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Immunosuppressive therapy and nutritional diseases of patients after kidney transplantation: a systematic review

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Abstract

Background Kidney transplantation (kTx) is by far the most effective method of treating end-stage renal disease, with immunosuppressive therapy being obligatory for all, except identical twins. Despite kTx being the most effective treatment for end-stage renal disease, the patients face significant morbidity. They are often burdened with diabetes, anaemia, lipid disorders, all of which pose heightened risks for cardiovascular disease. Knowing that nutritional status plays a significant role in post-transplant results including graft survival, we conducted this systematic review with the aim to summarise the evidence of nutritional diseases following exposure to immunosuppressive therapy among patients after kTx.

Methods This systematic review is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist. Our search encompasses observational studies (cohort, case–control, cross-sectional) and randomized controlled trials (RCTs), published and unpublished, completed, and ongoing, written in English from the last 10 years (up to 17th February 2023) in the following databases: MEDLINE (via PubMed), EMBASE (Elsevier), Scopus and Web of Science. Any settings were eligible for inclusion. Quality assessments were done using ROBINS-I and RoB2 tools. Results were summarised in a narrative synthesis. Quantitative analysis was conducted where feasible. The protocol for proposed systematic review was published elsewhere.

Results A total of 24 studies were included (participants $n=9{,}536$) in the review. The majority of studies were cohort ($n=16$), with moderate or low quality. Most of the studies ($n=16$) were conducted in hospital settings. All studies had a higher proportion of male participants compared to female participants, except for one. Diabetes emerged as the most frequent disease assessed ($n=14$), while tacrolimus (Tac) was the most commonly evaluated immunosuppressive medication used ($n=16$). As a result, Tac presented a higher risk factor for the development of diabetes compared to cyclosporine (CsA). In addition, Tac was linked to weight gain in post-transplant recipients. In contrary, no relationship was found between steroids and weight gain. Regarding other immunosuppressants, everolimus was found to be associated with lipid abnormalities. Though, the relationship between lipid abnormalities and steroid use yielded inconsistent results. Calcineurin inhibitors (CNIs) were studied in various research articles. Consequently, patients who were not using CNIs had a lower prevalence of hypomagnesaemia, hyperkalaemia, and metabolic acidosis compared to those treated with CNIs. Also, CNIs were found to have a negative impact on 25-hydroxyvitamin D (25(OH)D) levels. Another aspect was the use of slow and fast Tacrolimus metabolizers. There was no difference

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observed in phase angle, visceral fat area, lean body mass index, and the proportion of lean mass as a percentage of total body mass between them. Finally, mammalian target of rapamycin (mTOR) inhibitors was associated with bone status and mycophenolate mofetil was linked to Vitamin B_{12} deficiencies.

Conclusions To the best of our knowledge, this systematic review represents the first comprehensive overview of the evidence regarding immunosuppressive therapy and nutritional diseases in kTx patients. Our findings indicate an association between immunosuppressive therapy and nutritional diseases in this population. However, there is high heterogeneity and suboptimal quality of the included studies. Future researchers should prioritise high-quality, prospective randomized controlled trials to further elucidate these relationships.

Trial registration PROSPERO (CRD42023396773), dated 12 April 2023. Protocol publication: https://doi.org/10.3390/jcm12216955.

Keywords Kidney transplantation, Immunosuppressive therapy, Nutrition, Diet

Background

The kidney is the most transplanted organ followed by the liver and the heart. In 2022, there were a total of 157,494 organ transplants worldwide of which kidney accounted for 65% (102,090) [1, 2]. Despite kidney transplantation (kTx) being the most effective treatment for end-stage renal disease (ESRD), offering extended lifespan and significantly enhanced quality of life compared to dialysis, these patients face significant morbidity [3, 4]. They frequently contend with comorbidities such as hypertension, diabetes, anaemia, lipid disorders, overweight and obesity. Each of these conditions pose heightened risks for cardiovascular diseases (CVD) which stands as one of the leading causes for kidney transplant recipients [5]. In addition, osteoporosis and cancers are also prevalent among this population [6]. Immunosuppressive therapy among kidney transplant recepients is obligatory for all, except identical twins. The standard scheme includes the use of immunosuppressive medication and steroids, that are delineated as follows, (1) Calcineurin inhibitors (CNIs) – cyclosporine (CsA) and tacrolimus (Tac), (2) Mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus), (3) Antiproliferatives like azathioprine and mycophenolic acid derivatives, (4) Glucocorticosteroids, and (5) Biological immunosuppressive agents [7, 8]. Contemporary immunosuppressive protocols typically involve triple-drug therapy, including CNIs, corticosteroids, and antiproliferative drugs. Chronic immunosuppressive therapy exacerbates pre-existing metabolic disorders and instigates new ones. For instance, steroids like prednisone can lead to osteoporosis, fluid retention, hypertension, dyslipidaemia, NODAT increased appetite, and weight gain. Dyslipidaemia can also result from CNIs (e.g., tacrolimus and cyclosporine) and mTOR inhibitors (e.g., everolimus and sirolimus). Hypomagnesaemia may occur with cyclosporine, everolimus, and tacrolimus, while hyperkalaemia is linked to cyclosporine and tacrolimus. Furthermore, both CNIs are known to increase the incidence of hyperuricaemia compared to mycophenolate or mTOR inhibitors [9]. Nutrition plays a significant role for patients following kTx [9]. In the early post-transplant period, proper nutrition aids at facilitating wound healing, preventing infections, and addressing electrolyte and metabolic imbalances resulting from kidney function restoration and immunosuppressive medications. Over the long term however, maintaining proper nutrition is essential for stabilizing renal function and preventing various complications such as obesity, dyslipidaemia, anaemia, diabetes/ hyperglycaemia, hypertension, and bone disease. Nutritional habits can significantly impact the health and functioning of these patients [10]. The nutritional approach for patients after kidney transplantation was presented in Fig. 1.

Immunosuppressive therapy, while crucial for preventing rejection, can also induce side effects that may be influenced by dietary choices. Therefore, a tailored nutritional plan, possibly supervised by a dietitian or healthcare professional, is crucial for managing these side effects and promoting overall health and well-being post-transplantation. Knowing that the relationship between immunosuppressive therapy and nutritional diseases among kTx patients is complex and influenced by multiple factors, the aim of this systematic review is to address this gap [11]. Specifically, this review seeks to summarise the evidence on nutritional outcomes following exposure to immunosuppressive therapy among kTx patients. By synthesizing the findings from relevant studies, the aim is to provide insights into the potential impact of immunosuppressive therapy on the nutritional diseases among post-transplant patients.

Material and methods

Protocol and registration

This systematic review is reported according to the Preferred Reporting Items for a Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist [Supplementary File 1] [12]. The Protocol was registered at

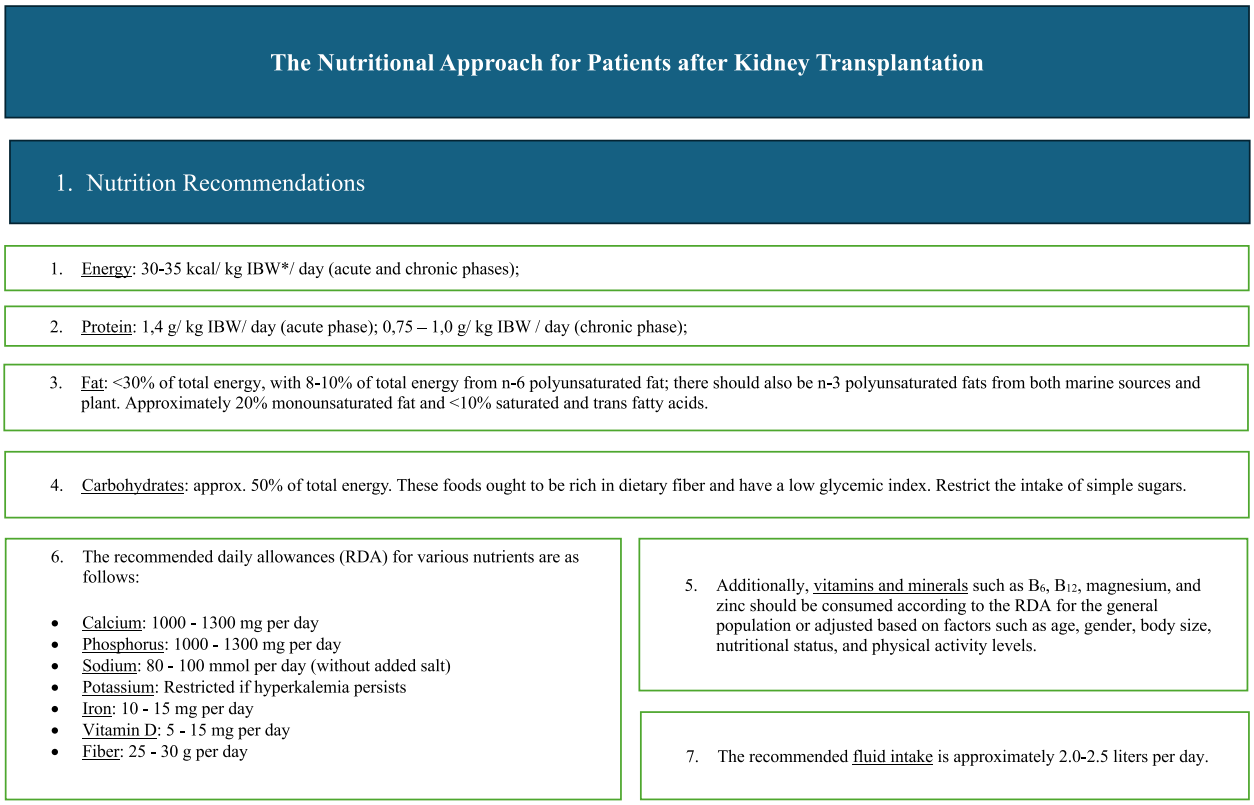


Fig. 1 The nutritional approach for patients after kidney transplantation

the International Prospective Register for Systematic Reviews (PROSPERO) [CRD42023396773] (registration date: 12 April 2023) [13]. The protocol for the proposed systematic review was published elsewhere [14].

Eligibility criteria

Types of participants

We included studies on adult patients (18 years of age or older). Studies based on children, adults younger than 18 years of age, and pregnant women were excluded.

Intervention

Studies with single kidney transplantation were included. Studies on multiple organ transplantation were excluded.

Exposure(s)

Exposure included different schemes of immunosuppressive therapy, such as types and doses of immunosuppressives used. Studies were included where the scheme of immunosuppression was stated in the protocol. We excluded studies in which the immunosuppressive regimen was not clearly specified.

Outcome(s)

Eligible outcomes included anthropometric measurements and biochemical markers, such as body composition, body weight, body mass index (BMI), vitamins (i.e., Vitamin B_6, Vitamin B_{12}, Vitamin D and Folic Acid) and minerals levels (i.e., Iron (Fe), Magnesium (Mg), Phosphorus (P), and Potassium (K)). As body composition we considered all relevant parameters such as i.e. waist and hip circumferences, waist-to-hip ratio, body fat percentage, and percentage changes in hip circumferences. As body weight, we specifically addressed weight gain, body mass index (BMI), and obesity, all of which emerged as notable outcomes in the studies referenced. In our review, we outlined post-transplant diabetes mellitus (PTDM), new-onset diabetes after transplantation (NODAT), and hyperglycaemia as key facets of diabetes under consideration. PTDM and NODAT were considered based on glycemic parameters (serum glucose levels). Lipid abnormalities were evaluated, taking into consideration factors such as HDL-cholesterol, LDL-cholesterol, and triglycerides. In addition, bioimpedance (BIA) analysis components such as i.e., per cent body fat, mass of body fat, lean body mass, total body water, body cell mass, skeletal muscle mass was considered. The outcomes

and outcomes measures for each study included in the review are presented in Table 1.

Setting and design

We included observational studies (cohort, case–control and cross-sectional) and RCTs, both published and unpublished, completed, and ongoing, written in English from the last 10 years (up to 17th February 2023). Qualitative studies, case studies, conference reports and literature reviews were excluded. Any settings were eligible for inclusion. The reference lists of the articles were searched additionally. For missing data authors were contacted.

Information sources and search strategy

We searched following databases: MEDLINE (via PubMed), EMBASE (Elsevier), Scopus and Web of Science. A search strategy was developed in collaboration with an experienced research librarian [Supplementary file 2]. To construct accurate search terms, we used subject headings and subheading as well as text words that will be used to describe words and phrases. For example, in MEDLINE (via PubMed) database for 'kidney transplantation' we used term "kidney transplantation" found in [All fields] as well as "organ transplantation", "Renal Replacement Therapy" and "Transplants" all found as MeSH terms; for 'immunosuppression therapy': "immunosuppression therapy" [MeSH Terms], ("Immunosuppressive Agents"), "Immunosuppressive Agents" [MeSH Terms], "Immunosuppressive scheme", "immunocompromised host" [MeSH Terms]; and for nutritional status "nutritional status", "body composition", "body composition" [MeSH Terms], "body mass index", "body mass index"[MeSH Terms] etc. Each group has been combined using operators AND, OR and NOT. According to each database guidelines: EMBASE (Elsevier); Scopus and Web of Science we applied all the rules in our search strategy. The search was revised and approved by all authors.

Study selection

The selection of studies was done in *Covidence*, which is a web-based systematic review management tool [15]. After removing duplicates, two authors (A.A.K., A.K.N.) blindly screened titles and abstracts for exclusion followed by full-text screening that was also conducted by two reviewers (A.A.K., A.K.N.). Disagreements were solved through discussion or with the help of the third reviewer (D.S.L.). The selection of studies is illustrated in the PRISMA flow chart 2020, which is presented in Fig. 2.

Data extraction

Data extraction and management of data were done by two reviewers (A.A.K., A.K.N.). Data were exported to the standardized MS Excel template. Disagreements were solved through discussion or with the assistance of the third reviewer (D.S.L.). The following data was extracted: 1) study reference (first author and year of publication), 2) study design, 3) country where the study was conducted, 4) settings, 5) sample size, 6) mean age of participants, 7) the number of males and females, 8) description of exposure, 9) description of outcome, 10) measures of effects and tools of measurements, and, 11) how the data was analysed, including statistical methods and any adjustments for confounding factors.

Quality assessment

Two investigators (A.A.K., M.K.) assessed the risk of bias of eligible studies. The quality of observational studies was assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool, which include: bias due to confounding, bias in the selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of outcomes, and bias in selection of the reported result, [Supplementary file 3] [16]. For RCTs the Cochrane Risk of Bias tool (RoB2, August 2019) was used, which consider five domains: risk of bias arising from the randomization process**,** risk of bias due to deviations from the intended interventions, missing outcome data, risk of bias in measurement of the outcome, and the risk of bias in the selection of the reported result, [Supplementary file 4] [17]. Risk-of-bias plots were generated using the web application *Robvis* [18].

Data analysis

Data from eligible studies was extracted and presented in a narrative synthesis. We grouped studies based on the exposures and outcomes assessed. We discussed how potential confounders were addressed and controlled in each study. In order to present quantitative data, we developed a forest plot that summarises the evidence of the effect of various immunosuppressants on NODAT among kTx patients (Fig. 3). Statistica 13.1 was used for data analysis. The studies were too heterogeneous to perform subgroup analysis.

Results

Description of search results

Our search yielded a total of 2682 results. After eliminating duplicates, 2322 results were screened for title and abstract. Of these, 2245 were excluded for not being relevant, with a total of 77 studies included. After further screening, 77 articles were accessed for eligibility and full texts were screened. Out of these, 53 were excluded for specific reasons such as wrong study design, duplicate,

Table 1 Outcomes and outcomes' measures of studies included in the review

Reference	Outcome(s)	Measure(s) of effect	Measure time [months after kTx] median ± SD	Tools for measurement(s)	Gather of data
Ajabnoor, 2020 [19]	PTDM[a]	PTDM incidence (%), Odds Ratio	0–66	ADA[b] criteria	medical records
Beilhack, 2020 [22]	Electrolyte disorders	prevalence of electrolyte disorders	8.2 ± 5.5	blood samples, serum, urine parameters	a single morning fasting blood collection and examination of a 24-hour urine collection was performed on the study day
Bergmann, 2015 [23]	Lipid abnormalities, glucose, body fat distribution, Cushingoid phenotype	spearman rank-order correlation	75 (median) (from 18–225)	UHPLC-MS[c] strategy	collection of blood samples, physical examination, biochemistry assessment
Borda, 2014 [20]	NODAT[d], IGT[e], IFG[f], normal glucose, albumin levels	incidence of NODAT	12	ADA criteria	zero-hour biopsy, check-up laboratory tests
Brzezińska, 2013 [24]	PTDM, IGT, IFG	frequency and incidence of PTDM, IFG and IGT	45.5 ± 33.6	ADA criteria	weight, height, and waist circumference were measured
Chen, 2015 [25]	NODAT	incidence of NODAT	24	ADA criteria	plasma levels of fasting insulin concentration (FINS) and C-peptide were determined by enhanced chemiluminescence immunoassay and ADVIA Centaur C peptide assay, respectively
de Lucena, 2020 [26]	PTDM	incidence of PTDM	0–36	ADA criteria	medical records
de Oliveira, 2014 [27]	Weight gain and obesity	BMI, nutritional status	1–36	ADA criteria	medical records
Filipov, 2015 [28]	Vitamin D	descriptive statistics	> 6	test for 25-hydrohyvitamin D [25(OH)D] was performed by a validated liquid chromatographytandem mass spectrometry method	determination of 25(OH)D was performed by a validated liquid chromatographytandem mass spectrometry (LC- MS/MS) method; Determination of CsA, Tac, sirolimus (SRL) and everoli- mus (EVR) was performed by a developed and validated in-house LC–MS/MS method
Gregorini, 2017 [29]	Bone status	prevalence of osteopenia, osteoporosis, bone fractures, and the associated risk factors	5.28 (median)	SIOMMMS[g] 2015 guidelines	biochemical measures, instrumental investigations, and follow-up visits + medical records

Table 1 (continued)

Reference	Outcome(s)	Measure(s) of effect	Measure time [months after kTx] median ± SD	Tools for measurement(s)	Gather of data
Ichimaru, 2015 [30]	Lipid abnormalities	risk factors and incidence of lipid abnormalities	100	fasting blood was sampled to evaluate serum lipid parameters, including total cholesterol (TCHO), low- density lipoprotein cholesterol (LDL-C), high- density lipoprotein cholesterol (HDL-C), and tri- glycerides (TG) Minimum blood concentrations (Cmin) of immuno- suppressants were measured in blood samples	medical records
Khalili, 2013 [31]	Hyperglycaemia	frequency and risk factors for hyperglycemia	No information	ADA criteria	laboratory data
Kolonko, 2021 [32]	Body composition	data presented as means with 95% CI, OR	In the "early transplantation" (not defined)	BIA[h]	data collection prospectively
Pontes, 2019 [33]	Vitamin B12	prevalence of vitamin B12 (B12) deficiency	kTx > 6	serum levels of B12	lab data, anthropometric measurements, X-ray absorptiometry
Ruangkanchanasetr, 2014 [34]	Obesity	prevalence of obesity	Within 12 to 36	International Obesity Taskforce-proposed classification	blood samples, blood pressure, anthropometric measurements
Sayilar, 2022 [35]	Anthropometric measurements	mean weight gain, BMI values	1–48	anthropometric measurements	hospital records, anthropometric measurements
Terrec, 2020 [36]	Glycaemic parameters (HbA1c[i]) = NODAT	improvement in HbA1c at 6 months post–belatacept conversion	at 6	NODAT was defined as patients with random glucose level ≥ 200 mg/dL (11.1 mmol/L) and/or HbA1c levels ≥ 6.5% and/or the need of diabetes medication post- transplantation	medical records + clinical and biological data
Tillmann, 2017 [37]	pre-diabetes and NODAT	HbA1c level	an average of 4.1 ± 3.0	ADA criteria	all data were extracted from clinical charts or electronic databases
Torres, 2018 [21]	PTDM	incidence of PTDM	3–12	ADA criteria	data collection
van der Burgh, 2019 [38]	PTDM	data are presented as n (%), mean ± SD or median (range)	12	ADA criteria	serum magnesium and tacrolimus at pre-specified time points
Wang, 2023 [39]	NODAT	Incidence of NODAT	12	The World Health Organization (WHO) considers NODAT to be secondary diabetes meeting the diagnostic criteria for diabetes after surgery, excluding acute dysglycemia	clinical data (retrospective study); The research team collected the clinical data of patients receiving renal transplantation in the hospital through follow-up

Table 1 (continued)

Reference	Outcome(s)	Measure(s) of effect	Measure time [months after kTx] median ± SD	Tools for measurement(s)	Gather of data
Xu, 2018 [40]	PTDM	CI of PTDM; Data are expressed as means ± SD or as otherwise indicated	3–36	ADA criteria	medical records
Xue, 2018 [41]	NODAT	the cumulative incidence of NODAT	3,6 and 12	ADA criteria	medical records
Yu, 2016 [42]	NODAT	the demographics and laboratory results were compared between NODAT and non-NODAT patient	3	ADA criteria	medical records

[a] Post-transplant diabetes mellitus

[b] American Diabetes Association

[c] Ultra-High Performance Liquid Chromatography-Mass Spectrometry

[d] New-onset diabetes mellitus

[e] Impaired Glucose Tolerance

[f] Impaired Fasting Glucose

[g] The Italian Society for Osteoporosis, Mineral Metabolism and Bone Diseases

[h] Hemoglobin A1c

[i] Bioelectrical Impedance Analysis

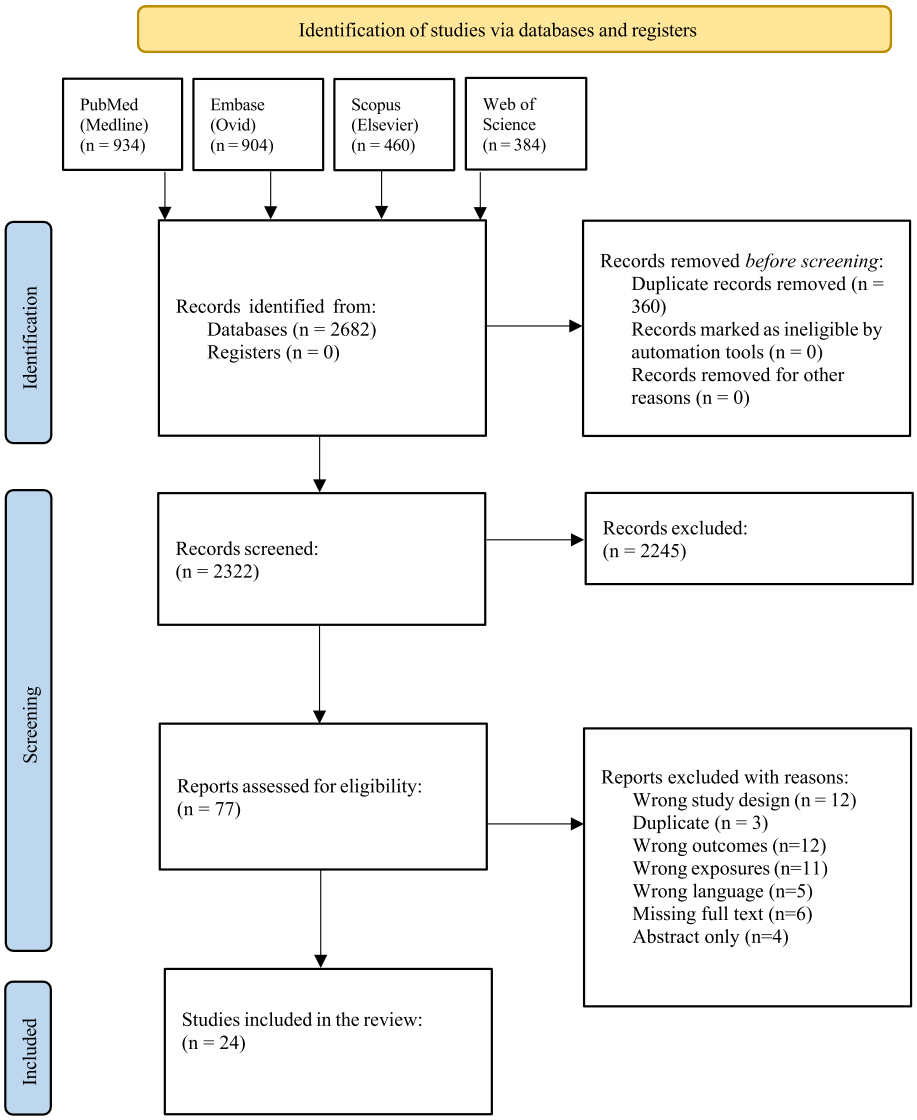


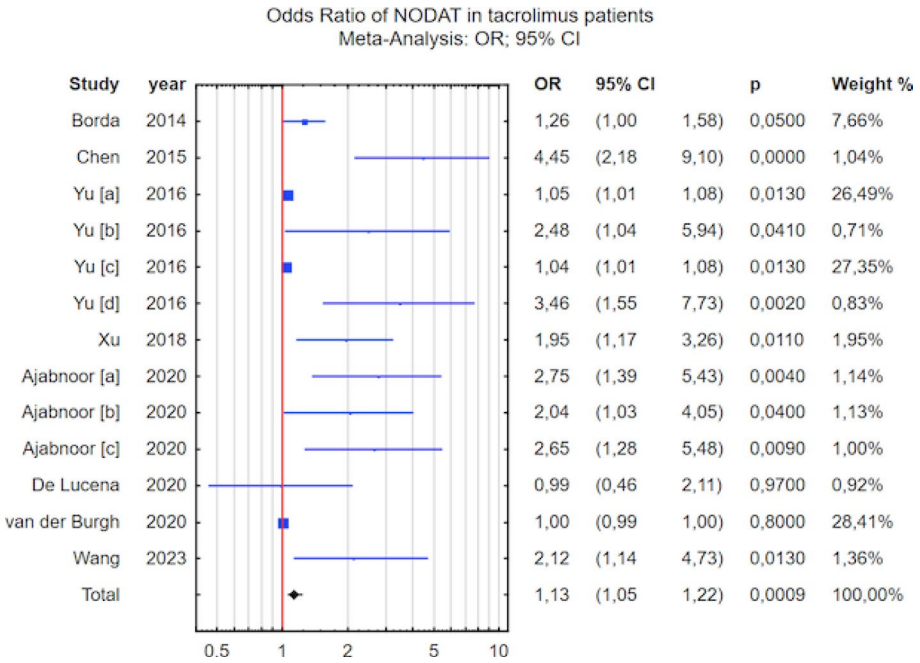
Fig. 2 PRISMA flow diagram of the review process

wrong exposure or outcome, wrong language (meaning different than English), or missing full text. Our final number of included studies was 24 [19–42] (Fig. 2).

Description of study characteristics

As presented in Table 2 most of the studies included in the review were cohort studies ($n=16$).

Further, two RCTs were included, and six cross-sectional studies. There was a total of 9,536 participants in the included studies, with a minimum and maximum sample size of 56 and 3342, respectively. The majority of studies were conducted in hospital settings ($n=16$). In all studies the percentage of male participants was higher than female, except one [35]. Studies were conducted in different parts of the world, from Saudi Arabia to Australia, with the highest number coming from China ($n=5$), Brazil ($n=3$), and Poland ($n=2$). The most common outcome assessed was diabetes ($n=14$). The other following outcomes considered body weight ($n=3$), lipid profile ($n=2$), body composition ($n=1$), electrolyte disorders ($n=1$), bone status ($n=1$), Vitamin D ($n=1$), and Vitamin B_{12} ($n=1$) deficiencies. The most common immunosuppressant assessed was tacrolimus ($n=16$). The time of participants after kTx being included in the studies varied from 0 to 8.4 years. The majority of studies were conducted 1 year after kTx ($n=9$). There were only five studies conducted within the 1-year post-transplant, and the majority of studies



*Yu [a] refers to old patients
**Yu[b] refers to family history of DM
***Yu [c] refers to pretransplant high serum glucose level
****Yu [d] refers to obesity

*Ajabnoor [a] refers to patients over 40 years old;
**Ajabnoor [b] refers to patients with BMI over 25 kg/m^2
***Ajabnoor [c] refers to patients with FK506 level > 10 ng/mL during the first 3 months.

Heterogeneity: Tau^2=0.005, Chi^2=75.42, df=12, p<0.001, I^2=84.09%

Fig. 3 The forest plot showing the relationship between tacrolimus and development of NODAT among kTx patients

($n=10$) were conducted long-term which means both within the 1 year after kTx and one-year post-transplant (Fig. 4).

Quality assessment

Figures 5 and 6 show quality ratings of the included studies for observational and RCTs, respectively. The twenty-two observational studies included present moderate ($n=13$), serious ($n=7$), or critical risk of bias ($n=2$). Two RCTs included in the review present 'some concerns' assessment and low risk of bias.

The summary of results

In the summary, seven main nutritional outcomes were assessed, described as follows: diabetes, body weight, lipid profile, body composition, electrolyte disorders, bone status, vitamin D and vitamin B_{12} deficiencies. The summary of results is presented in Table 3.

Diabetes

In total, fourteen studies assessed the effect of immunosuppressive therapy on the occurrence of diabetes following kidney transplantation [19–21, 24–26, 31, 36–42]. Among these, seven studies examined NODAT ($n=7$), six investigated PTDM ($n=6$), and one study focused on hyperglycaemia ($n=1$). In general, the immunosuppressive regimens under consideration predominantly included combinations involving calcineurin inhibitors, such as: i) Tac vs. CsA ($n=8$); ii) Tac alone ($n=4$), and CsA alone ($n=1$). Additionally, one study examined the transition from CNIs to belatacept. Overall, with the exception of two studies [73,91], all concluded that CNIs pose a risk factor for the development of diabetes. NODAT occurrence within the first year after kTx was investigated in three studies; however, comparing the findings proved challenging due to variations in the assessment of immunosuppressive regimens [36, 41, 42]. According to Xue et al., the incidence of NODAT stood at 20.3%, with the type of immunosuppressive regimen

Table 2 Characteristics of studies included in the review

Reference	Country	Design	Setting	Sample size	Age [years]	Male, %	Immunosuppressive scheme	Nutritional outcome(s)
Ajabnoor, 2020 [19]	Saudi Arabia	Cohort	Hospital and Research Center	235	44 ± 14 (PTDM); 34 ± 12 (non-PTDM)	51 (PTDM), 61.5; (non-PTDM)	Tac (FK 506) (6 to 10 ng/mL beyond 3 months) + prednisolone (20–5 mg) + MMF (1.5 – 2 g)[a]	PTDM
Beilhack, 2020 [22]	Austria	Cross- sectional	Outpatient clinic	576	55 ± 13	59	CNI inhibitors (Tac or CsA)	Electrolyte disorders
Bergmann, 2015 [23]	Australia	Cohort	Hospital	56	54 (mean)	100	Tac or CsA + prednisolone (5 – 12.5 mg)	Lipid abnormalities, glucose, body fat distribution, Cushingoid phenotype
Borda, 2014 [20]	Hungary	RCT	Clinical Center, University of Sheged	69	46.6 (mean)	53	Tac or CsA (steroid free therapy)	NODAT, IGT, IFG, normal glucose, albumin levels
Brzezińska, 2013 [24]	Poland	Cohort	Hospital Outpatient Transplantology Clinic	206	46.4 ± 12.3	61	Tac or CsA + prednisone + antiproliferative drug (azathioprine or MMF)	PTDM, IGT, IFG
Chen, 2015 [25]	China	Cohort	Hospital Organ Transplant Center	158	40.4 ± 9.4 (NODAT) 38.7 ± 8.2 (non- NODAT)	74	Tac or CsA + MMF or mizoribine + steroids	NODAT
de Lucena, 2020 [26]	Brazil	Cohort	Hospital	450	46.2 ± 1.3 (PTDM +); 40.7 ± 0.6 (PTDM-)	60	Tac (85%) + mycophenolate (53%) + prednisone (100%)	PTDM
de Oliveira, 2014 [27]	Brazil	Cohort	Hospital	203	37.1 ± 14.8	59.5	Tac (94.5%) or CsA (4.9%) + mycophenolate (99.9%) + steroids (41.3%)	Weight gain and obesity
Filipov, 2015 [28]	Bulgaria	Cross- sectional	Transplant Centre	289	42.69 ± 12.59	65	CNI inhibitors (steroids, pulse steroids within 12 months from 25 (OH)D testing, mycophenolic acid derivatives, azathioprine, CsA, Tac and mTOR	Vitamin D

Table 2 (continued)

Reference	Country	Design	Setting	Sample size	Age [years]	Male, %	Immunosuppressive scheme	Nutritional outcome(s)
Gregorini, 2017 [29]	Italy	Cross- sectional	Hospital and Pavia center	297	55.5 (median) (5.6—83)	65.3	CNI inhibitors (Tac or CsA), mammalian target of rapamycin (mTOR) inhibitors (imTOR; sirolimus or everolimus), antiproliferative drugs (MMF/ mycophenolic acid or azathioprine) and steroids	Bone status
Ichimaru, 2015 [30]	Japan	Cross- sectional	Outpatient clinic	386	52.2 ± 13.0	59.3	CNI inhibitors (Tac or CsA), antimetabolites (MMF, azathioprine, or mizorbine), Everolimus + steroids	Lipid abnormalities
Khalili, 2013 [31]	Iran	Cohort	Academic transplant centers	3342	37 ± 16 (mean)	63.4	CsA (300–150 mg) + MMF or Azathioprine + Prednisolone	Hyperglycemia
Kolonko, 2021 [32]	Poland	Cohort	Hospital	122	51.6 (48.5 ± 54.7) (SM); 44.7 (41.6 ± 47.9) (FM)	62	Tac + MMF + steroids	Body composition
Pontes, 2019 [33]	Brazil	Cross- sectional	Renal transplant outpatient clinic	225	47.5 ± 12.11	56	CNI inhibitors (Tac or CsA) or a mammalian target of rapamycin inhibitor (everolimus or sirolimus) + MMF or azathioprine + steroids (prednisolone 5 mg)	Vitamin B12
Ruangkanchanasetr, 2014 [34]	Thailand	Cross- sectional	Four Kidney Transplant Centers	267	49.32 ± 12.07 (BMI ≥ 25); 48.43 ± 9.2 (BMI 23–24.9); 44.08 ± 10.75 (BMI 18.5-22.9)	64.4 (BMI ≥ 25; 68 (BMI 23–24.9); 59 (BMI 18.5-22.9)	Various immunosuppressants (Tac)	Obesity

Table 2 (continued)

Reference	Country	Design	Setting	Sample size	Age [years]	Male, %	Immunosuppressive scheme	Nutritional outcome(s)
Sayilar, 2022 [35]	Turkey	Cohort	Hospital	128	44 (median) (CsA group); 36 (median) (Tac group)	46	CNI inhibitors (CsA 5 mg/kg/d or Tac 0.15 mg/kg/d) and mycophenolic acid [(MMF) 2.000 mg/d or entericcoated mycophenolate sodium (EC-MPS) 1.440 mg/d] + steroids	Anthropometric measurements
Terrec, 2020 [36]	France	Cohort	Hospital	103	58 ± 14	68	Conversion from CNIs to belacept[b]	Glycemic parameters (HbA1c) = NODAT
Tillmann, 2017 [37]	Germany	Cohort	Hospital	400	54.0 ± 11.9	56.5	CsA or Tac + 5 mg Prednisolone (76%) or steroid free (24%)	Diabetes
Torres, 2018 [21]	Spain	RCT	Hospital	128	61 ± 7.7	72.7	Tac or CsA + MMF + steroids (steroid minimization)	pre-diabetes and NODAT
van der Burgh, 2019 [38]	Netherlands	Cohort	University Medical Center	167	52 ± 14	60	Tac	PTDM
Wang, 2023 [39]	China	Cohort	University Hospital	396	44.4	59	Tac at 0.1 mg/(kg·d-1) or CsA at 5 mg/(kg·d-1) + MMF + 15–20 mg/d of methylprednisolone	NODAT
Xu, 2018 [40]	China	Cohort	Hospital	358	34.53 ± 9.03 (PTDM); 32.92 ± 8.79 (non-PTDM)	54	Tac or CsA + an antiproliferative medication (MMF or myfortic) + steroids	PTDM
Xue, 2018 [41]	China	Cohort	Hospital	557	39.18 ± 12.25	100	Standard triple immunosuppression (Tac or CsA + MMF or AZE (azetolamide) + steroids (+ use of IL-2Ra)	NODAT
Yu, 2016 [42]	China	Cohort	Hospital	418	47.82 ± 10.75 (NODAT); 4.85 ± 10.54 (Non-NODAT)	55	Standard triple immunosuppression (Tac or CsA + MMF or AZE (azetolamide) + steroids	NODAT

[a] Maintaince therapy

[b] Late conversion to belatacept was considered when the time between transplantation and the switch was performed at least 6 months after transplantation

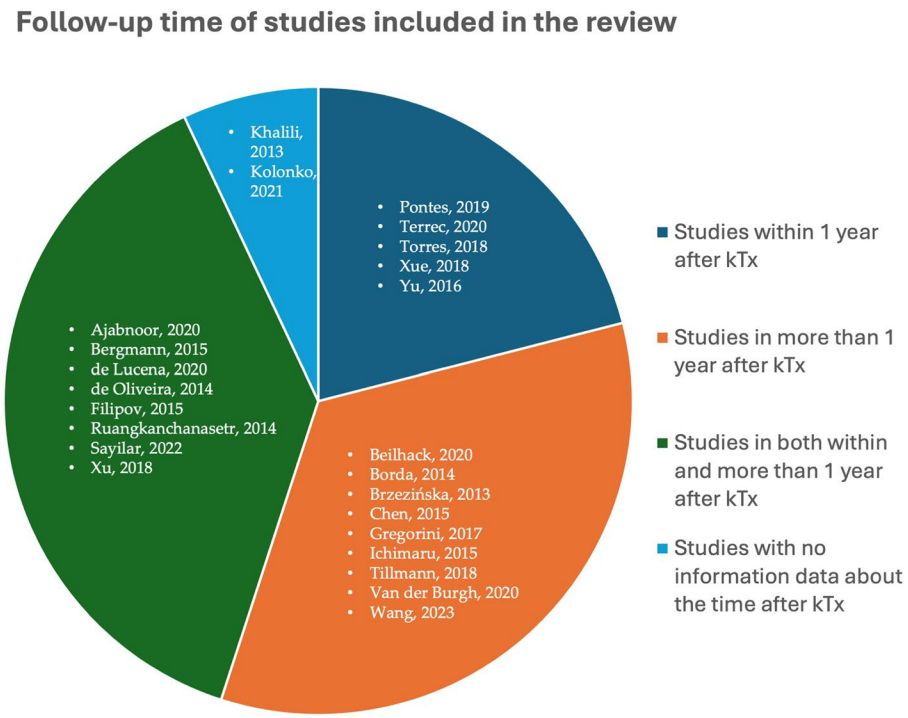


Fig. 4 Follow-up time of studies included in the review

demonstrating a consistent protective effect against its onset. On the contrary, Yu et al. discovered an association between the use of tacrolimus and the onset of NODAT. Finally, Terrec et al. concluded that a late transition from CNIs to belacept proved to be a beneficial therapeutic strategy, significantly enhancing glycemic parameters. NODAT incidence among patients beyond the first year post-kTx was delineated in four studies, all of which examined the impact of tacrolimus or cyclosporine (Tac vs. CsA) [20, 25, 37, 39]. Three of them identified tacrolimus as posing a higher risk for the development of NODAT compared to cyclosporine [20, 25, 37]. One of them found no difference in the occurrence of NODAT between tacrolimus and cyclosporine [39]. The forest plot showing the relationship between tacrolimus and development of NODAT among kTx patients is described in Fig. 3. Eight studies explored the relationship between developing NODAT and the use of tacrolimus. Six of the studies showed an increased risk of NODAT (OR > 1, $p < 0.05$). The studies were though too heterogeneous to perform subgroup analysis. Torres et al. described PTDM within the first year post-kTx, concluding that in high-risk patients, employing tacrolimus-based immunosuppression with steroid minimization provides the optimal balance between the incidence of PTDM [21]. Two studies examined PTDM incidence among patients beyond the first year post-kTx [24, 38]. Brzezinska et al. found no difference between tacrolimus and cyclosporine concerning the incidence of PTDM after kTx. However, van der Burgh et al. discovered that tacrolimus use posed a risk factor for PTDM development. Three studies examined the long-term incidence of PTDM [19, 26, 40]. In them, tacrolimus has been identified as a risk factor for developing PTDM. Finally, cyclosporine was identified as the higher risk factor for hyperglycaemia [31].

Body weight

Three studies analysed the effect of immunosuppressive therapy on body weight, of which two were cohort studies and one cross-sectional [27, 33, 34]. According to Ruangkanchanasetr et al., the prevalence of obesity stood at 12.6% during the initial year, escalated to 28.6% within the first three years, and surged to 39.7% beyond the third-year post-transplantation. mTOR inhibitor was administered more frequently to obese patients compared to those with normal BMI (16.1% vs 7%; $P = 0.056$). Conversely, obese recepients showed significantly lower usage of tacrolimus compared to those with normal BMI [8]. In contrast, Sayilar et al. observed notable rises in body weight and body mass index across both CsA and Tac groups. Following a successful kidney transplant, anthropometric measurements typically increase in most recipients. While the impact of calcineurin inhibitor type on weight gain remains unclear, regression analysis

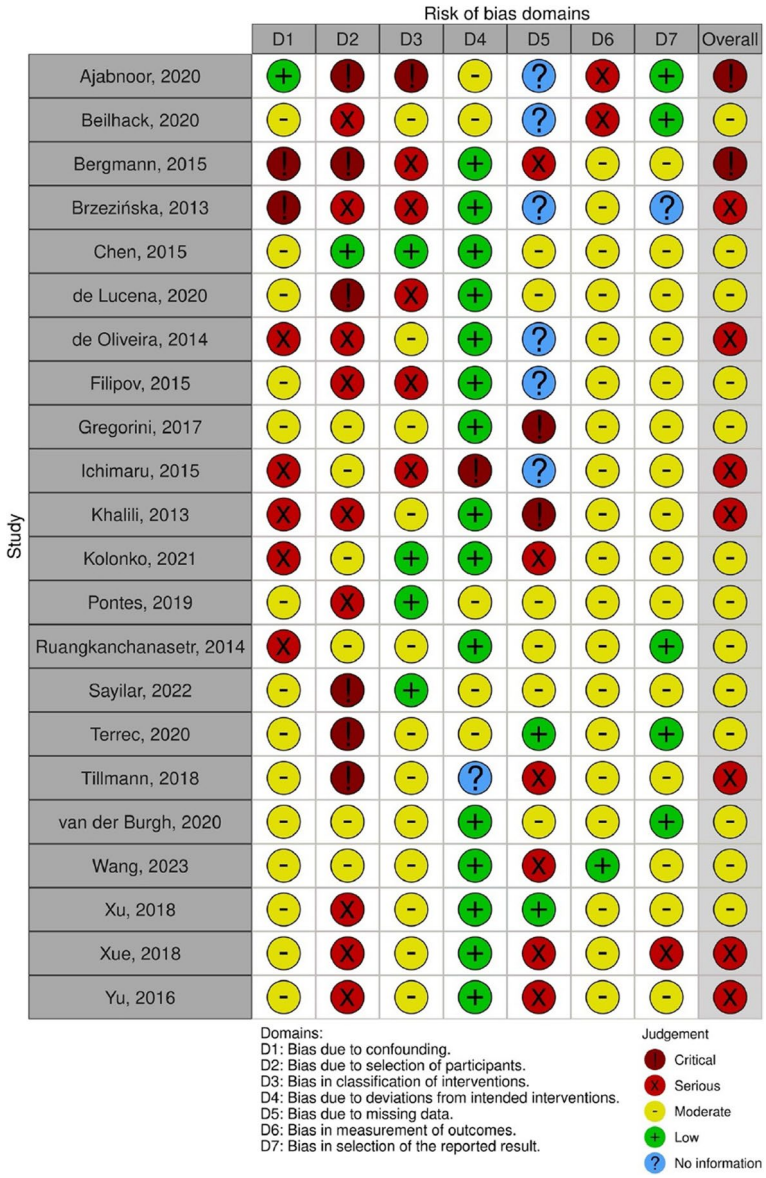


Fig. 5 Risk of bias assessment of observational studies included in the review using ROBINS-I tool

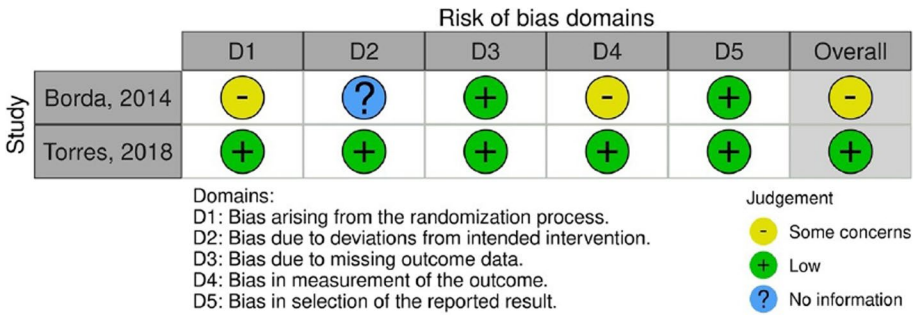


Fig. 6 Risk of bias assessment of RCTs included in the review using RoB 2 tool

Table 3 The summary of results from studies assessing the use of immunosuppressive therapy and the nutritional status of kTx patients

Reference	Nutritional outcome	Type of immunosuppressants used	Results	Association with the disease (Yes/No)
1. Diabetes				
Borda, 2014 [20]	NODAT	Tac vs. CsA (steroid free therapy)	The incidence of diabetes was significantly different in the CsA group compared to the Tac group (14% vs. 26%, $p=0.0002$). Tac (OR = 1.258, $p=0.05$); CsA (OR = 0.317, $p=0.077$)	Yes. Tac
Brzezinska, 2013 [24]	PTDM	Tac vs. CsA	In 103 patients (50%), we diagnosed glucose metabolism disorders. 19% of patients had PTDM, 14% IFG, and 17% IGT. We did not find any differences in the frequency of glucose metabolism disorders between patients treated with tacrolimus and with cyclosporine	No difference
Chen, 2015 [25]	NODAT	Tac vs. CsA	The incidence of NODAT at 24 months was 28.6%. Independent risk factors of NODAT, evaluated by logistic regression, were as follows: age > 50 ($p<0.001$), HCV infection ($p=0.004$), acute rejection episodes ($p=0.015$), and tacrolimus usage ($p<0.001$). Tac (OR = 4.45, 95%CI 2.18–9.10; $p=0.000$)	Yes. Tac
Tillman, 2018	NODAT	Tac vs. CsA	A small but statistically significant difference in HbA1c levels was observed between the control and the steroid groups (5.56 ± 0.54 vs. 5.67 ± 0.0.45%, $p=0.045$). The incidence rates of pre-diabetes and NODAT per 100 patients per year were 9.3 and 3.0, respectively. Regression analysis showed that low-dose steroids ($p=0.026$, RR = 1.789, 95%CI = 1.007–3.040) and age ($p<0.001$, RR = 1.037/year, 95%CI = 1.018–1.057) were associated with pre-diabetes, whereas BMI ($p<0.001$, RR = 1.190, 95%CI = 1.084–1.307), age ($p<0.001$,RR = 1.087/year, 95%CI = 1.047–1.129) and Tac use ($p=0.010$, RR = 3.300, 95%CI = 1.328–8.196) were associated with NODAT	Yes. Tac

Table 3 (continued)

Reference	Nutritional outcome	Type of immunosuppressants used	Results	Association with the disease (Yes/No)
Torres, 2018 [21]	PTDM	Tac vs. CsA (steroids or steroid free)	The study comprised 128 de novo renal transplant recipients without pretransplant diabetes (Tac- SW: 44, Tac-SM: 42, CsA-SM: 42). The 1-year incidence of PTDM in each arm was 37.8% for Tac-SW, 25.7% for Tac- SM, and 9.7% for CsA-SM (Tac-SW vs. CsA-SM 3.9 [RR = 1.2–12.4; $p = 0.01$]; RR Tac-SM vs. CsA-SM 2.7 [RR = 0.8–8.9; $p = 0.1$]). Antidiabetic therapy was required less commonly in the CsA-SM arm ($p = 0.06$); however, acute rejection rate was higher in CsA-SM arm (Tac-SW 11.4%, Tac-SM 4.8%, and CsA-SM 21.4% of patients; cumulative incidence $p = 0.04$). Graft and patient survival, and graft function were similar among arms. In high-risk patients, tacrolimus-based immunosuppression with SM provides the best balance between PTDM and acute rejection incidence	Yes. Better Tac
Wang, 2023 [39]	NODAT	Tac or CsA	The risk factors of NODAT include age, weight, BMI, smoking habits, drinking habits, preoperative fasting blood glucose, preoperative TG, preoperative TC, acute rejection, and exposure to immunosuppressive agents. Among them, only acute rejection and immunosuppressive agents are modifiable factors. The application of CsA as an immunosuppressive agent after surgery may decrease the incidence rate of NODAT and prolong the longevity of patients receiving renal transplantation. Tac (OR = 2.123; 95%CI 1.142–4.731; $p = 0.013$)	Yes. Both
Xu, 2018 [40]	PTDM	Tac vs. CsA	30.72% of participants were diagnosed with PTDM. Tacrolimus was a risk factor for developing PTDM: Tac (OR = 1.952; 95%CI 1.169–3.258; $p = 0.011$)	Yes. Tac

Table 3 (continued)

Reference	Nutritional outcome	Type of immunosuppressants used	Results	Association with the disease (Yes/No)
Xue, 2018 [41]	NODAT	Tac vs. CsA	The incidence of NODAT at the end of follow-up was 20.3%. Type of immunosuppressive regimen, and immunosuppressant concentration after renal transplantation, IL-2Ra use remained a protective factor against the development of NODAT (HR 0.12; 95% CI 0.03–0.51; $P=0.004$)	Protective effect
Ajabnoor, 2020 [19]	PTDM	Tac	22.5% ⟶ patients ⟶ (not ⟶ diabetic ⟶ before ⟶ kTx) ⟶ developed ⟶ PTDM [95%CI = 22,5%]. Age ≥ 40 years at transplant (OR = 2.75, $p=0.004$), BMI > 25 kg/ m 2 at transplant (OR = 2.04, $p=0.040$), and FK506 level ≥ 10 ng/mL during the first 3 months (OR = 2.65; 95% CI 1.28–5.48; $p=0.009$) were all significantly related to PTDM development	Yes
De Lucena, 2020 [26]	PTDM	Tac	Tac (OR = 0.99; 95%CI 0.46–2.11; $p=0.97$); CsA (OR = 1.45; 95%CI 0.50- 4.24; $p=0.49$)	Yes
van der Burgh, 2019 [38]	PTDM	Tac	Risk factors for the development of PTDM: 1) univariate analysis: Tac (OR = 1.06; 95% CI 0.99–1.00; p = 0.8), serum magnesium (OR = 0.98; 95% CI 0.96–1.00; $p=0.01$) 2) multivariate analysis: Tac (OR = 1.00; 95% CI 0.99- 1.00; p = 0.6); serum magnesium (OR = 0.98; 95% CI 0.96–1.00; p = 0.01)	Yes
Yu, 2016 [42]	NODAT	Tac	By multivariate analysis, old age (OR = 1.05; 95%CI = 1.01–1.08), family history of diabetes mellitus (OR = 2.48; 95%CI = 1.04–5.94), pre-transplant high serum glucose level (OR = 1.04; 95%CI = 1.01–1.08), and obesity (OR = 3.46; 95%CI: 1.55–7.73) were independent risk factors for NODAT. In contrast, serum magnesium levels and the use of tacrolimus are not associated with the development of NODAT (OR = 1.50; 95% CI 0.69–3.26; $p=0.311$)	No
Khalili, 2013 [31]	Hyperglycaemia	CsA	Risk factors for hyperglycaemia were higher Cyclosporine level, impaired renal function, and reduced HDL level.	Yes

Table 3 (continued)

Reference	Nutritional outcome	Type of immunosuppressants used	Results	Association with the disease (Yes/No)
Terrec, 2020 [36]	NODAT	Conversion from CNIs to belacept	A late switch from CNI to belatacept was a valuable therapeutic option for diabetic kidney recipients and substantially improved glycemic parameters.	Yes. Belacept better
2. Body weight				
Ruangkanchanasetr, 2014 [34]	Body weight	Tac (and other immunosuppressants checked)	Univariate Analysis of the Obesity Group and the At Risk of Obesity Group Compared with Normal BMI Patients: 1) obesity BMI > = 25: Cyclosporine (OR = 1.27; 95% CI 0.72–2.26; $p = 0.412$); Tacrolimus (OR = 0.52; 95%CI 0.28–0.95; $p < 0.05$); Mycophenolate mofetil (OR = 0.83; 95%CI 0.42–1.64; $p = 0.597$); Mycophenolic acid (OR = 0.66; 95%CI 0.33–1.31; $p = 1.31$); Azathioprine (OR = 0.89; 95%CI 0.38–2.08; p = 0.786); Sirolimus or everolimus (OR = 2.55; 95%CI 0.98–6.64; $p = 0.056$); Prednisolone (OR = 0.68; 95CI 0.33–1.43; $p = 0.309$); 2) at risk of obesity BMI = 23–24.9: Cyclosporine (OR = 0.72; 95%CI 0.36–1.44; $p = 0.354$); Tacrolimus (OR = 1.22; 95%CI 0.62–2.41; $p = 0.563$); Mycophenolate mofetil (OR = 0.8; 95%CI 0.36–1.77; $p = 0.563$); Mycophenolic acid (OR = 0.68; 95%CI 0.3-1.54; $p = 0.35$); Azathioprine (OR = 0.84; 95%CI0.3–2.33; $p = 0.734$); Sirolimus or everolimus (OR = 1.48; 95%CI 0.44–4.91; $p = 0.525$); Prednisolone (OR = 0.54; 95%CI 0.24–1.24; $p = 0.147$)	Yes. Tac

Table 3 (continued)

Reference	Nutritional outcome	Type of immunosuppressants used	Results	Association with the disease (Yes/No)
Sayilar, 2022 [35]	Body weight	Tac vs. CsA	Significant increases in body weight and body mass index (between 3 and 48 months), waist and hip circumferences (between 1and 48 months), waist-to-hip ratio (between 1 and 3 or 6 months) and neck circumference (between 1 and 12 or 24 months) were observed in both CsA and Tac groups. A significant increase was noted in post-transplant body fat percentage values for the 3 to 24 months in the CsA group, whereas for the 24 to 48 months in both CsA and Tac groups. Hip circumferences percentage changes from the pre-transplant period to the 1, 12 and 24 months were significantly higher in CsA than in the Tac group. At each time point, there was no significant difference in percentage changes for other anthropometric parameters between the CsA and Tac groups	Yes. Depends on the time measure
De Oliveira, 2014 [27]	Body weight	steroids vs. steroid-free therapy	The following variables were identified as significantly associated with a decreased risk of weight gain within 36 months post-transplantation: male gender of the recipient (OR = 0.304; $p = 0.001$; 95%CI = 0.147–0.631) and older age of the recipient (OR = 0.933; $p < 0.01$; 95%CI = 0.902–0.966)	No

Table 3 (continued)

Reference	Nutritional outcome	Type of immunosuppressants used	Results	Association with the disease (Yes/No)
3. Lipid profile				
Bergmann, 2015 [23]	Lipid profile	steroids vs. steroid-free therapy	There was no statistically significant correlation between total or free prednisolone exposure (tAUC0–6 h or fAUC0–12 h) and HDL, LDL, triglycerides or HbA1c. Free prednisolone AUC (fAUC0–12 h) was significantly positively correlated with a patient's waist to upper arm circumference ratio with a Spearman correlation coefficient ($r = 0.3$, $p = 0.02$). A trend towards a positive correlation between free prednisolone AUC and a patient's neck to upper arm circum- ference ratio was also observed, but this did not reach statistical significance (Spearman correlation coefficient $r = 0.24$, $p = 0.08$). No significant association was found between VACS (Cushing phenotype) score and total or free prednisolone exposure	No
Ichimaru, 2015 [30]	Lipid profile	Various immunosuppressants	The relationships among the patients' immunosuppressant use and lipid abnormalities: MMF (OR = 0.86; 95%CI 0.37–2.03; $p > 0.05$); Everolimus (OR = 2.26; 95%CI 1.17–4.38; $p < 0.05$); Mizoribine (OR = 0.08; 95%CI 0.28–2.28; $p = ?$); Azathioprine (OR = 1.28; 95%CI 0.48–3.40; $p > 0.05$); CsA (OR = 1.71; 95%CI 0.57–5.15; $p > 0.05$); Tac (OR = 1.15; 95%CI 0.38–3.45; $p > 0.05$); Corticosteroids (OR = 3.11; 95%CI 1.27–7.67; $p < 0.05$)	Yes—Everolimus and corticosteroids No – CsA

Table 3 (continued)

Reference	Nutritional outcome	Type of immunosuppressants used	Results	Association with the disease (Yes/No)
4. Body composition				
Kolonko, 2021 [32]	Body composition	Tac (slow and fast metabolizers)	There was no difference in phase angle, visceral fat area, lean body mass index (LBMI) and the proportion of lean mass as a percentage of total body mass between the subgroups of slow and fast metabolizers. However, subjects with LBMI ≥ median value of 18.7 kg/m^2, despite similar initial tacrolimus dose per kg of body weight, were characterized by a significantly lower tacrolimus C/D ratio (median 1.39 vs. 1.67, respectively; $p < 0.05$) in comparison with the subgroup of lower LBMI. Multivariate regression analysis confirmed that age (rpartial = 0.322; $p < 0.001$) and LBMI (rpartial = −0.254; $p < 0.01$) independently influenced the tacrolimus C/D ratio. A LBMI assessed by BIA may influence the tacrolimus metabolism in the early post-transplant period and can be a useful in the optimization of initial tacrolimus dosing	No
5. Electrolyte disorders				
Beilhack, 2020 [22]	Electrolyte disorders	CNI inhibitors	Patients without any CNI therapy ($n = 50$) had a lower prevalence of hypomagnesaemia, hyperkalaemia and metabolic acidosis compared with cal- cineurin inhibitor treatment (4% vs 26%; 2% vs 14.1% and 2% vs 11.4%; $p < 0.01$)	Yes
6. Bone status				
Gregorini, 2017 [29]	Bone status	Steroids, mTOR, CsA, Tac	A significant correlation ($p < 0.05$) was observed for both osteopenia and osteoporosis with menopause, transplantologic age, CSD, previous glomerulonephritis, and mammalian target of rapamycin (mTOR) inhibitors treatment (imTOR)	Yes
7. Vitamin D				
Filipov, 2015 [28]	Vitamin D	CNI inhibitors	There was negative association between the concentration of 25(OH)D and female gender, presence of DM and BMI. In addition, CNI intake was also found to negatively affect 25(OH)D	Yes

Table 3 (continued)

Reference	Nutritional outcome	Type of immunosuppressants used	Results	Association with the disease (Yes/No)
8. Vitamin B12				
Pontes, 2019 [33]	Vitamin B12	MMF	Among individuals with adequate intake of B_{12}, the deficiency of this vitamin was more frequently seen in those using MMF) (17%) vs. azathioprine (2%), $p=0.01$. In conclusion, the prevalence of B_{12} deficiency in kTx was estimated as 14% and was associated with reduced intake of B_{12} as well as higher adiposity, especially in women, and with the use of MMF	Yes

indicated that CNI type wasn't identified as a risk factor for obesity development by the 48th month. However, it's prudent to exercise caution regarding its dyslipidaemic effects in patients using CsA and the potential risks associated with Tac use in patients with a predisposition to diabetes [35]. In another study, assessing the prevalence and the influence of steroid-free therapy on obesity de Oliveira et al. found that on average, the percentage of weight gain reached 9% after 36 months post-transplantation, coinciding with a significant increase in the prevalence of overweight and obesity during this period. Interestingly, steroid therapy showed no influence on the percentage of weight gain post-transplantation. Instead, weight gain can result from factors such as increased appetite, fluid retention, or changes in energy balance that occur indirectly due to steroid use. It must be outlined though that low-dose steroids play a key role in managing chronic inflammatory and autoimmune conditions by reducing inflammation with fewer side effects than higher doses. Their use requires careful monitoring to balance benefits and risks, such as osteoporosis or adrenal suppression. Instead, associations were found between younger recipient age, female gender, younger donor age, and higher creatinine levels with the most substantial weight gain following transplantation [27]. All studies were conducted long-term which means within 1-year post-transplant and 1 year after.

Lipid profile

Two studies investigated the relationship between immunosuppressives and lipid profile among kidney transplant recepients [23, 30]. One study was conducted within 1 year after kTx and one was conducted long-term. The results were inconsistent. Bergmann et al. reported no statistically significant correlation between total or free prednisolone exposure (tAUC0–6 h or fAUC0–12 h) and serum levels of HDL-cholesterol, LDL-cholesterol, and triglycerides [23]. However, Ichimaru et al. found that everolimus and corticosteroid use were significant risk factors for lipid abnormalities. In the same study, cyclosporine was not identified as a significant risk factor for the development of lipid abnormalities [30].

Body composition

In our review, one study assessed the body composition among kidney transplant recepients [32]. In this cohort study, significant increases were observed in various anthropometric measurements in both CsA and Tac groups. These included waist and hip circumferences between the 1st and 48th months, waist-to-hip ratio between the 1st and 3rd or 6th months, and neck circumference between the 1st and 12th or 24th months. Additionally, a significant increase in post-transplant body fat percentage values was noted for the 3rd to 24th months in the CsA group and for the 24th to 48th months in both CsA and Tac groups. Moreover, percentage changes in hip circumferences from the pre-transplant period to the 1st, 12th, and 24th months were significantly higher in the CsA group compared to the Tac group. However, there were no significant differences in percentage changes for other anthropometric parameters between the CsA and Tac groups at each time point [35]. Acknowledging the integral role that body weight and BMI play in the care of patients following kidney transplantation, it merits a separate paragraph given its significance for their post-transplant health and well-being.

Electrolyte disorders

Electrolyte disorders in our review were described in one study [22]. Patients without any CNI therapy ($n=50$) had a lower prevalence of hypomagnesaemia, hyperkaliaemia

and metabolic acidosis compared to calcineurin inhibitor treatment (4% vs 26%; 2% vs 14.1% and 2% vs 11.4%; $p < 0.01$). The study was conducted above 1-year post-transplant.

Bone status

One study explored the relationship between immunosuppressive therapy and bone status among kidney transplant patients [29]. Gregorini et al. found that there is a significant correlation ($p < 0.05$) for both osteopenia and osteoporosis with mammalian target of rapamycin (mTOR) inhibitors treatment (imTOR) among kTx patients. The study was conducted above 1-year post-transplant. None of the studies included in this review mentioned the effect of the steroids on bone status among kTx patients.

Vitamin D

The relationship between immunosuppressive therapy and serum 25(OH)D level among kTx patients in our review was described in one study [28]. CNIs were found to negatively affect serum 25(OH)D level by Filipov et. al. In addition, there was a negative association between the concentration of 25(OH)D and female gender, presence of DM and BMI. The study was conducted long-term.

Vitamin B_{12}

The association between the immunosuppressive medication and vitamin B_{12} deficiency was described in one study [33]. Pontes et al., found that among individuals with adequate intake of B_{12}, the deficiency of this vitamin was more frequently seen in those using MMF) (17%) vs. azathioprine (2%), $p = 0.01$. In conclusion, the prevalence of B_{12} deficiency in kTx was estimated as 14% and was associated with reduced intake of B_{12} as well as higher adiposity, especially in women, and with the use of MMF.

Discussion

The aim of this systematic review was to summarise the evidence of nutritional diseases following exposure to immunosuppressive therapy among patients following kidney transplantation (kTx). A total of 24 studies met our inclusion criteria [19–42]. The assessed outcomes encompassed diabetes, body weight, lipid abnormalities, body composition, electrolyte disorders, bone status, and serum of the vitamin D and the vitamin B_{12} levels. The immunosuppressive medications comprised calcineurin inhibitors (CNIs), tacrolimus (Tac), cyclosporine (CsA), mTOR inhibitors, antiproliferative, and glucocorticosteroids. Our findings indicate that, overall, immunosuppressive therapy has an effect on nutritional diseases among kTx patients. Nutritional diseases are important because they affect the health of the patient and the success of the graft. Poor nutrition, whether due to malnutrition or obesity, can weaken the immune system, slow down healing, and increase the risk of complications like infections or graft rejection. Proper nutrition helps patients recover better and improves the chances of the graft functioning well over time. Furthermore, certain immunosuppressants demonstrate a stronger association than the others. Half of the studies regarding diabetes included in our review described Tac as a stronger risk factor for developing this disease compared to CsA. Our findings are in line with a systematic review conducted by Heisel et al., which examined diabetes and CNIs among solid organ transplant patients. Heisel et al. concluded that patients receiving Tac exhibited a higher incidence of post-transplant diabetes compared to those receiving CsA [43]. Additionally, other studies have linked diabetes to the use of immunosuppressive medications, which may be reversible after modifying the immunosuppressive treatment. This includes reducing the doses of steroid drugs and replacing Tac with CsA [10]. It is important though to consider the overall immunological risk when making decisions about immunosuppressive therapy, particularly regarding glycaemia control. Switching from tacrolimus to cyclosporine or adjusting steroid doses must be based on the patient's individual immunological risk and medically justified. Tac is a more potent immunosuppressant than CsA, and any changes should account for the risk of all immunity and graft rejection. However, in two RCTs studies concerning diabetes and immunosuppressive medications, the results from Torres and Borda were inconsistent. This underscores the necessity for further research in this area, emphasizing the importance of conducting studies of the highest quality, prospective RCTs. In the later post-transplant period, particularly in recipients where metabolic risks outweigh the risks of alloimmunity, switching from tacrolimus to cyclosporine may be a viable option. The importance of a dynamic, individualized approach, focusing on gradually reducing steroid dosages to levels that are proven to be safe while closely monitoring the patient's immunological and metabolic status. This personalized approach ensures that the benefits of immunosuppressive therapy are balanced with the need to minimize metabolic complications. The causes of increased body fat mass in patients after transplantation include factors such as improved appetite, enhanced sense of taste, lack of necessity to adhere to a restrictive diet, and the use of steroid medications [10]. In proposed systematic review, three studies analysed the effect of immunosuppressive medications on

body weight, of which two were cohort studies and one cross-sectional. It was observed that obese patients more frequently used mTOR inhibitors and less often Tac [34]. In contrast, another study noted significant increases in body weight and body mass index across both CsA and Tac groups [35]. Our findings are consistent with a scoping review that emphasized the limited evidence on this topic in the scientific literature, as well as the lack of high-quality evidence from intervention studies [44]. One of the complications associated with chronic steroid therapy is Cushing's syndrome, characterized by abdominal obesity and sarcopenia. Interestingly, steroid therapy did not demonstrate any influence on the percentage of weight gain post-transplantation in our review [27].

Dyslipidaemia represents a significant and frequently encountered burden post-transplant. In our review, two studies investigated the association between immunosuppressive medications and lipid profile. Everolimus emerged as a significant risk factor for lipid abnormalities, while CsA did not show the same association. However, the results regarding the use of steroids were inconsistent. Our findings contradict the existing literature, which suggests that components contributing to lipid abnormalities include immunosuppressive medications such as steroid drugs, calcineurin inhibitors like CsA rather than Tac, and mTOR inhibitors [45].

One study assessed the effect of fast and slow Tac metabolizers on body composition [32]. As a result, there was no difference in phase angle, visceral fat area, lean body mass index (LBMI) and the proportion of lean mass as a percentage of total body mass between the subgroups of slow and fast metabolizers.

In our review, mTOR inhibitors were found to be associated with the bone status post-transplant. Gregorini et al. concluded that there is a significant correlation for both osteopenia and osteoporosis with mammalian target of rapamycin (mTOR) inhibitors treatment (imTOR) among kTx patients [29]. What is more, CNIs were found to negatively affect serum 25(OH)D level [28]. Interestingly, none of the studies included in our review specifically addressed the impact of steroids on bone status, a crucial aspect given their widespread use in transplant patients. Steroids are known to affect bone metabolism, increasing the risk of osteoporosis and fractures. Future research should focus on this gap, as understanding the role of steroids in bone health could significantly improve patient management and outcomes. This topic is particularly relevant in the context of long-term immunosuppressive therapy and its associated risk [46].The association between the immunosuppressive medication and vitamin B_{12} deficiency was described in one study [33]. Pontes et al. established the B_{12} deficiency was linked to the use of MMF. Our findings are in line with the literature which states that immunosuppressive medications contribute to development of anemia (mycophenolate mofetil/Na, Tac, azathioprine, mTOR inhibitors), blockers of the renin–angiotensin–aldosterone (RAA) system (angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists), allopurinol, trimethoprim [10].

Patients without using CNIs had a lower prevalence of hypomagnesaemia, hyperkalaemia and metabolic acidosis compared with calcineurin inhibitor treatment. There was no difference in phase angle, visceral fat area, LBMI and the proportion of lean mass as a percentage of total body mass between the subgroups of slow and fast Tac metabolizers. Only one study assessed this relationship which found that patients without any CNI therapy had a lower prevalence of hypomagnesaemia, hyperkalaemia and metabolic acidosis compared with calcineurin inhibitor treatment. Our findings are in line with the existing literature [10]. It is necessary to monitor magnesium concentrations and in case of deficiency—depending on its severity—supplementation of this element via intravenous infusions (in the early period after transplantation) or in the form of tablets [38].None of the studies examined an important aspects which are serum potassium and calcium levels. Among patients following kTx, variations in serum potassium concentrations are evident, encompassing both hypo- and hyperkalaemia [20]. Furthermore, the distribution of studies across different outcomes may not accurately represent the prevalence or clinical significance of those outcomes post-transplant. While our review highlighted 14 studies on post-transplant diabetes, it's crucial to acknowledge that certain outcomes may garner more attention due to their clinical relevance, existing literature, or research priorities. For instance, lipid abnormalities are more prevalent than diabetes among kTx patients. The relatively low number of studies examining body weight may be due to various factors such as methodological challenges, limited resources, or research priorities. While it's important to acknowledge the discrepancies in the distribution of studied outcomes, it's also crucial to interpret the findings in the context of available evidence and research limitations. Future research efforts may benefit from addressing gaps in the literature and prioritizing areas with significant clinical implications for kTx patients.

Conclusions

To the best of our knowledge, this is the first systematic review that summarises the evidence of immunosuppressive therapy and nutritional diseases of patients following kidney transplantation. A strength of our review

is that we report on a large number of studies, including data from various populations. What is more, we have analysed the data both qualitatively and quantitatively. The limitations include high heterogeneity, and the low quality of studies incorporated in the review. Also, publication bias, language and access to certain studies as well as reviewer bias must be taken into consideration. Despite the above limitations, our findings carry significant clinical implications: i) Immunosuppressive therapy affects various nutritional diseases among post-kidney transplant patients; ii) Tac emerged as a higher potent risk factor for disease development compared to CsA; iii) Diabetes garnered the most attention in this research area. Given the heterogeneity and suboptimal quality of the studies included in our review, it is imperative that future research endeavors prioritize high-quality, prospective randomized controlled studies. These rigorous study designs can provide more reliable evidence regarding the association between immunosuppressive therapy and the nutritional status of kidney transplant recepients. Furthermore, additional longitudinal studies focusing on nutritional outcomes are warranted to enhance our understanding of the long-term effects of immunosuppressive therapy among this population. By conducting well-designed RCTs and longitudinal studies, researchers can contribute to filling the existing gaps in the literature and ultimately improve clinical management strategies for kTx patients, thereby enhancing their overall health and well-being. Finally, for a conclusive attribution of the increase in the mentioned diseases to immunosuppressive medications, forthcoming researchers ought to delve into the dietary habits of kidney transplant patients. This exploration will afford a more profound comprehension of the subject matter under study.

Abbreviations

95%CI	95% Confidence interval
CsA	Cyclosporine
CVD	Cardiovascular diseases
ESRD	End stage renal disease
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
kTx	Kidney transplantation/ kidney transplant
LBMI	Lean body mass index
MMF	Mycophenolate mofetil
NODAT	New-onset diabetes after transplantation
OR	Odds ratio
p	*p*-Value
PTA	Post transplantation anemia
PTDM	Post-transplant diabetes mellitus
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register for Systematic Reviews
RCTs	Randomized controlled trials
RoB 2	The Cochrane Risk of Bias tool
ROBINS-I	Risk of Bias in Non-randomized Studies of Interventions
Tac	Tacrolimus
TC	Total cholesterols

Supplementary Information

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Supplementary Material 1.
Supplementary Material 2.
Supplementary Material 3.
Supplementary Material 4.

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Authors' contributions
Conceptualization: A.A.K and D.S.L.; Methodology: D.S.L. and A.A.K.; Data Curation: M.K., A.K.N.N, and A.A.K; Data Analysis: K.K.; Narrative synthesis: A.K.K; Writing – original draft: A.A.K.; Review and Editing: All authors; Supervision: D.S.W and D.S.L. All authors have read and agreed to the published version of the manuscript.

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Data availability
Data is provided within the manuscript or supplementary information files. The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

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Competing interests
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