REVIEW PAPER

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Combined kidney and hematopoietic stem cell transplantation from the same donor: systematic review of clinical outcomes and limitations

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ABSTRACT

Background. Kidney transplantation is the most effective method of renal replacement therapy. The consequence of a conventional transplant is the need to use immunosuppressive drugs throughout life, which is associated with many side effects. A possible strategy for avoiding immunosuppressive therapy may be kidney transplantation from the same donor after hematopoietic cell transplantation (HSCT) or bone marrow transplantation (BMT).

Material and methods. A systematic literature search was conducted in the PubMed, Scopus, Web of Science, and Cochrane databases using various combinations of keywords related to simultaneous or sequential kidney and bone marrow (or hematopoietic stem cell) transplantation from the same donor.

Results. Combined kidney and hematopoietic stem cell transplantation from the same donor has shown promising results, particularly in HLA-matched recipients, enabling withdrawal of immunosuppressive therapy without rejection. In HLA-mismatched cases, success was observed mainly with intensive conditioning regimens (e.g., total lymphoid irradiation, antithymocyte globulin, fludarabine). Early outcomes often included stable graft function and absence of acute rejection, but long-term follow-up revealed risks such as chronic rejection and declining renal function.

Conclusions. Despite encouraging outcomes, the approach remains experimental due to the lack of standardised protocols, validated biomarkers, and a complete understanding of chimerism persistence. Further clinical trials with long-term follow-up are needed to identify predictors of success, optimise conditioning strategies, and evaluate safety. The method holds potential, especially for patients with hematologic malignancies, but routine clinical application is not feasible.

Introduction

The kidney is the most frequently transplanted organ. In 2019 alone, almost 25,000 people in the United States received a new kidney [1]. The most common indications for kidney transplantation are complications of diabetes, glomerulopathies and chronic hypertension. Kidney transplantation is the most beneficial method of renal replacement therapy [2]. The need for immunosuppressive drugs after transplantation is associated with multiple adverse effects, such as increased vulnerability to infections or increased risk of cancer [3]. A significant cause of renal failure may be hematologic diseases, primarily malignancies. Hematologic diseases may require treatment with hematopoietic stem cell or bone marrow transplantation. As a result, graft-versus-host disease and kidney failure may occur. A kidney transplant from the same donor may allow discontinuation of immunosuppression after transplantation. This idea began to be thought about in the 1990s [4]. This procedure is complicated and poorly known. Currently, Research is being conducted on the use of combined kidney-bone marrow transplantation (CKBMT) from the same donor in renal and haematological diseases to achieve chimerism and induce immunological tolerance. This is intended to maintain the graft's function without immunosuppressive treatment.

Immunosuppressive agents have improved outcomes in acute, cell-mediated rejection but remain insufficient against chronic, humoral-mediated rejection [5], and their use increases the risk of infections, cardiovascular complications, and malignancies [6]. Chimerism represents an alternative strategy involving the infusion of donor hematopoietic stem cells to induce tolerance to donor Major Histocompatibility Complex (MHC) antigens. Two forms are distinguished: complete chimerism, in which donor cells replace the recipient's hematopoiesis, and mixed chimerism, in which donor and host cell populations coexist [7]. Early attempts date back to 1952,

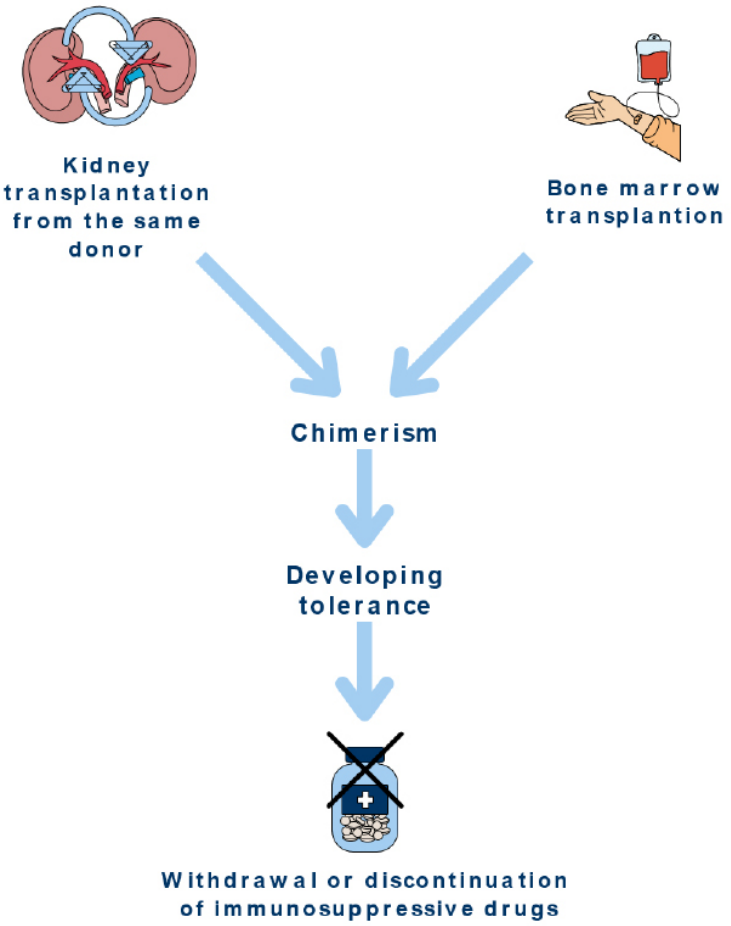

Figure 1. Graphical representation of simultaneous kidney and bone marrow transplantation.

when Billingham and Medawar [8] described graft tolerance in twins with placental vascular anastomoses. In the 1990s, McDaniel et al. [9] combined kidney and bone marrow transplantation, using pre-transplant immunosuppression. They observed a peak in chimerism during the first 3 months, followed by a decline that correlated with graft rejection. Notably, subsequent studies demonstrated that mixed chimerism promotes central tolerance through thymic adverse selection of alloreactive lymphocytes, thereby reducing the risk of Graft-Versus-Host Disease (GVHD), improving graft survival, and limiting humoral rejection [10].

The objective of this review was to analyse the literature and present the progress of research on kidney and hematopoietic cell (HSCT) or bone marrow transplantation (BMT). A graphic representation of the CKBMT procedure is shown in **Figure 1**.

Materials and methods

Search strategy

The preparation of this manuscript was based on the PRISMA Checklist. A simultaneous search on transplantation of bone marrow and kidney from the same donor, was conducted on the PubMed, Scopus, Web of Science and Cochrane databases using the keywords: 'simultaneous kidney and bone marrow transplantation' OR 'simultaneous kidney and hematopoietic stem cell transplantation' OR 'sequential bone marrow transplantation and kidney transplantation' OR 'sequential hematopoietic stem cell transplantation and kidney transplantation' OR 'combined kidney and bone marrow transplantation' OR 'combined kidney and hematopoietic stem cell transplantation'. The protocol of this systematic review was registered in the PROSPERO registry (CRD420251252170) on December 12, 2025 (https://www.crd.york.ac.uk/).

Inclusion criteria

Inclusion criteria included articles on simultaneous kidney and bone marrow transplantation from the same donor in humans, available in English. We searched for the following outcomes: chimerism, tolerance, immunological tolerance and discontinuation of immunosuppression. We included clinical trials, case reports and case series in the review.

Exclusion criteria

No time criterion was used; however, the time span covered by the reviewed articles is 1989–2023. Exclusion criteria were in vitro studies and studies in animal models, lack of access to the full text, and articles in a language other than English. There were no differences in search strategy (exact keywords, inclusion and exclusion criteria) between the databases used.

Data collecting process

The search and analysis of available scientific literature was performed independently by two authors (J.M. and K.S.). Literature search was conducted from June to December 2023. The search strategy involved an initial screening of titles and abstracts, followed by full-text evaluation against predefined inclusion criteria. During the identification stage, 2875 records were identified. A majority of these studies were excluded due to inadequate subject matter or form. Finally, 63 studies were involved in the current review. The stages of article search are presented in **Figure 2** as a PRISMA diagram.

Results

Characteristics of the studies and reports discussed in this review.

Our review includes 63 articles: 40 clinical trials, 18 case reports, and 5 case series. We excluded 1947 articles. The main reason for exclusion was the wrong intervention: simultaneous transplantation of an organ other than the kidney, bone marrow transplantation only, or kidney transplantation only. We excluded articles based on cell or animal models, review articles, and those not available in English. Characteristics of the studies and reports discussed in this article are presented in **Table 1**.

First attempts at the method

Initial successes in combined kidney and hematopoietic cell transplantation date to the late 1980s, involving kidney grafts from deceased donors followed by cryopreserved donor bone marrow infusion, with antithymocyte globulin

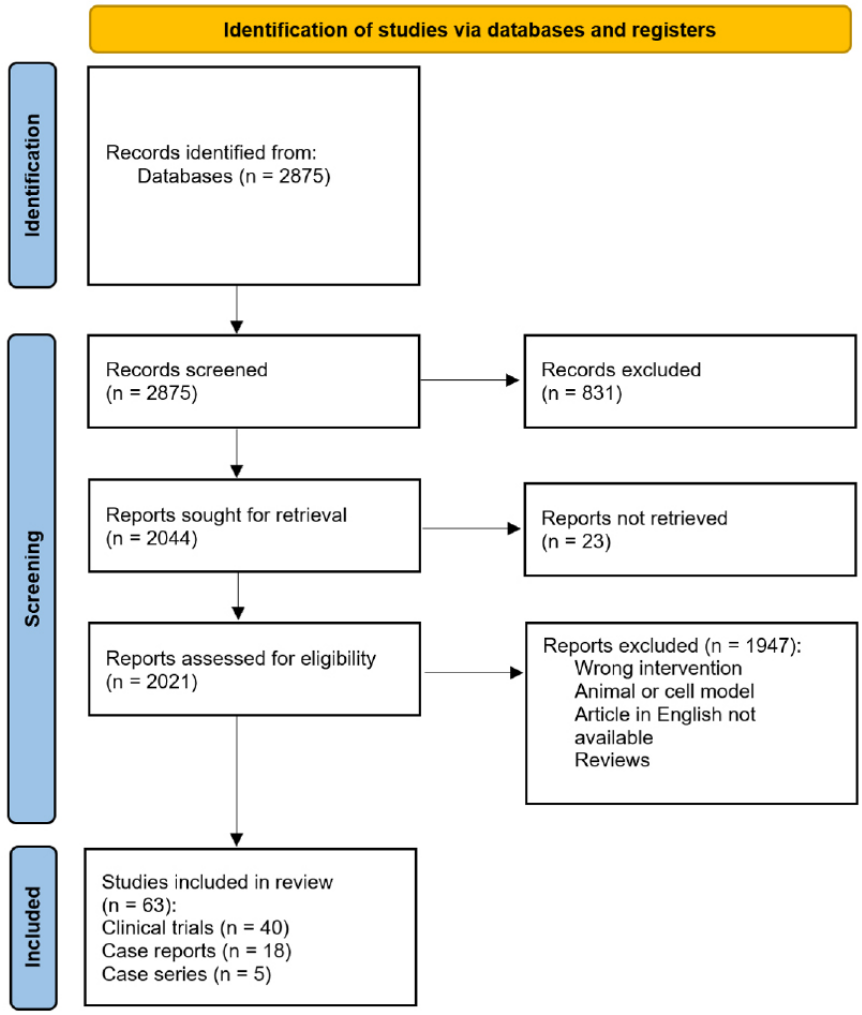

Figure 2. Flowchart of PRISMA.

Table 1. Summary of studies included in the manuscript.

Year	Group		Conclusion
	N study	N control	
1989	20	20	A transplant of kidney from deceased donor followed by a transfusion of cryopreserved donor bone marrow is a successful method of creating tolerance [12].
1994	17 (kidney n = 7)		Preoperative infusion of bone marrow is safe and leads to establishment of macrochimerism and donor-specific hyporeactivity [4].
1997	11	14	There are no statistical difference in the percentage of acute rejection episodes between the control and study groups, further research on the optimization of this procedure is needed [13].
1998	58	175	Using modern immunosuppressive drugs has a positive influence on creating tolerance in patients receiving DBMC infusion [14].
2001	63	219	DBMC infusions have positive influence on long-term graft survival. Degree of chimerism correlates with absence of graft loss [15].
2003	86	43	Infusion of unfractioned megadose of DBMC with infusions to the thymus and portal and systemic circulation is an effective way of creating tolerance [50].
2003	18	63	Patients receiving simultaneous kidney and donor-specific bone marrow have a lower percentage of acute and chronic rejection and a longer graft survival compared to the control group [42].
2004	12	12	Infusion of unfractionated hematopoietic stem cells into the thymus and peripheral blood to create tolerance is safe and gives better graft function compared to conventional renal transplant [48].
2005	33	33	High-dose HSCT, intrathymic donor renal tissue transplantation is a successful method of creating mixed hematopoietic chimerism [46].
2006	6		Combined kidney and BMT creates tolerance to the renal allograft and tumor responses in advanced MM [31].

Table 1 continuued.

Year	Group		Conclusion
	N study	N control	
2007	201	156	Injecting part of the bone marrow collected from the iliac crest of a deceased donor into the thymus and bone marrow of the recipient before kidney transplant surgery, and the rest into the peripheral blood is a successful method of creating tolerance [49].
2008	5		Combined HLA-mismatched bone marrow and kidney transplantation induces chimerism and allows discontinuation of immunosuppression therapy in some patients [57].
2009	5		This study proved the development of B-cell immunity in patients with T-cell tolerance to the donor graft [33].
2010	20	19	It is possible to predict if transplant recipients are unresponsive and if immunosuppression can be withdrawn through ex-vivo tests [43].
2010	5		Patients receiving CKBMT create transient mixed chimerism which is responsible for donor-specific tolerance [63].
2011	7		HLA-matched CKBMT induce mixed chimerism and create prolonged MM responses [32].
2011	5		HLA-mismatched CKBMT can lead to long-term, systemic donor-specific unresponsiveness [67].
2011	10		Engraftment syndrome occurs commonly in the combined bone marrow/kidney transplant protocol and is manifested by acute renal dysfunction [41].
2012	8		Transplantation of mobilized stem cells with nonmyeloablative conditioning is a safe way to induce prolonged chimerism and donor-specific tolerance in kidney transplant recipients [37].
2012	16		Protocol including total lymphoid irradiation and ATG induces chimerism and tolerance in patients receiving kidney transplant with HSCT [60].
2013	76		Living-donor renal transplant with preoperative HSCT and nonmyeloablative conditioning provides stable graft function and allows reduction of immunosuppressive drugs doses [68].
2013	10		Prolonged immunosuppression-free renal allograft survival can be achieved in both HLA-matched and mismatched donor-recipient pairs after CKBMT [56].
2013	15		Transplantation of bioengineered facilitating cell-based hematopoietic stem cell products can safely create durable chimerism in mismatched kidney recipients [38].
2013	6	6	Use of mesenchymal stem cells infusions can allow reduction of immunosuppressive drugs in kidney transplantation recipients [55].
2013	7		Donor mesenchymal stem cells injection into the iliac bone at the time of kidney transplant is safe and might be responsible for the inhibitory immune responses [52].
2014	10		Long-term stable kidney allograft survival without maintenance immunosuppression can be achieved in HLA-mismatched donor – recipient pairs through induction protocol [40].
2015	19		Chimerism can be induced by reduced intensity conditioning and can create tolerance to renal allografts and ability to respond to infectious complications [39].
2015	38		Tolerance protocol allows immunosuppressive drugs withdrawal in HLA-matched patients and provides long-term graft survival in both HLA-matched and mismatched patients [61].
2017	5		Enrichment of T-regs in the early post-transplantation period may contribute to tolerance after CKBMT [71].
2017	5		B cells can be detected in peripheral blood at different stages after CKBMT, which may indicate their role in tolerance induction [66].
2018	4		Early expansion of donor-specific T-regs is involved in tolerance induction following CKBMT [72].
2019	22	20	Patients who underwent HSCT have better graft function than controls with conventional immunosuppression [45].
2019	6		Combined haploidentical HCT/kidney transplantation is safe with posttransplantation cyclophosphamide, however, fludarabine also can be used in patients with end-stage renal disease in proper dose [34].
2019	50		It is possible to discontinue immunosuppression in fully HLA-matched patients but not in the haplotype matched recipients [55].
2020	8		Long-term renal allograft survival without maintenance immunosuppression can be achieved by induction of mixed chimerism following CKBMT [76].
2020	11		Combined kidney and hematopoietic stem cells transplantation allows low dose immunosuppression with long-term graft survival [65].
2020			The results of this trial will prove if treatment with recipient T-regs and donor bone marrow is a safe and efficacious procedure leading to transient chimerism. [73]
2021	6	20	The CD45RA-FOXP3++ T-reg cell subpopulation expands in CKBMT recipients and is a possible marker of patients eligible for discontinuation of immunosuppression [69].
2021	21		Changes in cell numbers after transplant include reduction in T lymphocytes and an increase in immunosuppressive polymorphonuclear myeloid-derived suppressor cells in the spleen and blood [70].
2022	3		Combined kidney and hematopoietic stem cell transplantation is a successful approach to induce specific immunological tolerance in recipients of kidney transplant from HLA-identical sibling donor. Tolerance protocol does not interfere with SARS-CoV-2 mRNA vaccine [59].

DBMC – donor bone marrow cells; HSCT – hematopoietic cell transplantation; BMT – bone marrow transplant; MM – Multiple Myeloma; HLA-mismatched – Human Leukocyte Antigen-mismatched; CKBMT – combined kidney-bone marrow transplantation; HLA-matched – Human Leukocyte Antigen-matched; ATG – antithymocyte globulin

(ATG) as the preconditioning agent. In this early trial, 40% of patients discontinued immunosuppressive therapy, though one case of graft failure occurred within three months [11].

Burke et al. [12] reported a protocol combining islet cell and kidney transplantation under a four-drug immunosuppressive regimen (OKT3, tacrolimus, azathioprine, methylprednisolone), with bone marrow infusions administered to the experimental group. No significant difference in acute rejection rates was found, indicating the need for further procedural refinement.

Ciancio et al. [13] compared outcomes in patients receiving combined kidney and hematopoietic cell transplantation from a single donor versus kidney transplantation alone over 36 months. The study group exhibited no acute rejection episodes, improved graft survival, and better overall health status. Over six years, a threefold increase in chimerism in bone marrow aspirates was observed only in the combined transplant group [14].

Salgar et al. [15] investigated the impact of perioperative infusion of unmodified donor bone marrow cells (DBMC) across 229 transplant recipients (85 kidney recipients), aiming to enhance chimerism and allograft tolerance. The procedure proved safe, with reduced acute rejection rates and higher peripheral blood chimerism in the experimental group, though overall graft function and survival were comparable between groups.

Combined kidney and hematopoietic cell or bone marrow transplant in patients with oncological diseases

CKBMT shows promise in patients with end-stage renal disease (ESRD) secondary to hematologic malignancies. Kosoku et al. [16] described a case of chronic myeloid leukaemia (CML) treated with allogeneic BMT, followed by kidney transplantation from a Human Leukocyte Antigen (HLA)- and ABO-incompatible donor due to therapy-induced ESRD. Despite immunosuppression (mycophenolate mofetil, cyclosporine, corticosteroids), the procedure was successful. Similar cases suggest that CKBMT from the same donor may facilitate immunosuppressive withdrawal in HLA- and ABO-compatible transplants [17].

In another report, a patient with acute myeloid leukaemia (AML) developed renal GVHD post-HSCT and later received a kidney from the same donor. Absence of T-cell reactivity and complete peripheral blood chimerism allowed immunosuppression-free transplantation, with stable renal function two years post-transplant [18]. Comparable cases also reported minimal immunosuppressive requirements [19 – 22].

Miller et al. [23] documented a 31-year-old female with ESRD following treatment for myelodysplastic syndrome. After allogeneic HSCT, she received a kidney from the same haploidentical donor (sister) 14 months later, without requiring systemic immunosuppression. Gajewski et al. [24] described an inverse scenario: kidney transplantation was followed by AML, and subsequent BMT from the original donor enabled cessation of immunosuppression with preserved renal function.

CKBMT has also demonstrated benefits in multiple myeloma (MM). In one case, a patient underwent non-myeloablative conditioning followed by HSCT and, two years later, kidney transplantation from the same haploidentical donor. Chimerism was achieved, and immunosuppression was not needed. The patient remained in MM remission with stable graft function after six years [25]. Similar outcomes have been reported in other MM cases [26 – 29].

Fudaba et al. [30] detailed a preparative regimen for MM and ESRD patients involving cyclophosphamide, ATG, and thymic irradiation to induce stable mixed chimerism. Long-term follow-up showed that immunosuppressive therapy could be withdrawn for 2–11 years, with preserved renal function and no MM relapse in most patients [31]. However, some required the reinstatement of immunosuppression, highlighting the need for standardisation and the identification of prognostic markers [32, 33].

Beyond MM and leukaemias, CKBMT has shown preliminary success in mantle cell lymphoma, acute lymphoblastic leukaemia (ALL), and aplastic anaemia, though further validation in larger cohorts is required [34, 35].

Bone marrow transplantation – HLA-mismatched

As previously mentioned, one of the key determinants of successful CKBMT is durable chimerism. This topic was extensively addressed in studies by Leventhal and colleagues [36], who

sought to enhance the efficacy of stable chimerism induction in recipients of HLA-mismatched organ transplants. Their protocol included mobilisation of hematopoietic stem cells, transplantation of a CD8 /TCR cell fraction, and a conditioning regimen consisting of fludarabine, cyclophosphamide, and total-body irradiation. Post-transplant, immunosuppressive therapy with tacrolimus and mycophenolate mofetil was initiated.

The research team observed that the non-myeloablative approach, combined with stem cell mobilisation, constituted a safe and reproducible method for chimerism induction, enabling the development of kidney allograft tolerance. However, the technique did not guarantee complete efficacy; some patients required continued low-dose immunosuppression. The authors emphasised the lack of sufficient biomarkers capable of accurately identifying patients likely to respond favourably to immunologic tolerance induction, which limited the ability to predict the risk of acute or chronic graft rejection.

In subsequent reports, Leventhal's team [37,38] demonstrated variability in chimerism maintenance among patients, with the most favourable outcomes persisting for over 18 months. Notably, this approach also preserved functional immunologic memory from prior vaccinations, underscoring its potential for broader clinical application.

The application of CKBMT in HLA-mismatched recipients appears to represent a promising strategy for achieving post-transplant survival without the need for long-term immunosuppressive therapy. Results presented by Kawai et al. [39] and Farris et al. [40] demonstrate the effectiveness of this approach in preventing acute graft rejection and in inducing immunologic tolerance. However, both groups emphasise that the later stages of treatment require further investigation to improve the therapy's long-term efficacy and safety. These studies reported cases in which patients developed antibody-mediated chronic rejection, necessitating the reintroduction of conventional immunosuppression. Additionally, in the analysis conducted by Farris et al. [40], some patients experienced complications in the later post-transplant period, including capillary leak syndrome (CLS) and engraftment syndrome (ES), which led to acute kidney injury (AKI). It has been suggested that these disorders may have resulted from transient autoimmune or alloreactive responses.

Bone marrow transplantation – HLA-matched

Ebrahimi-Rad et al. [41] conducted a case series comparing 18 CKBMT recipients with 63 kidney-alone transplant recipients, all receiving azathioprine. The CKBMT group showed reduced rates of acute and chronic rejection and improved graft survival.

Mathew et al. [42] investigated whether donor bone marrow cell infusion could minimise immunosuppression. Three groups were compared: haploidentical recipients with and without infusion, and HLA-identical recipients. Bone marrow-infused patients demonstrated higher graft survival and presence of functionally chimeric cells inhibiting anti-donor responses, supporting the role of chimerism in transplant hyporesponsiveness. A related case series included three recipients of HLA-identical sibling kidneys, followed by hematopoietic stem cell infusion. Immunosuppressive therapy was successfully withdrawn at 16 and 32 months in two cases, with stable graft function maintained for over five years [43].

Further studies comparing CKBMT to conventional transplantation found no graft losses in the CKBMT group, compared with 3 in the control group. Additionally, serum creatinine was 29% lower in the CKBMT group, indicating superior long-term graft function without the need for chronic immunosuppression [44].

Another trial involving 66 patients with chronic kidney disease and negative lymphocytotoxicity crossmatch tested a comprehensive approach including thymic transplantation, donor-specific transfusions, low-intensity conditioning, high-dose hematopoietic stem cell transplantation, and plasmapheresis with IVIG. Among the 33 patients who received CKBMT, stable mixed chimerism and optimal graft function were observed over 210 days [45].

Spitzer et al. [46] presented a 20-year follow-up of the first 10 patients treated with CKBMT at their centre. One patient maintained normal kidney function without immunosuppression for 20 years. Chimerism was sustained for 49 days to 14 years, and long-term graft survival was

achieved in 7 of 10 patients, confirming the method's long-term safety and efficacy.

Other modifications to the procedure

Injection of bone marrow cells into the thymus

In other studies, Trivedi et al. [47,48] proposed creating tolerance by injecting part of the bone marrow collected from the iliac crest of a deceased donor into the recipient's thymus and bone marrow before kidney transplant surgery, and the rest into the recipient's peripheral blood. The experimental results, measured as mean serum creatinine concentration and graft survival, were better in the study group (n = 12), suggesting that this approach may also be a beneficial method for inducing tolerance. Trivedi et al. [49] also conducted a similar study of living-related kidney donors. In the group of patients who received bone marrow cells as an additional injection into the thymus, there were no episodes of rejection or cytomegalovirus infection.

Human embryonic stem cells

An alternative approach to enhancing recipient tolerance to transplantation may involve the application of human embryonic stem cells (hESCs). Trivedi et al. [50] described a case in which a patient with chronic kidney failure qualified for a kidney transplant from her HLA-identical sister. The research team, aiming to induce tolerance, opted to generate hESCs from the donor's ovaries. A suspension of pluripotent cells was administered into the recipient's peripheral blood, followed by kidney transplantation one week later. The study did not observe graft-versus-host disease, and chimerism induction was achieved. According to the authors, this was the first such attempt.

Bone marrow mesenchymal stem cells

An attempt was also made to inject donor mesenchymal stem cells directly into the recipient's hip bone marrow [51]. Biopsy-proven acute rejection occurred in 3 of 7 patients. Immunosuppressive mechanisms, such as lymphocyte proliferation, were observed in some patients.

In a study by Peng et al. [52] aimed at minimising the use of calcineurin inhibitors in post-kidney transplant patients, the impact of infusing donor-derived bone marrow mesenchymal stem cells on recipient tolerance to the transplanted kidney was investigated. Six patients who received kidneys from living donors, with varying HLA compatibility, participated in this study. Subsequently, these patients were administered tacrolimus at a 50% reduced dose compared to the standard dosage. The patients were then followed for 12 months. No adverse effects of the reduced immunosuppressive drug dose were observed, including no detrimental impact on graft viability. No chimerism was detected in the patients.

Pre-transplant modifications

Across the available studies, several preparative strategies were used before transplantation, most of which included some combination of total lymphoid irradiation (TLI) and ATG. An early pilot study in HLA-mismatched recipients applied TLI and ATG followed by Granulocyte Colony-Stimulating Factor-mobilised CD34 cell infusion [53]. A larger cohort of 29 fully HLA-matched recipients later received a similar non-myeloablative regimen with TLI, ATG, and infusions of CD34 and CD3 cells [54], with clearly better outcomes observed in the HLA-matched group [55]. Several U.S. centres subsequently explored this approach, although long-term reproducibility was achieved only by the Stanford team [56,57,36]. Their protocol was later adopted in a European study from Zurich, which applied the same conditioning – TLI, ATG, CD34 progenitors, and donor T cells to three HLA-matched sibling pairs, with favourable four-year outcomes [58].

Other teams introduced modifications to reduce toxicity or improve chimerism durability—adjustments involved lowering cyclophosphamide exposure and using smaller ATG doses. Lee et al. [64] documented a stepwise evolution of their regimen in eight patients, ultimately incorporating fludarabine and reduced-dose ATG. Although mixed chimerism was achieved, longer-term tolerance could not be assessed within the study timeframe.

Post-transplant modifications

Post-transplant management mainly consisted of donor-cell infusions combined with gradual tapering of immunosuppression. In the fully HLA-matched cohort treated with TLI and ATG, 24 of 29 recipients were able to discontinue immunosuppression entirely, with only one patient requiring later reinitiation due to rejection

[54]. In contrast, among haploidentical recipients, despite the achievement of mixed chimerism in some cases, ongoing therapy, often as tacrolimus monotherapy, was typically required because chimerism was insufficiently durable to allow complete withdrawal [55].

A similar pattern was described by Scandling et al. [59,60]. In their series, many HLA-matched patients successfully ceased immunosuppressive therapy, whereas those with partial or complete mismatch demonstrated only transient chimerism and required continued treatment. Individual case reports support these findings: haploidentical recipients frequently lost chimerism within weeks to months, followed by rising creatinine levels and the need to restart immunosuppression [61,62]. A 10-year follow-up study from China, which mainly included mismatched recipients, confirmed that although GVHD did not occur, sustained immunosuppression withdrawal was feasible only for a minority of patients [63].

Another aspect of post-transplant monitoring involved analysing B-cell repopulation as a potential indicator of developing tolerance. In a small series of five haploidentical recipients undergoing gradual tapering of immunosuppression, three developed stable tolerance, which coincided with reconstitution of peripheral B cells approximately one year after transplantation. The early predominance of CD20 CD27 memory B cells was also noted and suggested as a possible contributor to the tolerance process [65].

Regulatory T cells.

Andreola et al. [66] reported five patients who underwent kidney transplantation after a preparatory phase of immunosuppressive drugs, followed by BMT from the same HLA-haploidentical donor. The patients were then monitored for transplant tolerance and their overall condition for over 18 months, during which no concerning signs of rejection or deterioration of the transplanted kidney were observed. The research team emphasised the significant role of donor-reactive T cells, which may be responsible for the mechanism of transplant tolerance, together with regulatory T cells (T-reg cells).

In another study, Trivedi et al. [67] treated 76 patients with a living-donor kidney transplant preceded by HSCT. All patients successfully discontinued immunosuppressive medications, except for prednisone. The authors theorised that the lack of chronic rejection was related to the production of T-reg cells, with an average level of 3.5%. A putative marker enabling discontinuation of immunosuppressive drugs was also identified: CD45RA-FOXP3++ T-reg cells [68]. Other changes in cell numbers confirmed in human studies include profound reductions in T lymphocytes and an increase in immunosuppressive polymorphonuclear myeloid-derived suppressor cells in the spleen and blood following transplant [69].

Sprangers B et al. [70] investigated the effect of T-reg cells on graft survival. Enriching the T-reg population may be key to increasing the likelihood of successful graft tolerance induction and prolonging graft survival. Other researchers have also focused on T-reg cells and found that early donor-specific T-reg cell expansion is a significant factor in tolerance after CKBMT [71].

Oberbauer et al. [72] focused on incorporating T-reg cells into the procedure of mixed bone marrow and kidney transplantation from the same HLA-mismatched donor. The researchers noted the absence of standardised guidelines for the widespread adoption of CKBMT, as no established protocol exists for effective chimerism induction. They proposed a method in which the recipient would receive T-reg cells and tocilizumab before transplantation, along with thymoglobulin, belatacept, sirolimus, and steroids. Six months post-kidney transplantation, immunosuppressive drugs could be gradually tapered in stable patients. The study monitored the function of the transplanted kidney.

Additionally, changes in lymphocyte composition were monitored to demonstrate chimerism induction. It is worth noting that the transplant recipient did not undergo myeloablative conditioning, reducing the method's overall toxicity. The primary objective was not to achieve permanent chimerism, which, as intended, lowered the risk of graft-versus-host disease. Furthermore, immunosuppressive drugs were not completely discontinued in patients (belatacept was maintained), improving the condition of the transplanted tissue. The researchers demonstrated that the proposed approach enables transient chimerism using T-reg cells, thereby positively influencing tolerance development in the recipient. **Figure 3** presents different approaches to the CKBMT method.

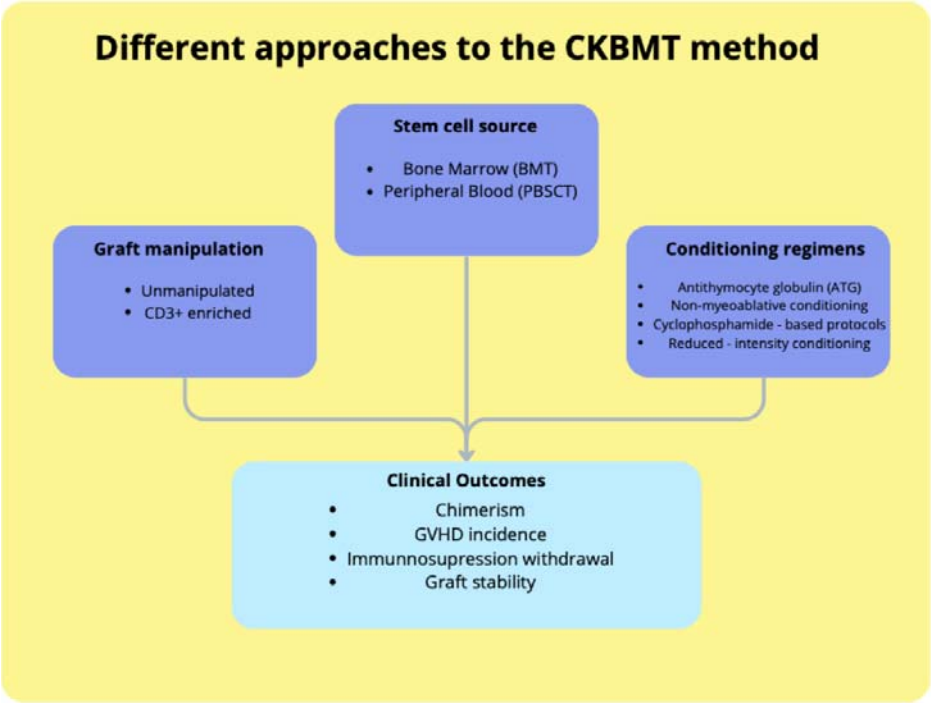

Figure 3. Different approaches to the CKBMT method.

Discussion

Analysis of available data indicates that kidney transplantation from the same donor who previously provided hematopoietic stem cells is an increasingly investigated strategy to induce immunological tolerance and enable the discontinuation of immunosuppressive therapy in transplant recipients. Among the studies analysed, the most favourable clinical outcomes have been observed in transplants from HLA-matched donors, in which chimerism was more sustained and immunosuppressive drugs could be safely withdrawn without signs of rejection [42,43,46].

Attempts to apply this approach in HLA-mismatched settings have also yielded some positive results, particularly when extensive preparative regimens were employed, including TLI, ATG, and fludarabine [36–40].

Despite these promising outcomes, there remains a lack of clearly defined clinical protocols that can reliably and reproducibly achieve long-term immunological tolerance. This is partly due to the limited availability of validated biomarkers for chimerism and tolerance, the heterogeneity of individual immune responses, and the potential complications associated with conditioning regimens, such as toxicity and renal injury. Clinical trials have employed diverse strategies for recipient conditioning, including thymic irradiation, administration of ATG, infusion of T-reg cells, infusion of adipose-derived mesenchymal stromal cells, and various chemotherapy and immunosuppressive protocols. While these efforts reflect dynamic progress in the field, they also underscore the absence of standardised methodologies [53–58].

In the early postoperative period, this combined approach demonstrated high efficacy, as evidenced by the absence of acute rejection episodes. However, long-term follow-up reveals potential complications, including chronic rejection and deterioration of graft function, manifested by decreased glomerular filtration rate (GFR) and lymphocytic infiltration on biopsy [30, 31, 39–41, 45, 46].

Currently, this strategy is primarily applied in patients undergoing treatment for hematologic malignancies. Preliminary findings suggest that in selected cases, substantial reduction or even complete withdrawal of immunosuppressive therapy may be feasible without compromising clinical efficacy [16–24].

Nonetheless, this approach remains associated with significant limitations. The key mechanisms governing chimerism persistence in

recipients are not yet fully understood, and it is not possible to predict with certainty whether reinitiation of immunosuppression will eventually be necessary. Variability in outcomes observed despite the use of identical conditioning and post-transplant protocols suggests that success depends on multiple, as yet incompletely characterised factors.

The aforementioned limitations and the heterogeneity of published results underscore the urgent need for well-designed, long-term clinical trials. Such studies are essential for identifying predictive markers of successful tolerance, optimising conditioning protocols, and refining donor selection criteria. The prospect of employing combined kidney and bone marrow transplantation (CKBMT) as a standard therapy for end-stage renal disease, particularly in patients concurrently receiving hematologic treatment, is promising, though it remains experimental.

Although CKBMT offers a theoretical path to achieving immune tolerance, this approach remains limited by significant clinical risks. It is associated with a significant burden of complications, including prolonged cytopenias, opportunistic infections, and graft failure. Equally important is the potential risk of developing acute or chronic graft-versus-host disease, which remains one of the most challenging and unpredictable consequences of this procedure. In light of these risks, the clinical use of CKBMT has been limited to a few highly specialised centres, and its wider implementation has not yet been realised. These limitations should be considered when interpreting current clinical results and considering the potential for further expansion of this strategy.

The strength of this review article lies in its extensive literature selection, encompassing both historical works that introduce the problem of chimerism and recent publications. In conclusion, we also propose directions for further research, lending the work practical application value. However, we also recognize the limitations of the study. The analysis remains too brief in some places, underscoring the need to draw on extensive literature. Another significant limitation is that the discussed issue concerns a relatively small group of patients, which may limit its practical utility in broader scientific and clinical contexts.

Declarations

Ethics approval and consent to participate
Not applicable

Consent for publication
Not applicable

Availability of data and materials
All data generated or analysed during this study are included in this published article [and its supplementary information files].

Authors' contributions
Conceptualisation, M.M. and I.I-P; Methodology, J.M., K.S. and M.M.; Formal analysis, I.I.-P.; Writing-original draft preparation, J.M., K.S.; Writing-review and editing, M.M., A.C.D. and I.I.-P.; Visualisation, K.S.; Supervision, I.I.-P.; Project administration, M.M.; Funding acquisition, M.M. and I.I-P.

Conflict of interest statement
The authors declare no conflict of interest.

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