirolimus-based immunosuppression in renal transplantation without the need for any maintenance steroids.

**Table 1.** Continued

First author	N	Age (y)	Design	Conclusion
Podder et al (28)	470	Not reported	RCT	A concentration-controlled sirolimus-cyclosporine-prednisone regimen (with steroid withdrawal by 3 months) reduced the incidence of acute rejection episodes and increased 6-year graft survivals.
Romagnoli et al (29)	86	47.7 ± 9	RCT	Careful monitoring of blood levels is mandatory in the SRL + CsA combination to avoid pleiotropic toxicity.
Steigerwalt et al (30)	40	54.7±9.0 vs. 51.8±10.5	RCT	The lower 24-hour SBP seen in the SRL group by AMBP may lead to improved cardiovascular and renal outcomes over time. Long-term patient follow-up will be needed to clarify the effect of the lower 24-hour SBP.
Sundberg et al (31)	21	23-70	Retrospective	Daclizumab bridge therapy provides safe and effective immunosuppressive coverage while converting renal transplant recipients from CI- to SRL-based maintenance immunosuppressive therapy.
Veroux et al (32)	344	48 ± 12	RCT	Conversion from CNI to SIR in patients could improve significantly the metabolic parameters of patients with NODAT, without increasing the risk of acute graft rejection.
Teutonico et al (33)	26	42.8±10.4 vs. 46.9±10.6	RCT	In conclusion, the discontinuation of calcineurin inhibitors and their replacement by sirolimus fail to ameliorate the glycometabolic profile of kidney transplant recipients. Rather, it is associated with a worsening of insulin resistance and an inappropriately low insulin response
Veroux et al (34)	396	52.3 ± 8 9.4 vs. 49.28±11.4	RCT	Sirolimus-based immunosuppression is safe and efficacious in type 2 diabetic patients who underwent a kidney transplantation, allowing a better glucose metabolism control.
Lebranco et al (35)	162	47.4±11.9 vs.47.7 ±10.5	RCT	Renal benefits associated with conversion of CsA to SRL, at 3 months post-transplantation, in combination with MMF were maintained for 4 years post-transplantation.

CsA; cyclosporine A, Tacro; tacrolimus, Siro; sirolimus; RCT, randomized controlled trial.

### Ethical considerations

Ethical subjects such as plagiarism and double publication have observed in this study.

### Funding/Support

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