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Immunosuppressive Regimens and Serum Testosterone in Male Kidney Transplant Recipients: A Systematic Review and Network Meta-Analysis

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Abstract
Introduction: *Testosterone below 12 nmol/L may indicate hypogonadism in symptomatic male kidney transplant recipients.* ***Objective:*** *To compare testosterone levels across immunosuppressive regimens.* ***Method:*** *This PROSPERO-registered review (CRD420261502758) searched PubMed, ScienceDirect, SpringerLink, OpenAlex, and Google Scholar through 2 September 2026. Eligible studies compared immunosuppressive regimens and reported total testosterone in adult male recipients. ROBINS-I assessed bias. Frequentist random-effects network meta-analysis used SMDs and 95% CIs. Four comparator nodes were defined: CNI-based (tacrolimus/cyclosporine), mTORi-based (sirolimus/everolimus), mTORi plus CNI, and a mixed non-mTORi control group, comprising non-mTORi regimens (mostly CNIs, with mycophenolic acid, azathioprine, and/or corticosteroids) that could not be separated.* ***Results and Discussion:*** *Seven observational studies were included; four (n=256) informed the network. mTORi-based regimens showed lower testosterone than the pooled non-mTORi control groups (SMD −0.65, 95% CI −1.01 to −0.29), but not significantly versus CNI-based regimens (SMD −0.37, 95% CI −0.76 to 0.02). Comparisons involving mTORi plus CNI were nonsignificant. P-scores were 0.896 for mixed non-mTORi, 0.568 for CNI-based, 0.481 for mTORi plus CNI, and 0.055 for mTORi-based regimens.* ***Conclusions:*** *All studies were observational; six had serious bias, and certainty was very low (CINeMA). Findings are hypothesis-generating and do not justify selecting immunosuppression based on testosterone alone.*

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Introduction

Sexual and reproductive difficulties are common but often overlooked after kidney transplantation. Erectile dysfunction and other sexual problems may persist even after graft function has been restored (Dell'Atti, 2024; Lee et al., 2005). Testosterone deficiency has been linked to sexual symptoms, tiredness, mood changes, and lower muscle and bone mass (Boeri et al., 2026). Chronic kidney disease and end-stage renal disease can disrupt the hypothalamic–pituitary–gonadal (HPG) axis, leading to low testosterone, increased LH and FSH, and hyperprolactinemia. Although transplantation can improve these abnormalities, normal hormonal function is not always fully restored, and long-term immunosuppressive treatment may also affect gonadal function (David et al., 2026; Nieszporek et al., 1989; Tondolo et al., 2005). Male hypogonadism arises from impaired function of the hypothalamic–pituitary–testicular axis (De Silva et al., 2024).

Total-testosterone reference intervals differ by age and assay. Among male kidney transplant recipients, one study reported ranges of 9.1–55.2 nmol/L for men aged 18–49 years and 6.3–26.3 nmol/L for those aged 50–79 years; another used a range of 3.5–10 ng/mL. The European Association of Urology applies a total testosterone threshold of 12 nmol/L (about 350 ng/dL or 3.5 ng/mL) when evaluating symptomatic men for hypogonadism, and recommends confirming low concentrations with repeated morning measurements (Colak et al., 2014; Salonia et al., 2025; Tondolo et al., 2005).

Maintenance immunosuppression after kidney transplantation mainly relies on calcineurin inhibitors and mycophenolic acid. Sirolimus is used less widely because its potential benefits must be weighed against its risks (Khan et al., 2025); the 2024 EAU Guidelines identify tacrolimus, mycophenolate, corticosteroids, and induction therapy as the initial regimen (Faba et al., 2025). Earlier studies have described variable effects of calcineurin inhibitors and azathioprine on the pituitary–gonadal axis (Diker Cohen et al., 2025; Kantarci et al., 2004; Nieszporek et al., 1989). Several reports found lower testosterone and higher gonadotropin concentrations in patients receiving sirolimus-based regimens than in those receiving regimens without sirolimus or based on CNI therapy (Fritsche et al., 2004; Hazir et al., 2026; Lee et al., 2005; Tondolo et al., 2005). Results involving everolimus and tacrolimus, however, have not been consistent (Hazir et al., 2026; Szypulska-Koziarska et al., 2021). CNIs remain a mainstay of maintenance treatment, whereas mTOR inhibitors are alternatives for selected patients (Abu Jawdeh & Me, 2024; Udomkarnjananun et al., 2024). The evidence is difficult to compare because studies vary in design, sample size, hormonal assays, comparator regimens, and follow-up duration (Colak et al., 2014; Hazir et al., 2026; Kantarci et al., 2004).

Earlier systematic reviews have summarized post-transplant changes in sex hormones, sperm measures, and fertility, but have not quantitatively compared testosterone across immunosuppressive regimens (Hazir et al., 2026). This systematic review and network meta-analysis therefore compared serum total testosterone among adult male kidney transplant recipients receiving different regimens, including CNI-, sirolimus-, and combination-based treatment, without limiting inclusion by publication year.

Method

Study Design and Registration

The systematic review and network meta-analysis was registered in PROSPERO under registration number CRD420261502758. The review was conducted in accordance with the registered protocol, with no deviations.

Literature Search Strategy

The final database search was completed on 2 September 2026.

Table 1
Search Strategies

Database	Search strategy	Filters / Records identified
PubMed	("Kidney Transplantation"[Mesh] OR "renal transplantation"[Title/Abstract] OR "kidney transplant*"[Title/Abstract] OR "renal transplant*"[Title/Abstract]) AND ("Immunosuppressive Agents"[Mesh] OR immunosuppress*[Title/Abstract] OR sirolimus[Title/Abstract] OR rapamycin[Title/Abstract] OR cyclosporine[Title/Abstract] OR ciclosporin[Title/Abstract] OR tacrolimus[Title/Abstract] OR FK506[Title/Abstract]) AND (testosterone[Title/Abstract] OR "sex hormone*"[Title/Abstract] OR androgen*[Title/Abstract] OR "gonadal function"[Title/Abstract])	74 records
ScienceDirect	("kidney transplant" OR "renal transplant") AND (sirolimus OR cyclosporine OR tacrolimus) AND testosterone	Research articles; 274 records
SpringerLink	("kidney transplant" OR "renal transplant" OR "kidney transplantation" OR "renal transplantation") AND (immunosuppress* OR sirolimus OR rapamycin OR cyclosporine OR ciclosporin OR tacrolimus OR FK506) AND (testosterone OR "sex hormone" OR "sex hormones" OR androgen OR androgens OR "gonadal function")	Research article; 374 records
OpenAlex	("kidney transplant" OR "renal transplant" OR "kidney transplantation" OR "renal transplantation") AND (immunosuppress* OR sirolimus OR rapamycin OR cyclosporine OR ciclosporin OR tacrolimus OR FK506) AND (testosterone OR "sex hormone" OR "sex hormones" OR androgen OR androgens OR "gonadal function")	148 records
Google Scholar	("kidney transplant" OR "renal transplant") (sirolimus OR rapamycin OR cyclosporine OR ciclosporin OR tacrolimus) (testosterone OR "sex hormones" OR androgen OR "gonadal function")	First 300 records screened; 7,350 records identified

Eligibility Criteria

Studies were eligible if they enrolled adults aged 18 years or older who had received a kidney transplant, compared immunosuppressive regimens, and reported serum total testosterone. The review focused on male recipients. Studies involving both sexes could be included in the qualitative synthesis when relevant results were available, but the network meta-analysis used only compatible data reported specifically for men. Eligible designs included randomized trials, comparative investigations, cohort studies, case-control studies, and cross-sectional studies. Full-text articles written in English were included, regardless of publication year. The primary outcome was serum total testosterone at the study assessment point; whether samples were collected in the morning was recorded when this information was available.

Study Selection, Data Collection, and Data Items

Reviewers screened the records independently and settled disagreements through discussion. Using a prespecified form, they extracted study characteristics, the immunosuppressive regimens being compared, and serum total-testosterone data.

Data Synthesis and Network Meta-Analysis

A frequentist random-effects network meta-analysis was run with netmeta in R version 4.6.1. Hedges' g standardized mean differences (SMDs) and 95% confidence intervals (CIs) were calculated from group means, standard deviations, and sample sizes to account for differences in testosterone units and assays. Treatment was assigned to one of four nodes: CNI-based (tacrolimus or cyclosporine), mTORi-based (sirolimus or everolimus), mTORi plus CNI, and mixed non-mTORi regimens. Tacrolimus and cyclosporine were combined because both inhibit calcineurin; sirolimus and everolimus were grouped because both bind FKBP12 and inhibit mTORC1. The mixed non-mTORi node included heterogeneous comparator regimens whose reported components comprised CNIs, mycophenolic acid, azathioprine, and corticosteroids. A separate non-CNI node was not formed because it could overlap with the mTORi-based node. The nodes were defined according to the immunosuppressive mechanism of interest. The mixed non-mTORi node represents regimens without mTOR inhibitors rather than a single, uniform drug regimen.

Only comparisons between different nodes were analyzed, and four studies contributed to the network. Kantarci et al. (2004) was omitted because both study arms were assigned to the same CNI node. Szypulska-Koziarska et al. (2021) was not included because its comparator could not be placed in one predefined node. Nieszporek et al. (1989) remained in the qualitative synthesis but was excluded from the network because testosterone was assessed 6–10 months after transplantation, during early recovery of the gonadal axis, and reported as mean ± SEM in a protocol that included an LHRH stimulation test. All network findings were treated as exploratory. Transitivity was assessed qualitatively by considering potential effect modifiers, including age, time since transplantation, testosterone assay, and background immunosuppressive therapy. Differences in these characteristics across studies may limit the transitivity assumption.

Risk of Bias, Certainty of Evidence, and Inconsistency

Risk of bias was evaluated with ROBINS-I, and the certainty of network estimates was judged using CINeMA. Overall inconsistency was examined with the design-by-treatment interaction model; node-splitting was used to assess local inconsistency when feasible. Because the network contained few studies and had limited connectivity, these assessments were interpreted with caution.

Publication Bias

Potential reporting bias was considered qualitatively. Funnel plots and statistical tests were not used because fewer than 10 studies contributed to the network meta-analysis.

Result and Discussion

1. Result

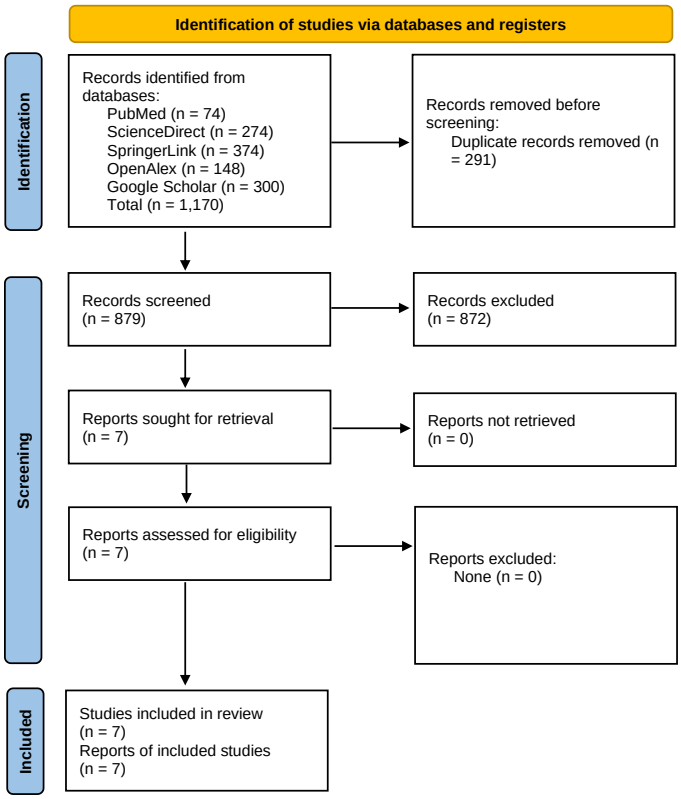


Figure 1. PRISMA 2020 Flow Summary.

Table 2
Characteristics and Findings of Included Studies

Study (Country)	Design, n	Regimen comparison	Main testosterone finding	NMA
Tondolo 2005 (Italy)	Comparative, 59	CNI (15) vs. SRL (15) vs. SRL + CNI (29)	4.39 ± 1.53 vs. 3.12 ± 1.23 vs. 3.97 ± 1.90 ng/mL; SRL vs. CNI, p = 0.0197	Yes
Lee 2005 (USA)	Cross-sectional, 66	SRL (32) vs. non-SRL (34)	393.3 ± 188 vs. 537.4 ± 231; p = 0.008	Yes
Fritsche 2004 (Germany)	Retrospective case-control, 56	SRL (28) vs. non-SRL (28)	11.2 ± 6.3 vs. 15.5 ± 7.7 nmol/L; p = 0.022	Yes
Colak 2014 (Turkey)	Retrospective cross-sectional, 75	CNI (47) vs. mTORi (28)	8.8 ± 2.0 vs. 8.2 ± 4.0 nmol/L; not significant	Yes
Kantarci 2004 (Turkey)	Cross-sectional, 37	CsA vs. TAC	474.8 vs. 386.4 ng/mL; p = 0.09	No
Nieszporek 1989 (Poland)	Cross-sectional comparative, 24	AZA + prednisone (12) vs. CsA + prednisone (12)	Low testosterone in both groups; no between-group test	No
Szypulska-Koziarska 2021 (Poland)	Cross-sectional, 121 (62 men)	TAC+ vs. TAC−	Median 4.04 vs. 3.47 ng/mL; p = 0.042	No

Abbreviations: AZA, azathioprine; CNI, calcineurin inhibitor; CsA, cyclosporine; mTORi, mTOR inhibitor; SRL, sirolimus; TAC, tacrolimus.

Szypulska-Koziarska et al. (2021) reported 121 recipients overall and 64 men in the text and demographic table, while the hormone results listed 62 men. Consequently, the sex-specific totals in the hormone results add up to 119 (57 women and 62 men), not 121. Male hormone results were extracted (n = 62; TAC+ n = 44; TAC− n = 18). Kantarci et al. (2004) labeled its testosterone results as ng/mL in the original paper (474.8 ± 193 and 386.4 ± 169); these values are reproduced as reported, without conversion, because the stated units appear compatible with ng/dL. Since SMDs are unit-free, no conversion was applied. For Lee et al. (2005), p = 0.008 and SD = 231 pg/mL were taken from the table and the results section, although the abstract gave p = 0.08 and SD = 232 pg/mL, indicating a discrepancy within the original report. Kantarci et al. was excluded from the NMA because both arms belonged to the same CNI node. Nieszporek et al. (1989) reported baseline testosterone of 14.8 ± 2.73 versus 12.9 ± 3.35 nmol/L (mean ± SEM) among 12 men receiving AZA plus prednisone and 12 receiving CsA plus prednisone.

Table 3.
Extracted Data Used in the Network Meta-Analysis

Study	Regimen	n	Mean	SD
Tondolo 2005	CNI	15	4.39	1.53
Tondolo 2005	mTORi	15	3.12	1.23
Tondolo 2005	mTORi + CNI	29	3.97	1.90
Lee 2005	mTORi	32	393.3	188
Lee 2005	Non-mTORi	34	537.4	231
Fritsche 2004	mTORi	28	11.2	6.3
Fritsche 2004	Non-mTORi	28	15.5	7.7
Colak 2014	CNI	47	8.8	2.0
Colak 2014	mTORi	28	8.2	4.0

Note: Mean and SD are reported as extracted; testosterone units differ across studies.

Risk of Bias Assessment

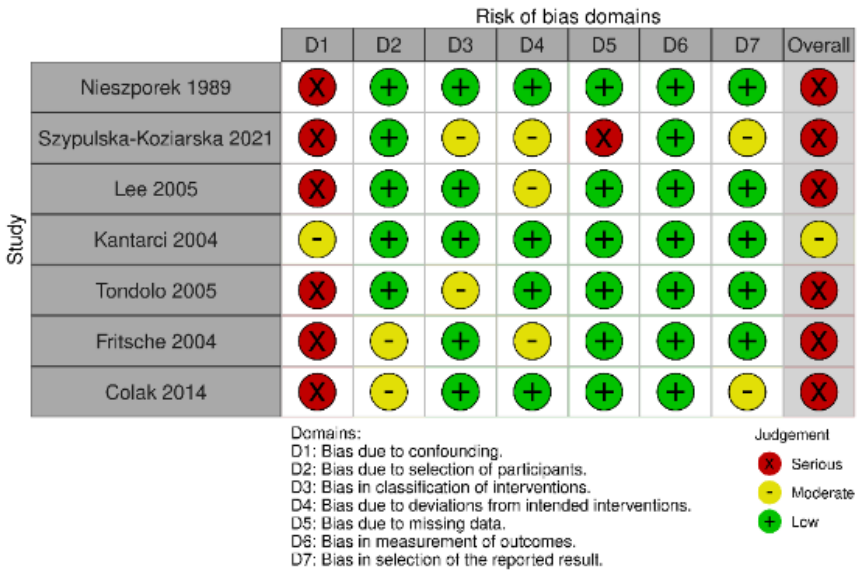


Figure 2. ROBINS-I Traffic-Light Summary

All seven included studies were observational and were assessed with ROBINS-I. Six studies., Nieszporek et al. (1989), Szypulska-Koziarska et al. (2021), Lee et al. (2005), Tondolo et al. (2005), Fritsche et al. (2004), and Colak et al. (2014) were judged to have serious risk of bias; Kantarci et al. (2004) was judged to have moderate risk. Kantarci et al. received the moderate rating because testosterone was compared between cyclosporine and tacrolimus groups matched for age and graft function. Dialysis duration and time since transplantation differed numerically (28 vs. 16 months and 73 vs. 46 months, respectively), but the differences were not statistically significant ($p = 0.1$). The main limitations across the evidence were confounding, observational designs, and inadequate adjustment for clinically important factors.

Direct Evidence

Direct comparisons of sirolimus-based treatment with other regimens were reported by Tondolo et al. (2005), Lee et al. (2005), and Fritsche et al. (2004); all three found lower testosterone levels in the sirolimus groups. By contrast, Colak et al. (2014) detected no significant difference between CNI-based and mTORi-based treatment, with the latter including sirolimus or everolimus. These observational comparisons remain vulnerable to confounding.

Network Meta-Analysis and Network Geometry

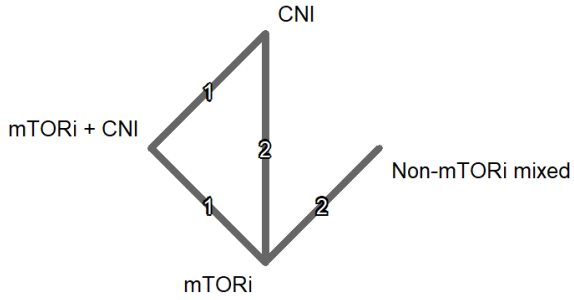


Figure 3. Network Geometry (Network Plot)

Four studies, Tondolo et al. (2005), Lee et al. (2005), Fritsche et al. (2004), and Colak et al. (2014), with 256 participants contributed to the four-node network: CNI-based treatment, mTORi-based treatment, mTORi plus CNI, and mixed non-mTORi comparator regimens. The mTORi node included different treatment combinations, while the mixed non-mTORi node comprised comparator groups from Lee et al. (2005) and Fritsche et al. (2004). Notably, only 18 of the 28 controls in Fritsche et al. (2004) received a CNI, highlighting the heterogeneity of this comparator group. Two studies informed the mTORi versus mixed non-mTORi and CNI versus mTORi comparisons. Only Tondolo et al. (2005) contributed to comparisons involving mTORi plus CNI. The mixed non-mTORi node had no direct comparisons with CNI or mTORi plus CNI; therefore, these estimates relied on indirect evidence and may be affected by limited transitivity. The only closed loop was CNI–mTORi–mTORi plus CNI, informed by Tondolo et al. (2005), while Colak et al. (2014) added evidence to the CNI–mTORi comparison. The network provided limited evidence for assessing consistency. SMDs were used because testosterone assays and measurement units differed across studies.

League Table

1	CNI	0.37 (-0.02 to 0.76)	0.25 (-0.37 to 0.88)	.
2	0.37 (-0.02 to 0.76)	mTORi	-0.51 (-1.14 to 0.12)	-0.65 (-1.01 to -0.29)
3	0.06 (-0.49 to 0.60)	-0.31 (-0.86 to 0.24)	mTORi_CNI	.
4	-0.28 (-0.82 to 0.26)	-0.65 (-1.01 to -0.29)	-0.34 (-1.00 to 0.32)	nonmTORi_mixed

Figure 4. League Table (Pairwise Comparison Matrix). Each cell reports the SMD (95% CI) for the regimen appearing earlier in the diagonal order (CNI, mTORi, mTORi + CNI, non-mTORi mixed) compared with the regimen appearing later. Positive values indicate higher testosterone for the regimen listed first. The upper triangle contains direct estimates and the lower triangle contains network estimates; "." indicates no direct evidence.

The network estimates indicated lower testosterone levels in the mTORi-based group than in the mixed non-mTORi group. Comparisons involving CNI-based and mTORi plus CNI regimens showed no statistically significant differences. Direct estimates are presented in the upper triangle and network estimates in the lower triangle of Figure 4; a dot indicates the absence of direct evidence.

Forest Plot

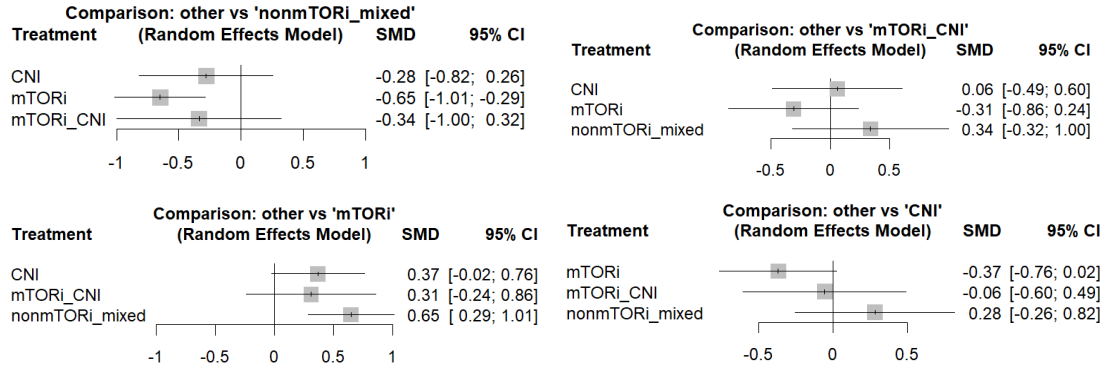


Figure 5. Forest Plot

Using mixed non-mTORi regimens as the reference, only mTORi-based treatment showed a statistically significant difference in testosterone levels. Comparisons involving CNI-based and mTORi plus CNI regimens were not statistically significant. Detailed network estimates are presented in Figure 5.

Treatment Ranking

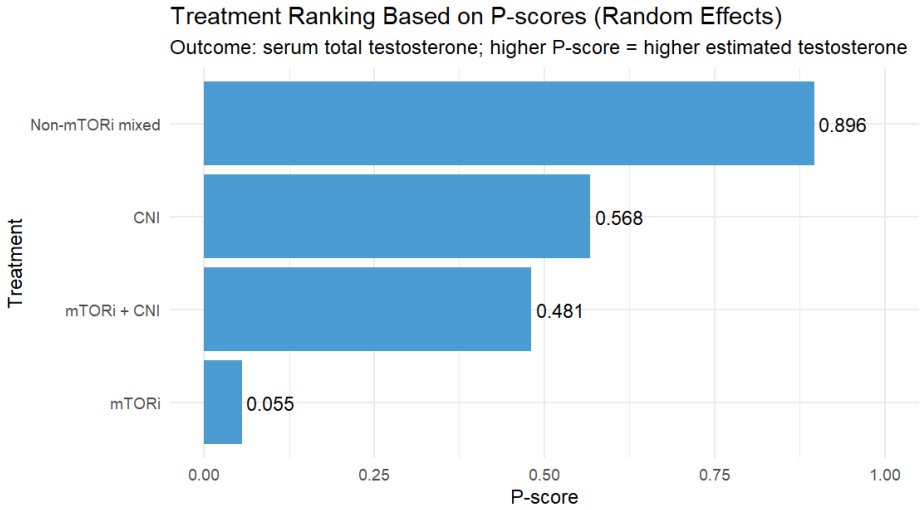


Figure 6. Treatment ranking by P-score for serum total testosterone (random-effects network meta-analysis). Higher P-scores indicate higher estimated testosterone relative to the other nodes. P-scores reflect relative ranking only, are not a measure of effect size or clinical superiority, and are exploratory given the small network and very low certainty of evidence. CNI, calcineurin inhibitor; mTORi, mTOR inhibitor.

P-scores, where larger values indicate higher estimated serum total testosterone, were 0.896 for mixed non-mTORi regimens, 0.568 for CNI-based regimens, 0.481 for mTORi plus CNI, and 0.055 for mTORi-based regimens (Figure 6). Thus, mTORi-based treatment ranked lowest and mixed non-mTORi treatment highest; CNI and mTORi plus CNI had intermediate scores that were close to one another. P-scores reflect the direction and relative precision of network estimates, but they do not measure the magnitude of an effect or clinical benefit and have no accompanying uncertainty interval. Given the very low certainty of evidence (Table 4), the small network, and the fact that the mixed non-mTORi node connects to the network only through mTORi, this ranking is exploratory and should be interpreted together with the SMDs and 95% CIs (Figure 4). In particular, the difference between CNI and mTORi plus CNI should not be regarded as meaningful.

Inconsistency

The global inconsistency test was not statistically significant (design-by-treatment interaction: Q between designs = 1.59, df = 1, p = 0.208; total Q = 1.62, df = 2, p = 0.44). Within-design heterogeneity was also low (Q = 0.04, df = 1, p = 0.85), based only on the mTORi versus mixed non-mTORi comparison in Lee et al. (2005) and Fritsche et al. (2004), whose Hedges' g estimates were −0.67 and −0.60, respectively. Nonetheless, the small number of studies limits what can be concluded from these tests. Node-splitting could be performed for only two comparisons, and both yielded p = 0.208. For mTORi plus CNI versus CNI, direct and indirect estimates pointed in opposite directions (SMD −0.25 vs. +0.58). Direct and indirect estimates for CNI versus mTORi could not be separated independently because both depended on the same three-arm study, Tondolo et al. (2005). The sole closed loop was informed by Tondolo et al. (2005) and Colak et al. (2014), limiting the ability to detect inconsistency. The CNI–mTORi estimates differed between these studies (SMD −0.89 vs. −0.20), which may indicate between-study heterogeneity rather than true network inconsistency. Possible explanations include the

presence of everolimus, concomitant mycophenolate and corticosteroids, and greater variability in testosterone measurements in Colak et al. (2014); these explanations remain speculative.

CINeMA Assessment

Confidence in the network meta-analysis findings was assessed with CINeMA rather than conventional GRADE alone. GRADE considers five main domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. CINeMA assesses six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence. The four treatment nodes produced six unique pairwise comparisons, calculated as $n \times (n - 1) / 2$. Two comparisons had no direct evidence but could still be assessed through indirect network estimates. Indirectness—the degree to which the available evidence differs from the comparison of interest—was rated major for three comparisons (mTORi versus mixed non-mTORi, CNI versus mixed non-mTORi, and mTORi + CNI versus mixed non-mTORi) because of heterogeneous comparator regimens and reliance on indirect evidence. The other three comparisons were rated as having some concerns because the drugs, concomitant therapies, and testosterone assays differed. Imprecision, which reflects uncertainty arising from limited data, was judged to present no concerns for mTORi versus mixed non-mTORi because its 95% CI excluded zero. Some concerns were assigned to mTORi versus CNI because its 95% CI crossed zero slightly. The remaining four comparisons—CNI versus mixed non-mTORi, mTORi + CNI versus mixed non-mTORi, CNI versus mTORi + CNI, and mTORi versus mTORi + CNI—were rated major for imprecision because few studies informed them and their confidence intervals were wide.

No validated minimal important difference (MID) is available for total testosterone expressed as an SMD. Accordingly, an SMD of zero was treated as the null effect, while SMD values from −0.2 to 0.2 were used after the analysis as an exploratory reference for a small effect, not as a validated MID. Imprecision was considered cautiously against this benchmark. Heterogeneity was judged by considering variation between studies, while incoherence was assessed by comparing direct and indirect estimates where a closed loop was available. Because only a few studies were included, both domains were rated conservatively. Comparisons without a closed loop received a rating of “some concerns” for incoherence because agreement between direct and indirect evidence could not be tested. Overall confidence was rated very low for all six network comparisons, mainly because of major within-study bias and, for several comparisons, indirectness and imprecision. The small network, lack of a closed loop for comparisons involving the mixed non-mTORi node, and limited independent evidence in the only closed loop prevented reliable assessment of heterogeneity and incoherence. These domains were therefore rated as having some concerns rather than no concerns.

Table 4
CINeMA Confidence Assessment

Comparison	WSB	RB	Ind	Imp	Het	Inc	Overall
mTORi vs non-mTORi	Major	Some	Major	No concerns	Some concerns	Some concerns	Very low
mTORi vs CNI	Major	Some	Some	Some	Some concerns	Some concerns	Very low
CNI vs mTORi + CNI	Major	Some	Some	Major	Some concerns	Some concerns	Very low
mTORi vs mTORi + CNI	Major	Some	Some	Major	Some concerns	Some concerns	Very low
CNI vs non-mTORi	Major	Some	Major	Major	Some concerns	Some concerns	Very low
mTORi + CNI vs non-mTORi	Major	Some	Major	Major	Some concerns	Some concerns	Very low

Abbreviations: WSB, within-study bias; RB, reporting bias; Ind, indirectness; Imp, imprecision; Het, heterogeneity; Inc, incoherence; CNI, calcineurin inhibitor; mTORi, mammalian target of rapamycin inhibitor.

2. Discussion

This systematic review and network meta-analysis brought together evidence on the relationship between immunosuppressive treatment and serum testosterone in male kidney transplant recipients, a population in which sexual and gonadal problems remain common and underrecognized (Lee et al., 2005). Testosterone deficiency has been associated with cardiovascular abnormalities, and a study found serum testosterone to be an independent factor associated with the inferior vena cava collapse index, systolic blood pressure, and left atrial parameters in male kidney transplant recipients and patients with chronic kidney disease (Colak et al., 2014).

The network included four regimen categories: CNI-based treatment (cyclosporine or tacrolimus), mTORi-based treatment (sirolimus or everolimus), mTORi combined with CNI, and heterogeneous mixed comparators without mTOR inhibitors. The reported components of the mixed group included CNIs, mycophenolic acid, azathioprine, and corticosteroids, although the exact combinations were not consistently described. Because the non-mTORi group mixed CNI-, MPA-, azathioprine-, and steroid-based regimens, its difference from mTORi cannot be attributed to any single drug.

Overall, mTORi-based regimens appeared to be associated with lower serum testosterone than mixed non-mTORi regimens, while the difference compared with CNI-based treatment showed a similar direction but remained statistically uncertain. Comparisons involving mTORi plus CNI did not demonstrate significant differences. This pattern broadly agrees with earlier sirolimus studies and raises the possibility of an association between mTOR inhibitor exposure and changes in gonadal hormone balance. However, the apparent difference between mTORi and mixed non-mTORi regimens was based on only two small studies and a heterogeneous comparator group. Therefore, this finding should be interpreted cautiously and cannot establish a causal relationship between mTOR inhibitor exposure and reduced testosterone levels (Colak et al., 2014; Fritsche et al., 2004; Lee et al., 2005; Tondolo et al., 2005).

Fritsche et al. (2004) first reported significantly lower testosterone and higher FSH and LH in sirolimus-treated patients than matched controls. Lee et al. (2005) similarly reported lower testosterone in sirolimus-treated patients than in non-sirolimus controls, while Tondolo et al. (2005) reported the lowest testosterone with sirolimus alone, intermediate levels with sirolimus plus CNI, and the highest levels with CNI alone. In contrast, Kantarci et al. (2004) found no significant differences in testosterone, FSH, LH, or prolactin between cyclosporine and tacrolimus, while Colak et al. (2014) found

significantly higher serum testosterone concentrations in both CNI- and mTOR inhibitor-treated transplant recipients than in patients with chronic kidney disease, with no significant difference between the CNI and mTOR inhibitor groups. Inclusion of Colak et al. (2014) attenuated the pooled mTORi versus CNI estimate, because its CNI versus mTORi difference was smaller than that of Tondolo et al. (2005), leaving a confidence interval that included no difference. This discordance may reflect between-study heterogeneity, including the inclusion of everolimus in the mTORi group of Colak et al., universal mycophenolate and steroid co-treatment in that cohort, and a wide standard deviation in its mTORi group, although these explanations remain hypothetical.

Beyond testosterone, Lee et al. (2005) found no corresponding difference in self-reported erectile function despite lower testosterone among men receiving sirolimus. A biochemical finding of hypogonadism therefore may not always coincide with clinically apparent sexual dysfunction. Lower testosterone is a biochemical finding and does not by itself establish symptomatic hypogonadism, sexual dysfunction, or impaired fertility; these outcomes were rarely assessed in the included studies. Gonadal function may be worth considering when reviewing immunosuppressive treatment for selected reproductive-age male recipients, especially those concerned about fertility or sexual health, but should not be the sole basis for treatment selection.

In the study by Szypulska-Koziarska et al. (2021), men receiving tacrolimus had higher testosterone concentrations than those not receiving tacrolimus; however, the TAC− group included patients receiving sirolimus or everolimus, so the observed difference cannot be attributed specifically to tacrolimus. The findings should also be interpreted within broader hypogonadism management, as the 2025 European Association of Urology guidelines recommend testosterone therapy only for appropriately diagnosed patients with documented hypogonadism and require longitudinal assessment of treatment response and safety (Salonia et al., 2025). Most included studies were small and observational, limiting causal inference and adjustment for confounders such as age, transplant duration, and renal function (Fritsche et al., 2004; Kantarci et al., 2004; Lee et al., 2005; Tondolo et al., 2005). In Lee et al. (2005), the sirolimus group was younger and had a shorter post-transplant duration than the non-sirolimus group, potentially contributing to residual confounding. Differences in hormone assays and multidrug regimens further limited comparability and attribution of effects to individual agents (Szypulska-Koziarska et al., 2021). Prospective studies using standardized assays and appropriate confounder adjustment are needed.

Most contributing studies were published between 2004 and 2014, when immunosuppressive practices may have differed from those used in contemporary kidney transplantation. Current maintenance regimens commonly consist of tacrolimus combined with mycophenolate, with or without corticosteroids, while belatacept- and mTOR inhibitor-based strategies remain alternatives for selected patients. Therefore, the applicability of our findings to contemporary practice should be interpreted with caution (Wojciechowski & Wiseman, 2021).

Limitations

The network meta-analysis contained only four observational studies, leaving it vulnerable to confounding, variation in regimens, and weak support for indirect comparisons. The small network also limited the reliability of heterogeneity and inconsistency assessments. The results are therefore exploratory and cannot demonstrate causal effects. In addition, treatment nodes were heterogeneous, background drugs were

not fully described, and some participants in the mTORi-based node also received a CNI. The mTORi results primarily reflect sirolimus, because everolimus appeared only as part of a mixed mTORi group. Certainty of evidence was very low for all comparisons (CINeMA).

Conclusion

This systematic review and network meta-analysis indicates that mTORi-based regimens may be associated with lower serum total testosterone than mixed non-mTORi regimens, while the difference compared with CNI-based treatment was not statistically significant. All included studies were observational, and several had serious risk of bias and potential confounding. The network comprised only four studies, and the certainty of evidence was very low for all comparisons (CINeMA). The findings should therefore be viewed as hypothesis-generating rather than causal. Prospective studies with standardized assays, clearly defined regimens, and appropriate adjustment for confounders are needed.

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