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## ABOUT COVER

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*REVIEW*

# Current status of glucocorticoid usage in solid organ transplantation

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## Abstract

Glucocorticoids (GCs) have been the mainstay of immunosuppressive therapy in solid organ transplantation (SOT) for decades, due to their potent effects on innate immunity and tissue protective effects. However, some SOT centers are reluctant to administer GCs long-term because of the various related side effects. This review summarizes the advantages and disadvantages of GCs in SOT. PubMed and Scopus databases were searched from 2011 to April 2021 using search syntaxes covering "transplantation" and "glucocorticoids". GCs are used in transplant recipients, transplant donors, and organ perfusate solution to improve transplant outcomes. In SOT recipients, GCs are administered as induction and maintenance immunosuppressive therapy. GCs are also the cornerstone to treat acute antibody- and T-cell-mediated rejections. Addition of GCs to organ perfusate solution and pretreatment of transplant donors with GCs are recommended by some guidelines and protocols, to reduce ischemia-reperfusion injury peri-transplant. GCs with low bioavailability and high potency for GC receptors, such as budesonide, nanoparticle-mediated targeted delivery of GCs to specific organs, and combination use of dexamethasone with inducers of immune-regulatory cells, are new methods of GC application in SOT patients to reduce side effects or induce immune-tolerance instead of immunosuppression. Various side effects involving different non-targeted organs/tissues, such as bone, cardiovascular, neuromuscular, skin and gastrointestinal tract, have been noted for GCs. There are also potential drug-drug interactions for GCs in SOT patients.

**Key Words:** Corticosteroids; Glucocorticoids; Solid organ transplantation; Liver; Kidney; Heart; Lung

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**Core Tip:** Due to their potent immunosuppressive and anti-inflammatory effects, glucocorticoids (GCs) are widely used in solid organ transplantation (SOT). We review the current status of GC usage in SOT, including the different clinical uses in transplant recipients and donors, new strategies for targeted organ delivery of GCs, and enhancement of immune-tolerance *vs* immunosuppressive effects. Major concerns about GCs, such as their adverse effects on various organs and their potential drug-drug interactions in SOT patients, are also discussed.

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## INTRODUCTION

Glucocorticoids (GCs) have long been used as induction and maintenance immunosuppressive therapy, as well as treatment of acute allograft rejection in solid organ transplant (SOT) patients. However, complications of GCs make them undesirable for long-term use. Therefore, steroid sparing regimens have been used in different types of SOT[1-3].

French insurance data in 2014 showed that only 54% of patients who received kidney transplantation in 2012 were taking prednisolone[4]. A large cohort study on adult liver transplant patients who were transplanted between 2006 and 2014 showed that during 6 mo after transplantation approximately 43% of the liver transplant recipients were treated with three immunosuppressive drugs, including prednisolone, a calcineurin inhibitor (CNI), and mycophenolate/azathioprine, while 15.4% of the patients were on steroid sparing regimens; however, approximately 34% of the patients on triple therapy changed to a steroid sparing regimen between months 7 to 12 after liver transplantation[2]. It should be kept in mind that these data underestimate the number of patients who discontinued steroids because patients who received only tacrolimus have been categorized as antimetabolite sparing and not steroid sparing.

Regarding heart transplantation, a report from International Society of Heart and Lung Transplantation Registry on adult heart recipients who were transplanted between 2000 and 2008 indicated that long-term use of steroids (use for more than 5 years after transplantation) has declined over time from 60% in the year 2000 to 43% in the year 2008, and early GC withdrawal (discontinuation between 2 to 5 years after transplantation) has increased from 19% to 33% during these years[3]. Here, we review different advantages and disadvantages of GCs in SOT (Figure 1).

## DOCUMENT RETRIEVAL

PubMed and Scopus databases were searched from January 2011 to April 2021 using search syntaxes: (transplantation [Title/Abstract] OR transplant [Title/Abstract]) AND (corticosteroid* [Title/Abstract] OR glucocorticoid* [Title/Abstract] OR steroid* [Title/Abstract] OR prednisolone [Title/Abstract] OR prednisone [Title/Abstract] OR methylprednisolone [Title/Abstract] OR dexamethasone [Title/Abstract] OR hydrocortisone [Title/Abstract]). Articles' references were reviewed for relevant publications.

## MECHANISMS OF ACTIONS OF CORTICOSTEROIDS IN SOLID ORGAN TRANSPLANTATION

For many years, the adaptive immunity system (T and B cells) has been focused on preventing allograft rejection. However, the innate immune system (dendritic cells, phagocytes [monocytes, macrophages, neutrophils], and natural killer [NK] cells) also

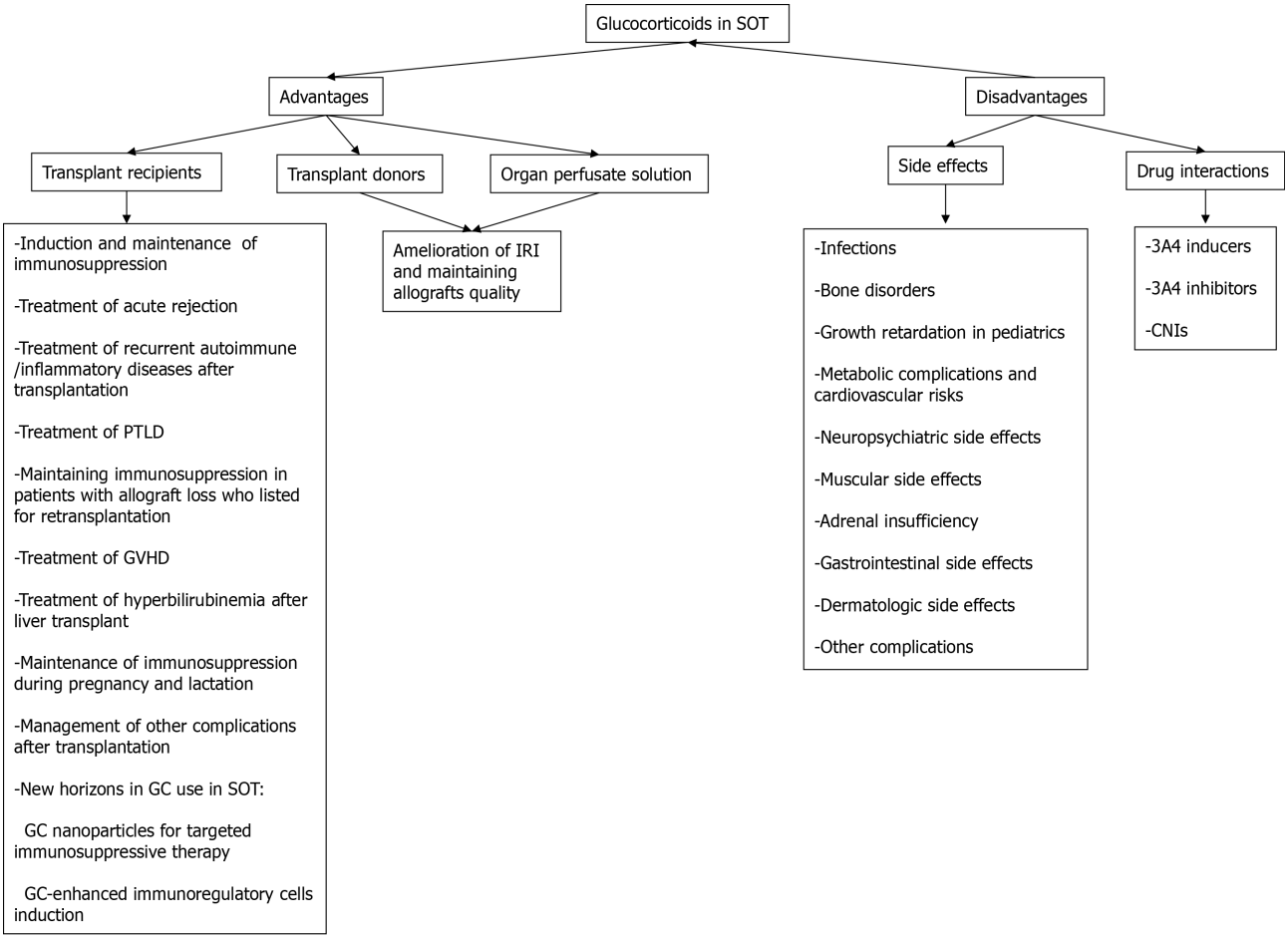


**Figure 1 Advantages and disadvantages of glucocorticoids in solid organ transplantation.** CNI: Calcineurin inhibitor; GC: Glucocorticoid; GVHD: Graft *vs* host disease; IRI: Ischemia-reperfusion injury; PTLD: Post-transplant lymphoproliferative disorder; SOT: Solid organ transplantation.

plays major roles in the peritransplant immunologic process. Innate immunity is activated peritransplant by donor brain death, ischemia-reperfusion injury (IRI), non-adherence to immunosuppressive therapy, and infections. Innate immune activation ultimately induces acute allograft rejection and chronic allograft damage[5]. GCs exert a wide range of anti-inflammatory and immunosuppressive impacts, mainly through their genomic and partly *via* their non-genomic effects. Their genomic effects, that usually have prolonged onset of action, are mediated by binding of GCs to their cytosolic receptors, entering the nucleus, and activating GC response elements that induce anti-inflammatory genes (transactivation) while repressing elements that induce expression of inflammatory factors, such as nuclear factor kappa-light-chain enhancer of activated B-cells (NF-kB) and activator protein-1 (AP1) (transrepression). Anti-inflammatory effects of GCs are related to both transactivation and transrepression effects, while their adverse effects mainly correlate to their transactivation impacts. Genomic effects usually depend on the cumulative dose over the duration of GC administration[1,5,6]. The non-genomic mechanism of GCs has been less known and is partly mediated by membrane receptors that modulate anti-inflammatory and anti-oxidant effects. Their non-genomic effects are of rapid onset, short duration of action, and happen with high or pulse doses (prednisolone doses of > 30 mg/day)[1,6,7].

In the innate immunity system, GCs decrease the production of inflammatory cytokines (tumor necrosis factor-alpha [TNF-á] and interleukin [IL]-1β) in dendritic cells in response to CD40L and lipopolysaccharide (LPS). GCs also inhibit upregulation of costimulatory molecules (CD40, CD80, CD83, CD86 and MHC-II) in dendritic cells in response to LPS. In monocytes, GCs increase the expression of anti-inflammatory cytokines (IL-10) and repress production of inflammatory cytokines (TNF-α, IL-1β, IL-12), reduce expression of CD80 in response to inflammatory stimuli, impair monocyte antigen presenting activity, and down-regulate expression of TLR4 on the surface of monocytes, leading to a subsequent monocyte hypo-responsiveness to endotoxin. In neutrophils, GCs inhibit neutrophil activation (by reducing the ex-

pression of NADPH oxidase, inducible nitric oxide synthase [iNOS], and cyclooxygenase 2), reduce chemotaxis, phagocytosis and cytokine secretions, increase the expression of some receptors for ILs and proinflammatory leukotrienes (IL1R1, BLT1), and reduce neutrophil sensitivity to apoptosis that leads to increased neutrophil life span. GCs reduce NK cell cytolytic activity and increase their production of pro-inflammatory cytokines[8]. By repressing the expression of IL-1, IL-2, IL-3, TNF-α, and IFN-γ, the T-cell activation process (a part of adaptive immunity) is inhibited by GCs [5]. These mechanisms have been summarized in Figure 2. Considering the above-mentioned mechanisms, GCs have various advantages and disadvantages in SOT patients that are reviewed here.

## ADVANTAGES OF GCs IN SOT

GCs are administered pre-transplant to potential donors and organ perfusate solution to decrease IRI and preserve organs quality; moreover, GCs are given peri- and post-transplant to recipients as induction or maintenance immunosuppression, treatment of acute rejection, or for management of some post-transplant complications.

## TRANSPLANT RECIPIENTS

### *GCs as induction and maintenance immunosuppressive therapy*

GCs are commonly used as induction and maintenance immunosuppressive agents in SOT patients[1-3]. As maintenance immunosuppressive therapy, some centers are shifting toward steroid sparing maintenance immunosuppressive regimens by different steroid withdrawal or avoidance protocols[1-3]. Steroid sparing means rapid, early, or late steroid discontinuation (within 1 wk to several months after transplantation), while steroid avoidance refers to avoiding steroid use in regimens with or without initial high corticosteroid induction therapy[3,9-12]. Although old studies on steroid sparing regimens (GC minimization or discontinuation after 3 mo of transplant surgery) showed higher rates of acute rejection and graft loss, in those studies immunosuppressive regimens contained cyclosporine as a CNI[13]. Nowadays, induction therapies with thymoglobulin or IL2 receptor antagonists and new maintenance immunosuppressive regimens, such as tacrolimus instead of cyclosporine as CNI or mTOR inhibitors, in combination with low doses of CNIs and/or mycophenolate, provided the opportunity for successful steroid-sparing immunosuppression regimens[1,9-11,14,15]. Although, steroid sparing immunosuppressive regimens were used for low immunological risk patients, an analysis of 169479 renal transplant patients using the Scientific Registry of Transplant Recipients found that rapid discontinuation of steroids can be used in all adult and pediatric first kidney transplant recipients from either a deceased or living donor and in second kidney transplant recipients from a living donor or patients at risk for rejection or recurrence of underlying diseases without decreasing patients' or graft survival rates. Rapid steroid withdrawal was only associated with worse graft survival[9] in adult patients after a second kidney transplantation from a deceased donor. Another systematic review and meta-analysis consisting of seven cohort studies that included high-risk kidney transplant patients, such as re-transplanted patients, African-American ethnicity, or recipients with panel reactive antibody (referred to as PRA) of 20% or more, found that acute rejection episodes and graft loss were comparable between patients maintained on steroids compared with steroid withdrawal or avoidance group. Steroid withdrawal was initiated within 1 wk after transplantation in many of these patients. Based on this meta-analysis, steroid withdrawal within 1 wk after transplantation was associated with significant reduced risk of patient death[10].

Steroid withdrawal regimens are used in most liver transplant patients. A Cochrane systematic review consisting of 1347 liver transplant patients revealed that early steroid withdrawal or steroid avoidance (excluding intraoperative GC use) have been beneficial in some patients, especially those at risk for hypertension or diabetes mellitus[11]. Although steroid avoidance after using a high intraoperative dose may be beneficial in liver transplant recipients, data showed that complete steroid avoidance (even avoiding intraoperative use) decreased patient and graft survival[12].

Most centers that perform simultaneous kidney and pancreas transplantations are also shifting toward steroid avoidance, or early or late steroid withdrawal[16].

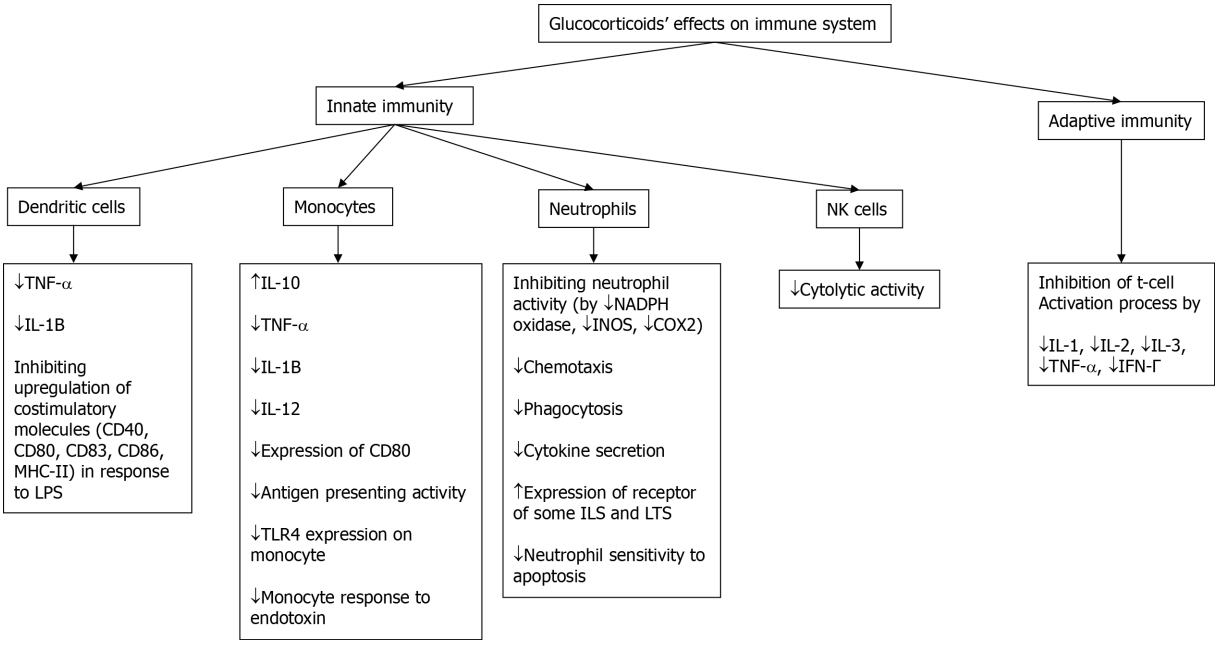


**Figure 2 Effects of glucocorticoids on the immune system.** COX2: Cyclooxygenase 2; IFN-γ: Interferon-gamma; IL: Interleukin; iNOS: Inducible nitric oxide synthase; LT: Leukotriene; NK: Natural killer; TNF-α: Tumor necrosis factor-alpha.

Long-term GC therapy had been the cornerstone of immunosuppressive therapy in heart transplant patients. However, a report from the International Society of Heart and Lung Transplantation Registry on adult heart recipients who were transplanted between 2000 and 2008 showed that early or late GC withdrawal has increased among heart transplant patients. Compared to long-term steroid users (GC use for > 5 years after transplantation), 10-year patient survival was significantly higher among early (GC discontinuation between 2 years to 5 years after transplantation) or late (GC discontinuation after year 5 of transplant) steroid withdrawal (73%, 82% and 80%, respectively)[3]. Steroid discontinuation within 1 wk of transplantation has also been applied in low-risk heart transplant pediatric patients with acceptable 1-year outcomes [17].

Corticosteroids are usually a part of maintenance immunosuppression in lung transplant patients as well. Glucocorticoid receptor (GR) in lung epithelia is essential for lung development, and GCs are widely used to treat certain lung diseases[18]. It seems that there is a difference in lung transplant outcomes between patients with different variants of glucocorticoid-induced transcript 1 gene (GLCCI1) that modulates GC sensitivity. A study on 71 lung transplant recipients showed that compared with those with the CC variant (wild type allele), patients with the TT variant (homozygous for mutant allele) had lower total lung capacity and forced expiratory volume in 1 sec at 3 years after transplantation and also had significantly decreased chronic allograft dysfunction-free survival at year 3 after transplantation[19].

Despite available data regarding efficacy of steroid sparing regimens in SOT patients, systemic steroids are still used at least for several weeks in maintenance immunosuppression regimens, even in low immunologic transplant types, such as liver transplantation[20]. Budesonide is a synthetic corticosteroid with minimal systemic bioavailability of about 10% due to extensive first-pass hepatic metabolism that results in decreased side effects[21]. On the other hand, compared to methylprednisolone and prednisone, budesonide possesses strong local anti-inflammatory effect in the liver due to approximately 15-times higher affinity for GR[22]. A phase 2 clinical study in first liver transplant recipients compared budesonide (tapering from 9 mg to 3 mg over 12 wk) with prednisolone in the maintenance immunosuppressive regimen containing CNI and mycophenolate. Patients were followed for 2 years. Biopsy-proven acute cellular rejection was the same between the two groups (5% in each group), while post-transplant diabetes mellitus (PTDM) (0% *vs* 15%) and infection rates (0% *vs* 30%) were significantly lower in the budesonide-taking group[23].

### *Treatment of acute rejection*

High doses of intravenous (methylprednisolone or dexamethasone) or oral (prednisolone or prednisone) GCs have been historically administered for the treatment of

acute cellular and antibody-mediated rejections in different types of SOT[24-28]. Recently, a United States center retrospectively assessed the 6 mo outcomes of 29 pediatric liver transplant patients who were prescribed oral budesonide in an outpatient setting for treatment of biopsy-proven (19 patients) or presumed (based on blood biochemistry tests; 10 patients) mild to moderate acute cellular rejection. In these patients, budesonide was administered at daily doses of 6 mg to 9 mg for several weeks, tapering down thereafter. Only 3 patients needed to be switched to systemic GCs (methylprednisolone or prednisone). All other patients experienced significant decreases in liver transaminases without progressive graft injury or chronic allograft rejection[29].

### Post-transplant malignancies

A main complication after SOT is post-transplant malignancies, including post-transplant lymphoproliferative disorders (PTLD). Immunosuppression reductions or changes are recommended in patients with PTLD. However, GCs are a basis of chemoimmunotherapy in some malignancies, including PTLD, and are usually kept in the immunosuppressive regimen of SOT recipients with PTLD[30]. Sometimes, under the umbrella of corticosteroids, other chemotherapeutic agents (with some safety concerns in SOT recipients) are administered. Although immune checkpoint inhibitors have increasingly been successful in treating multiple types of cancer, the risk of allograft rejection with these drugs in SOT patients is concerning[31]. A pilot study showed that immune checkpoint inhibitors, along with prophylactic steroids, may be a safe and effective treatment for some SOT patients with advanced cutaneous squamous cell carcinoma[32]. While a Danish historical cohort study revealed a tendency toward a higher occurrence of post-transplant cancer in patients treated at a kidney transplant center that applied a steroid-free immunosuppressive regimen compared to patients treated at centers that adhered to GC-containing immunosuppressive protocols[33], another Danish registry analysis on over 59000 patients found a standardized incidence risk of 1.32 (95% confidence interval [CI]: 1.09-1.59) for cutaneous squamous cell cancer among GC users; however, this increased risk was seen across all patients in that study, not just transplant patients[34].

### Prevention or treatment of recurrent autoimmune diseases

Diverse *de novo* autoimmune diseases in different organs can happen after SOT and these cases are usually treated similarly to patients in the general population; this topic, however, is out of the scope of this review. Recurrent glomerulonephritis (GN) after renal transplantation is the fourth most common cause of allograft loss, with a reported recurrence rate of 2.6% to 50% and average graft loss risk of 8.4% over 10 years. Data from Australia and New Zealand Dialysis and Transplant Registry over 30 years reported that focal segmental glomeruosclerosis (FSGS), IgA nephropathy, membranous GN, and membranoproliferative GN (MPGN) showed recurrence after renal transplantation. Different risk factors have been reported for these GN recurrences. Regarding the role of GCs, when all GNs were included, multivariate analysis found baseline steroid use in maintenance immunosuppression had a protective effect (adjusted hazard ratio [HR]: 0.54; 95%CI: 0.37-0.76; $P < 0.001$). When FSGS and IgA nephropathy were analyzed separately, baseline steroid use was a protective factor only for transplant recipients with IgA nephropathy[35]. Another study also revealed that the rate of recurrence of IgA nephropathy after kidney transplantation was higher among patients with steroid withdrawal at any time after transplant[36]. There is a lack of evidence for treatment and outcomes of recurrent GN after transplantation. Recurrent GN after transplantation is usually managed similar to *de novo* cases in the general population, although sometimes with different protocols and responses. GCs are usually a part of GN management regimen[37,38]. Recurrent IgA nephropathy after renal transplantation is treated with GCs[39].

Autoimmune liver diseases (autoimmune hepatitis [AIH], primary biliary cirrhosis [PBC], and primary sclerosing cholangitis [PSC]) may recur after liver transplantation, with varying rates of 10% to 50%. Recurrence of PBC or PSC has not been associated with dose or duration of GC administration or discontinuation of GCs. Recurrent PBC is traditionally treated with ursodexycholic acid, with varying results. Recurrent PSC usually causes progressive allograft damage and requires repeat liver transplantation. Although overall dose and duration of GC treatment pre- and post-liver transplantation are not related to AIH recurrence, rapid weaning of GC after liver transplantation has been associated with higher AIH recurrence rate. AIH recurrence is usually treated with GCs[40,41].

### *Maintaining immunosuppression in patients with graft loss who listed for re-transplantation*

Although maintenance of low-dose CNI after kidney allograft loss can decrease the development of donor-specific antibody and repress the rise in PRA in patients listed for repeat kidney transplantation, such effects were not observed with GCs[42]. Meanwhile, some clinicians continue low dose prednisolone in kidney recipients with graft loss more than 1 year after transplantation who are planned for repeat renal transplantation within 1 year[43].

### *Graft vs host disease (GVHD) after SOT*

Although rare after SOT, GVHD may still occur. Case series show administration of methylprednisolone for treatment of GVHD in some SOT patients; however, there are GC-treatment refractory patients, with high mortality rate of 82%[44,45].

### *Hyperbilirubinemia after liver transplantation*

Hyperbilirubinemia after liver transplantation is common and is sometimes due to early allograft dysfunction. A randomized controlled trial assessed the effect of low-dose steroid in combination with ursodeoxycholic acid in liver transplant patients. The control group received only ursodeoxycholic acid. Patients with hyperbilirubinemia due to biliary complications and acute rejection were excluded from the study. Both groups had comparable immunosuppressive regimens, donor and recipient characteristics, and time after transplantation surgery. The steroid group had significantly lower bilirubin concentration 1 d and 15 d after intervention was completed and had shorter hospital stay compared with the control group[46].

### *Pregnancy and lactation*

GCs cross the placenta, but nearly 90% of the dose of prednisolone and methylprednisolone (and to lesser extent dexamethasone and betamethasone) is metabolized by placenta 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2) to an inactive metabolite. Although there have been concerns about oral-facial clefts, hypothalamus-pituitary-adrenal (HPA) axis dysfunction, or retarded growth in newborns from GC-taking mothers, the risk seems minimal unless there is a 11β-HSD2 dysfunction (*e.g.*, due to preeclampsia in the mother). It is also possible that GCs may predispose pregnant women to hypertension and preeclampsia. Taken together, GCs in daily doses equivalent to less than 20 mg prednisolone are considered acceptable in pregnant women, and GCs are usually continued in transplanted mothers. GCs are also considered compatible with breast-feeding[47].

### *Management of other complications*

The number of patients with pulmonary complications after hematopoietic stem cell transplantation (HSCT) is increasing, and some of these patients need lung transplants to survive. Steroid therapy is the current treatment for pulmonary complications in HSCT patients. A retrospective study that compared 9 patients on low-dose and 13 patients on high-dose GCs for post-HSCT pulmonary complications and before their lung transplantation showed that taking low-dose *vs* high-dose GCs before lung transplantation in these patients was associated with significantly fewer complications during the first year after lung transplantation and improved long-term survival[48].

### *New horizons of GCs use in SOT recipients*

Targeted delivery of GCs to the affected organ is a favorable method to reduce GC side effects when used for treatment of inflammatory diseases and in SOT patients. After parenteral administration, nanoparticles largely translocate into the liver by passive targeting. Therefore, nanoparticle-mediated drug delivery would be a promising method for treatment of inflammatory liver diseases. In several studies, different nanoparticles have been used for transportation of dexamethasone, such as biodegradable polymers (PLGA, PLLA, PCL, cellulose, cyclodextrin, chitosan, polyglutamic acid, and lipids), inorganic materials, polymer micelles, liposome, and carbon nanotubes. Entrapment of dexamethasone in these nanoparticles resulted in prolonged and sustained release of dexamethasone, but premature release out of the target organ is an undesired consequence. To overcome this possibility, dexamethasone in concentrations up to 100 mg/mL in olive oil were encapsulated in core-shell silica nanocapsules. During an experimental study, these nanocapsules were internalized by non-parenchymal murine liver cells and resulted in suppression of inflammatory response of liver macrophages and a significant decrease in inflammatory cytokines.

Pegylation of these nanocapsules led to good stability in plasma and controlled interaction with blood proteins[49].

With the hope of improving efficacy while decreasing side effects, another animal study compared liposomal encapsulated prednisolone *vs* conventional prednisolone in a murine model of acute renal allograft rejection. The liposomes were 100 nm phospholipid bilayer vesicles coated with polyethyleneglycol. These liposomes remained in blood for several days after intravenous injection. Liposomes prevent the encapsulated drug from diffusing over blood vessel endothelial cells and spreading throughout the body, while they are small enough to extravasate and accumulate in inflamed sites with increased vascular permeability, where macrophages and other phagocytic cells digest the vesicles and release the entrapped GC. The results of that animal study showed improved renal bioavailability of prednisolone, increased renal perfusion, and decreased cellular infiltrate in allograft by liposomal prednisolone compared with conventional prednisolone. In that study, liposomes were detected in other organs, such as liver, stomach, and intestine, but in much lower density than in the kidney allograft[50]. More animal studies are needed before clinical studies to bring these bench findings to the bedside.

Inducing immune tolerance and eliminating the need for long-term immunosuppressive therapy has been an old ideal in SOT. Modulating immunoregulatory cells represents a potential target for this purpose. Myeloid-derived suppressor cells (MDSCs) are novel immunoregulatory cells induced by granulocyte macrophage colony stimulating factor (GM-CSF). In an *in vitro* study, the combination of dexamethasone with GM-CSF was successful for enhanced production of the phenotype of MDSCs with enhanced *in vitro* immunosuppressive activity. Adoptive transfer of these MDSCs significantly enhanced expansion of regulatory T cells and prolonged heart allograft survival in a mouse model. Mechanistic studies showed that iNOS signaling was required for MDSCs in the control of the T cell response. GR signaling had a major role in the recruitment of transferred MDSCs into the allograft, through upregulating CXCR2 expression on MDSCs. These findings revealed that co-administration of dexamethasone and GM-CSF may be a new and applicable strategy for the induction of immune tolerance in SOT[51].

## TRANSPLANT DONORS

The brain death process induces an inflammatory response in the donor. Increased intracranial pressure and decreased cerebral blood flow during the brain death process activate neurohormonal systems and the inflammatory cascade. Increased release of inflammatory cytokines, chemokines, and adhesion molecules leads to infiltration of T lymphocytes and macrophages into the organs[52]. This inflammatory response causes allograft injury that, in combination with IRI, increases the risk of initial allograft poor function[53]. There are two separate stages for IRI. Ischemia leads to cellular metabolic disturbances, glycogen consumption, lack of oxygen supply, and ATP depletion, which lead to initial parenchymal cell death. Reperfusion injury results from both metabolic disruptions and intense inflammatory response. IRI triggers inflammatory response mainly through innate immune response. Innate immune activation leads to increased production of cytokines, chemokines, and reactive oxygen species (ROS), and increased expression of adhesion molecules. Moreover, cross-talk between innate and adaptive immunity trigger an adaptive immune response that results in tissue infiltration by lymphocytes and monocytes, and graft rejection[54]. IRI is an important cause of early allograft dysfunction[54]. Therefore, several investigators have administered anti-inflammatory drugs to deceased donors to ameliorate IRI. Although animal[55,56] and small clinical[57] studies have shown that administering GCs to brain dead donors decreased IRI in kidney, heart, or liver grafts[55-57] and is recommended by organ procurement guidelines[58], the effect of pretreatment of brain dead donors with anti-inflammatory agents on long-term allografts outcomes are not promising[59,60]. A multicenter randomized controlled trial consisting 455 kidney transplant recipients from 306 deceased donors were followed for 5 years after transplantation. These deceased donors were randomized to receive 1 g of methylprednisolone or placebo before organ procurement. The incidence of biopsy-confirmed rejection (Banff > 1) at 3 mo after transplantation and 5-year graft survival and the mean estimated glomerular filtration rates were comparable between steroid and placebo groups[59]. In addition, a meta-analysis on methylprednisolone treatment of brain dead liver donors (two studies, 183 participants) showed no effect of the treatment on rates of acute rejection (Table 1)[61]. Interestingly, an animal study

**Table 1 Effect of pretreatment of transplant donors with methylprednisolone on outcomes of solid organ transplantation**

| Type of the study | Type of SOT | Follow-up duration | Findings |
|---|---|---|---|
| RCT[57] | Liver | 6 mo | Significant lower liver enzymes in GC *vs* placebo group at 1$^{st}$ and 10$^{th}$ d after transplantation; No difference in PNF rate between groups (2 of 50 patients in GC and 3 of 50 patients in the placebo group); Lower acute rejection during 6 mo in GC group (22% *vs* 36%; $P < 0.05$) |
| RCT[60] | Liver | Maximum 3 yr | No difference in liver enzymes between GC and placebo groups during 1$^{st}$ wk after transplantation; Acute rejection during 3 mo after transplantation was 24% in each group; 1 yr graft loss of 15% in GC and 24% in the placebo group ($P = 0.41$); Relative risk of acute rejection in GC *vs* placebo group: 1.02 (95%CI: 0.5-2.1; $P = 1$); Relative risk of mortality in GC *vs* placebo group: 0.63 (95%CI: 0.29-1.36; $P = 0.31$) |
| Meta-analysis of two above RCTs[61] | Liver | Maximum 6 mo | Risk ratio for incidence of acute rejection during 1 mo to 6 mo after transplantation: 0.72 (95%CI: 0.44-1.19; $P = 0.2$) |
| RCT[59] | Kidney | 5 yr | 3 mo BPAR: 10% in GC and 12% in placebo group ($P = 0.468$); 5 yr graft survival: 84% in GC and 82% in placebo group ($P = 0.941$); Mean eGFR at 5 yr: 47 mL/min/1.73 m$^2$ in GC and 48 mL/min/1.73 m$^2$ in placebo group ($P = 0.756$) |

BPAR: Biopsy-proven acute rejection; CI: Confidence interval; eGFR: Estimated glomerular filtration rate; GC: Glucocorticoid; PNF: Primary non-function; RCT: Randomized clinical trial; SOT: Solid organ transplantation.

showed that pretreatment with methylprednisolone markedly prevented warm liver IRI in normal rats, but aggravated IRI in the steatotic livers of the diabetic Zucker rats with deficiency of the leptin receptor[62]. Leptin resistance is common in diabetes. Thus, more studies are needed to understand how deficiency in the leptin signaling may switch the GC action from protection to aggravation in liver IRI and thus affect GC action in SOT of liver and other organs in humans.

The pro-inflammatory state induced by the brain death process also decreases the quality of lungs for donation. To preserve lung quality, methylprednisolone is administered to donors with various doses. To assess the dose-effect association between methylprednisolone and brain death lung inflammation, an animal study compared low (5 mg/kg), intermediate (12.5 mg/kg), and high (22.5 mg/kg) doses of methylprednisolone. All methylprednisolone doses decreased inflammatory cytokines, such as TNF-α, IL-6, and IL-1β. Intermediate and high doses of methylprednisolone also increased protective anti-inflammatory response as established by increased IL-10 expression. Macrophage chemotaxis was attenuated with all doses of methylprednisolone, while neutrophil chemotaxis was more evident with intermediate and high doses of methylprednisolone. Considering dose-related side effects of methylprednisolone, this study suggested the intermediate dose of methylprednisolone reduced brain death-induced inflammatory responses in donors' lungs[63]. These findings need human studies before extrapolation to routine clinical use.

## ORGAN PERFUSATE SOLUTIONS

Animal studies have shown decreased generation of pro-inflammatory cytokines, IRI, and donated tissues edema by adding (methyl)prednisolone to perfusate STEEN solution™ and Perfadex® solution for heart and lung grafts[64,65]. Recently, normothermic *ex vivo* heart perfusion using the Transmedics organ care system™ (OCS) has been used clinically for preservation of hearts donated after circulatory death. Based on the Transmedics OCS protocol, methylprednisolone is added to the perfusate solution to reduce IRI and preserve cardiac function[66].

## DISADVANTAGES OF GCS IN SOT

The main drawback of GCs is their diverse adverse effects on various tissues. Side effects are usually related to genomic mechanism of action of these drugs, mainly transactivation ones; therefore, these side effects usually have prolonged onset and are associated with the cumulative dose of GC over the duration of its administration[1,5,6]. Another aspect that should be considered, especially in SOT patients, is drug interactions of GCs with other drugs in these patients. These aspects are briefly reviewed below.

## SIDE EFFECTS

### *Infections*

GCs increase the risk of bacterial, fungal and viral infections[6]. A multivariate regression analysis on data of 45164 kidney transplant recipients in 2000-2011 from the United States Renal Data System (USRDS) showed that a steroid-free immunosuppressive regimen was associated with reduced risk of pneumonia (adjusted HR: 0.89; $P$ = 0.002) and sepsis (adjusted HR: 0.80; $P$ < 0.001)[67]. A multicenter, case-control study on 988 episodes of Enterobacterales-induced blood stream infection among SOT patients showed that about 40% of these episodes are caused by extended-spectrum β-lactamase (ESBL)-producing organisms. Taking corticosteroid-containing immunosuppressive regimens was identified as a risk factor for ESBL-Enterobacterale-induced blood stream infection (adjusted odds ratio [OR]: 1.3; 95%CI: 1.03-1.65; $P$ = 0.03)[68]. Nocardiosis is another bacterial infection reported among immunocompromised patients, such as SOT recipients. A retrospective study compared 60 adult patients who were hospitalized with nocardiosis to a group of 120 patients which had been randomly selected from among hospitalized patients with community-acquired pneumonia. Multivariable logistic regression analyses showed that immunosuppressive therapy was positively associated with nocardiosis (matched OR: 4.40; 95%CI: 2.25-8.62; $P$ < 0.001). Among immunosuppressive therapy, GC therapy was a typical risk factor for nocardiosis (matched OR: 4.69; 95%CI: 2.45-8.99; $P$ < 0.001), especially for pulmonary nocardiosis (matched OR: 5.90l 95%CI: 2.75-12.66; $P$ < 0.001). The positive association between SOT and nocardiosis was mitigated following adjustment for GC administration in a multivariate model. The association between taking GC and developing nocardiosis was stronger in patients with chronic pulmonary disease (OR: 5.74; 95%CI: 2.75-12.66; $P$ < 0.001) than in the pooled analysis of all nocardiosis cases [69]. Another analysis on 112 patients with nocardiosis, among which 67 were immunocompromised patients, showed that pulmonary nocardiosis among immunocompromised patients was significantly associated with taking high-dose GC. Immunocompromised patients showed more disseminated forms of infection, with the highest rate in SOT recipients, and had significantly higher mortality compared with immunocompetent patients[70].

Taking GCs is a risk factor for fungal infections, including mucormycosis[71] and invasive *Aspergyllosis*[72,73]. Although the American Society of Transplantation suggests re-initiation of *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis with intensification of immunosuppression, such as treatment of acute rejection with GCs [74], the association between GC bolus for acute rejection and PJP remains controversial[75]. While a French case-control study exhibited GC bolus administration for acute rejection in kidney transplant patients as an independent factor correlated with PJP[76] and a Korean study showed that taking GCs is significantly associated with PJP[77], a meta-analysis found that GC injections for acute rejection did not increase the risk of PJP[75]. On the other hand, a retrospective case series showed that adding GCs to PJP treatment of non-human immunodeficiency virus (HIV)-infected patients (3 of 28 were SOT patients) was associated with lower mortality[78], while an older retrospective study comparing PJP-infected non-HIV patients with or without adjunctive steroid therapy (12 of 59 patients in the GC-taking group and 14 of 29 patients in no-GC group were SOT patients) found that GC use may not improve outcome of moderate to severe PJP in these patients[79].

Regarding viral infections, it has been reported that prednisolone daily doses of 10 mg or higher is associated with higher risk of respiratory viral infection[80]. Community-acquired viral respiratory infections (rhinovirus followed by coronavirus and respiratory syncytial virus) has been reported in approximately 25% of lung transplant recipients during the first year after transplantation, especially in those receiving nasal glucocorticoids[81]. Corticosteroid use is a risk factor for adenovirus infections, including urinary tract infection with this virus (OR = 3.86; 95%CI: 1.21-12.24; $P$ = 0.02 for acquiring urinary tract infections)[82]. It has been reported that kidney transplant patients on maintenance GCs are more likely to be admitted with coronavirus disease-2019 (COVID-19)[83]. Some authors reported that one of the major risk factors associated with survival among kidney transplant patients infected with the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) is receipt of prednisolone (OR: 5.98; 95%CI: 1.65-21.60; $P$ < 0.01)[84].

BK (polyoma) virus infection is common during 6 mo after renal transplantation and may lead to BK virus associated nephropathy (BKVAN). There are case reports of BKVAN that resulted in native kidney failure in other types of SOT patients. A GC pulse for the treatment of acute allograft rejection has been reported in these patients before BKVAN[85]. Causality assessment needs more studies.

Regarding cytomegalovirus (CMV) infection, a retrospective study evaluated 71 SOT patients during the same time period; among them, 49 patients were tested for genotypic resistance CMV variants, while 22 were not because of no clinical suspicion for the resistance variants. This study compared the patients in the following three groups: group 1, patients with resistant CMV infections (defined as document of failure to reach at least 1 $\log_{10}$ decline in CMV DNA load after 2 wk of treatment with (val)ganciclovir, foscarnet, cidofovir, and at least 1 CMV resistant genotypic mutation); group 2, patients with refractory CMV infection (defined as documented failure to achieve 1 $\log_{10}$ or more decline in CMV DNA level after at least 2 wk of treatment with (val)ganciclovir); and group 3, no suspected CMV resistance and not tested for such. Results showed that patients in groups 1 and 2 were taking higher mean daily doses of prednisolone compared with patients in group 3 (10 mg a day or higher *vs* 5 mg daily); however, in the final model, daily GC dose was not a significant risk factor for resistant or refractory CMV infection[86]. An experimental study indicated that GCs activate the major immediate-early promoter (MIEP), which drives CMV gene expression. This GC effect is mediated *via* the GR pathway and leads to reactivation of latent CMV from primary monocytes. To investigate the clinical relevance of this experimental finding, the same researchers retrospectively analyzed data of liver transplant patients and found that taking prednisolone as baseline immunosuppression and/or methylprednisolone as augmented immunosuppression can trigger CMV reactivation in intermediate-risk patients (D+/R+) to the levels comparable with high-risk patients (D+/R-)[87].

One-year cumulative doses of 1830 mg or more of GCs has been associated with tuberculosis infection in patients with systemic lupus erythematosus (OR: 2.74; 95%CI: 1.26-5.98; $P = 0.011$)[88] that may be true for SOT patients as well.

Severe *Sterongyloides stercolaris* infection is associated with high morbidity and mortality among kidney transplant patients and is usually accompanied by gastrointestinal and respiratory symptoms. A multicenter cohort study consisting of 46 kidney transplant patients with severe *Sterongyloides stercolaris* infection and 92 matched control patients found that cumulative GC dose was an independent risk factor for severe *Sterongyloides stercolaris* infection (median [IQR] of doses of 73.32 [40.93-157.46] mg/kg in the case group *vs* 65.23 [32.05- 155.28] mg/kg in controls) (OR: 1.005; 95%CI: 1.001-1.009; $P = 0.008$)[89]. As seen, the calculated OR is approximately 1, which may not be of clinical importance despite statistical significance.

Although rare, visceral leishmaniasis may occur after SOT relating to general prevalence of this parasite in that geographic area. High-dose prednisolone within the preceding 6 mo has been associated with this infection in SOT patients[90].

### Bone disorders

GCs antagonize the effects of vitamin D, decrease intestinal absorption of calcium, inhibit secretion of growth hormone, inhibit bone formation (by inhibiting osteoblasts differentiation and increasing their apoptosis), increase bone resorption (by enhancing osteoclasts formation), and finally lead to osteoporosis and an increased risk of fractures, especially in trabecular bones[6]. Chronic kidney disease-mineral bone disorder (CKD-MBD) after kidney transplantation is a mix of pre-existing disorders and new alterations. The final results are abnormal mineral metabolism (hypercalcemia and hypophosphatemia) and bone changes (high or, more commonly, low bone turnover disease), with consequences of decreased bone mineral density and increased risk of bone fractures[91]. Although not completely clarified, several factors play roles in post-transplant bone disorders, such as immunosuppressive treatment, especially corticosteroids, persistently high levels of PTH, vitamin D deficiency, and hypophosphatemia. Transplant recipients are at a four-fold higher risk of fracture compared with the general population. One of the most relevant risk factors is high-dose or prolonged GC therapy[91,92]. Kidney transplant recipients with early steroid withdrawal have shown higher bone mineral density in the lumbar spine and femoral neck and less osteopenia[93]. On the other hand, one study followed 36 renal transplant patients who continued low daily dose of 5 mg prednisolone from day 42 after transplantation onward for 1 year. None of these patients received any treatment for bone disorders. In addition to bone mass densitometry, novel bone quality parameters, including trabecular bone score and bone material strength index, were evaluated for these patients. Findings indicated a small decrease in bone mineral density in the femoral neck at 3 mo and in the lumbar spine at 12 mo after transplantation, while, no changes in trabecular bone score and bone material strength index were found, showing limited effects of low daily doses of GCs on bone[94]. Osteonecrosis of the hip is another side effect of corticosteroids in SOT patients[95]. Although some studies showed that the cumulative dose of methylprednisolone/prednisolone after kidney

transplantation has been a risk factor for avascular osteonecrosis[96,97], a meta-analysis found little correlation between cumulative doses and duration of administration of methylprednisolone/prednisolone and avascular osteonecrosis of the femoral head[98].

### Growth in pediatric transplant recipients

By inducing abnormal growth hormone secretion and response, GCs impair stature growth in children and prepubertal adolescence[6]. In contrast, GR in hepatocytes is essential for postnatal body growth by mediating the growth hormone signaling in mice[99]. New animal data also suggests that GCs decrease longitudinal bone growth by upregulation of fibroblast growth factor-23 (FGF23) and its receptor (FGF23R3) expression[100]. GC-induced growth retardation in pediatric transplant patients encouraged SOT teams to apply steroid minimization protocols in prepubertal kidney transplant patients with better bone health, growth outcome, and comparable allograft rejection rates[14,101,102].

### Metabolic complications and cardiovascular risks

Obesity and metabolic syndrome with the three components of hyperglycemia, hyperlipidemia, and hypertension are common long-term side effects of GCs; these adverse effects increase atherogenesis and the risk of cardiovascular events[6]. Adipocyte GR deficiency promotes adipose tissue expandability and improves the metabolic profile during GC exposure[103]. In contrast, GR in cardiomyocytes is essential in cardio protection; deletion of cardiomyocyte GR increases mortality due to the development of spontaneous cardiac pathology in both male and female mice [104]. The mechanism of GC-induced hyperglycemia is insulin resistance followed by increased hepatic gluconeogenesis[1]. PTDM is associated with higher risk of mortality and graft loss[105]. PTDM incidence in SOT patients varies from 10% to 74% depending on the country and ethnicity of the patients and diagnostic criteria[105-107]. There are several risk factors for PTDM, such as viral infections, underlying kidney diseases, and different immunosuppressive drugs, that can confound causality assessment between steroid dose and duration and PTDM in SOT patients[1]. A Malaysian study of 168 patients without diabetes before transplantation showed the PTDM incidence was 17% up to 1 year after renal transplantation. In that study, the daily prednisolone dose was not associated with the development of PTDM[107]. Another 4-year follow-up study on 400 kidney transplant patients without history of diabetes before transplantation (96 patients on steroid-free and 304 patients on 5 mg/day prednisolone in immunosuppressive regimen) indicated that taking 5 mg daily prednisolone was associated with a small but not statistically significant increase in HbA1c and significantly higher risk of prediabetes (relative risk [RR]: 1.789; 95%CI: 1.007-3.040; $P$ = 0.026) but not PTDM compared with a steroid withdrawal regimen. Although other components of the immunosuppressive regimen, such as the type of CNI (tacrolimus *vs* cyclosporine A), can affect PTDM risk, as in the multivariate analysis of Tillmann *et al*'s[108] study showed higher risk of prediabetes with long-term low-dose steroid, independent of the higher risk of tacrolimus inducing PTDM compared with cyclosporine. On the other hand, a meta-analysis on more than 22000 kidney transplant patients found that early steroid withdrawal during 1 wk after transplantation is associated with less PTDM risk (RR: 0.91; 95%CI: 0.37-0.97; $P$ = 0.04) [10]. Association between new-onset hyperglycemia and GC-containing maintenance immunosuppression among liver transplant recipients is controversial[109,110]. While a Japanese retrospective analysis on 461 adult liver transplant recipients from living donors did not find any association between taking GC and PTDM[109], a randomized clinical trial on live donor liver transplant patients reported significantly higher incidences of PTDM among patients taking steroids *vs* steroid-free group at 3 mo and 6 mo follow-ups[110]. One confounding factor in data interpretation is the use of different diagnostic criteria for PTDM in different studies. For example, in the Toshima *et al*[111] study, fasting plasma glucose of 110 mg/dL or higher was used as a cut-off for PTDM definition[109], while based on the standard criteria of the American Diabetes Association, s plasma glucose level of 126 mg/dL or higher is defined as diabetes.

Hyperlipidemia is another known metabolic side effect of GCs. Increased total cholesterol, very low-density lipoprotein (VLDL) cholesterol, and triglyceride levels and decreased high-density lipoprotein (HDL)-cholesterol concentration have been reported with GCs, depending on the dose and duration of their administration[6]; however, a large United States cohort study showed beneficial effect of GCs on increasing HDL cholesterol among patients older than 65 years of age[112]. Wide ranges of mechanisms have been supposed for GC effects on the lipid profile,

including increased activity of acetyl-Coenzyme A carboxylase and free fatty acids synthetase and enhanced hepatic synthesis of VLDL, inhibition of lipoprotein lipase, alteration in the insulin signaling pathway, and possible inhibition of the activity of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG-CoA) reductase[6]. The latter mechanism can theoretically have positive effects on the lipid profile, which may explain some controversies regarding GC-induced lipid changes in the literature. Regarding organ transplant patients, a study on liver transplant recipients showed that taking maintenance GCs was an independent factor associated with hyperlipidemia but not with the two other components of metabolic syndrome (hyperglycemia and hypertension) in this patient population[109]. In contrast, another study that compared steroid-free *vs* steroid-taking immunosuppressive regimens in living donor liver transplant recipients found significantly higher incidences of all components of metabolic syndrome, including new-onset hyperglycemia, new-onset hypertension, and post-transplant hypertriglyceridemia among the steroid-taking group[110].

Although the effect of steroid withdrawal on hypertension after transplantation is controversial, a study on pediatric liver transplant patients that followed the patients with ambulatory blood pressure monitoring found that blood pressure improved, especially nocturnal hypertension, and the circadian rhythm of blood pressure was restored after GC discontinuation in these patients[113]. A Saudi study on adult kidney transplant patients found that patients on steroid sparing regimens had significantly lower weight gain and a non-statistically significant improvement in blood pressure and lipid control[114]. Different mechanisms have been reported for GC-induced arterial hypertension, including salt and water retention by activating renal mineralocorticoid receptor (MR) and regulating vascular activity by activating GR in endothelial and vascular smooth muscle cells. Interestingly, GR in vascular endothelial cells is required for dexamethasone-induced hypertension[115], while loss of endothelial GR increases hemodynamic instability, inflammation, and mortality in sepsis, and GR deficiency in endothelial cells prevents the therapeutic protection by dexamethasone after LPS treatment[116,117]. Hypertension is more common among patients taking daily doses of more than 20 mg prednisolone. Metabolic changes and hypertension increase atherogenesis and risk of cardiovascular events in patients taking long-term GC[6].

### Neuropsychiatric side effects

Most immunosuppressive drugs, especially CNIs, glucocorticoids and mTOR inhibitors, can induce neurologic side effects. Sometimes the assessment of causality is hard and all drugs work together to manifest the side effect(s). Glucocorticoids easily pass the blood-brain barrier and reach all brain cells, which results in HPA axis suppression and neuropsychiatric and neurodegenerative side effects. Prolonged exposure to glucocorticoids in SOT patients and high GC doses and concentrations ( *e.g.*, during treatment of acute rejection) increase the risk of neuropsychiatric side effects because of structural remodeling in neurons, synoptic loss, and maladaptive alterations in glial function[118]. GCs cause different neurologic side effects, such as headache, tremor, seizure, stroke, and pseudotumor cerebri. GC-induced psychiatric adverse effects vary from minor mood changes and confusion, sleep disorders, anxiety to severe psychotic features[6,118].

### Muscular side effects

GCs have catabolic effects on muscles, leading to muscular atrophy, cramping and progressive symmetrical muscle deficit. They can induce acute or chronic myopathy. Tendon rupture is a rare side effect of GCs[6]. High doses of GCs cause muscular atrophy *via* activating GR in the muscle[119].

### Adrenal insufficiency

Suppression of the activity of the HPA axis and the subsequent adrenal insufficiency are well-known side effects of GCs. Adrenal insufficiency may be potentially life-threatening because of the risk of acute adrenal crisis. A study on renal transplant patients treated with oral prednisolone at daily doses of 5 to 7.5 mg for 6 mo or more found insufficient adrenal response to Synacthen in about 43% of the patients, which shows a high prevalence of adrenal insufficiency due to long-term low dose GCs in these patients[120].

In addition to a decrease in endogenous GC production, exogenous GC, such as prednisolone, may also enhance the activity of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), the enzyme that is responsible for regeneration of cortisol from the inactive metabolite, cortisone. A cohort study investigated this hypothesis in

prednisolone-treated kidney transplant patients compared with healthy controls. The median daily dose of prednisolone in these patients was 10 mg (IQR of 7.5-10 mg). The 24-h urinary cortisol, cortisone, tetrahydrocorisol (THF), allotetrahydrocortisol (alloTHF), and tetrahydrocortisone (THE) were measured. The 24-h urinary excretion of cortisol and its metabolites were used as measures of endogenous glucocorticoid production, while (THF + alloTHF)/THE and cortisol/cortisone ratios were used as reflectors of 11β-HSD1 activity. Findings revealed that urinary cortisol and metabolite excretion were significantly lower (indicating reduced endogenous cortisol synthesis), while (THF + alloTHF)/THE and cortisol/cortisone ratios were significantly higher (indicating increased 11β-HSD1 activity) in kidney transplant recipients compared with healthy controls. Daily doses of prednisolone had a significant inverse association with reduced endogenous cortisol synthesis and significant and a positive association with markers of 11β-HSD1 activity. Such changes in endogenous GC production and regeneration were associated with increased risk of mortality in kidney transplant patients even after adjustment for confounders such as patients' age, gender, estimated glomerular filtration rate, C-reactive protein, body surface area, and daily doses of prednisolone[121]. Some researchers found significant associations between HPA suppression and higher prevalence of metabolic syndrome and its individual components (central obesity, dyslipidemia, hypertension, and hyperglycemia) in kidney transplant patients taking prednisolone[122].

### Gastrointestinal side effects

Gastrointestinal side effects of GCs include peptic ulcers, upper gastrointestinal bleeding, pancreatitis, diverticular perforation, and colonic malakoplakia (a chronic granulomatous disease)[123].

Immunosuppressive therapy after SOT may change gut microbiota and be associated with increased rates of overall and infection-related mortality, rates of all infections, including nosocomial infections, duration of infections, infections complications, rejection rates and graft loss. Some studies tried to differentiate the effect of different types of immunosuppressive drugs that are used in combination in SOT patients. Regarding corticosteroids, a study on liver-transplanted mice showed that prednisolone administration reduced the concentration of *Bacteroidetes* while increasing the concentration of *Firmicutes* in the feces. In that study, prednisolone, in combination with mycophenolate and tacrolimus, increased *Escherichia coli* colonization. Serial testing of fecal samples of kidney transplant recipients revealed that compared to those remaining on maintenance corticosteroid, patients with early GC withdrawal had numerically but not statistically significant lower *Clostridiales* and *Erysipelotrichales*[124].

### Dermatologic effects

Cushingoid appearance, facial erythrosis, skin thinning, rosacea, acne that may rarely progress to nodulocystic transformation, impaired wound healing, purpura after minor trauma, hirsutism, and striae rubrae are dermatologic side effects of GCs that are usually dose- and treatment duration-dependent[6].

### Other complications

GCs increase the risk of thrombosis due to endothelial damage and inducing hypercoaguable state and stasis[6]. Posterior subcapsular cataract and glaucoma are dose-related ophthalmologic side effects of GCs[6]. Hernia occurrence is common after liver transplantation and attributed to several factors, one of them being taking steroids [125].

A retrospective analysis on surgery complications of 382 patients with metabolic and bariatric surgery and prior history of SOT showed that while taking GCs are associated with a two-fold increase in overall morbidity, it did not contribute to morbidities related to bariatric surgery[126].

Pretransplant administration of GCs in patients with idiopathic pulmonary fibrosis may decrease graft survival after lung transplantation compared with GC-free patients [127]. Although concerns have arisen regarding airway anastomotic complications after lung transplantation in patients who were treated with GCs before transplantation, a retrospective study on 66 double-lung transplant recipients (40 used steroids prior to transplantation) found that early development of airway complications was not significantly higher in patients who took steroids before lung transplantation. In addition, in preoperative steroid users, the dose of steroid was not associated with the rate of post-transplant airway complications[128].

## DRUG-DRUG INTERACTIONS

GCs are primarily metabolized by the CYP450 3A4 isoenzyme and are also substrates for the energy-dependent efflux pump P-glycoprotein[123,129]. GC metabolism may or may not be affected by CYP450 3A4 inhibitors, such as macrolide antibiotics, azole antifungal medications, and protease inhibitors. Studies have shown decreased clearance of methylprednisolone, but not prednisolone, with co-administration of CYP3A4 inhibitors[130,131]. CYP450 3A4 inducers (rifampin, carbamazepine, phenobarbital, phenytoin) can decrease GC's serum levels[129]. GCs can induce CYP450 3A4/5 isoenzymes[129], and therefore increase the metabolism of CNIs (cyclosporine and tacrolimus) as the substrates of CYP450 3A4/5[132]. Clinical studies have shown a significant increase in dose-adjusted tacrolimus blood levels in patients on GC withdrawal regimens compared with patients taking GC-containing maintenance immunosuppression[132]. Interactions between GCs and tacrolimus are more seen in patients carrying the CYP3A5*1 allele[133]. GCs significantly contribute to inter-individual variability of apparent clearance of oral tacrolimus[134]. On the other hand, some studies reported that cyclosporine decreases prednisolone clearance by 25%-30% in kidney transplant patients[135], while others found no difference in dose-adjusted exposure of prednisolone when co-administered with cyclosporine or tacrolimus[136].

### *Possible need for therapeutic drug monitoring*

Prednisolone is a standard component of most immunosuppressive protocols after SOT. Therapeutic drug level monitoring is not usually done for GCs. A study evaluated the pharmacokinetic characteristics of prednisolone, prednisone, and also cortisol and cortisone profiles, after treatment with prednisolone in adult kidney transplant recipients in the early 8-wk post-transplant period. Blood samples were obtained pre-dose and during a 24-h dose interval. Findings showed that renal transplant recipients experienced a relatively high prednisolone exposure, in parallel with strong suppression of endogenous cortisol profile as confirmed by a low evening-to-morning ratio of cortisol. A significant negative correlation ($r$ = -0.83) between prednisolone area under the curve (AUC) 0-24 and morning cortisol concentrations was seen. AUC 0-24 of prednisolone and cortisol varied by three-fold and eighteen-fold, respectively, among patients. These results reveal large inter-individual variability in both prednisolone exposure and suppression of endogenous cortisol that signify a possible need for therapeutic drug monitoring of GCs[137].

## CONCLUSION

GCs have been the mainstay for SOT for decades due to GC's potent anti-inflammatory and immunosuppressive effects on the innate immunity and the significant tissue protective effects of GR on liver, kidney, and heart. In contrast, many of the side effects of GCs are on the non-target organs/tissues, such as bone, neuromuscular, adipose tissue, GI tract, and skin. Thus, specific delivery of GCs, *via* nanoparticles or transporter-mediated prodrugs, to the target organs of liver, kidney, and/or heart will enhance the efficacy and decrease the side effects of GCs in SOT. GCs' side effects are generally associated with long-term use of high doses. It is noteworthy that most GCs activate both GR and MR. Recent studies indicate that some of the side effects of GCs on the liver, heart, kidney, and adipose tissues may be due to the activation of MR by GCs[138-141]. Therefore, GCs with higher selectivity for GR over MR, such as dexamethasone and budesonide, may have fewer side effects in SOT patients[23,142]. Additionally, GCs' metabolic actions can be modulated by AMP-activated protein kinase (AMPK), a master regulator of energy metabolism. Activation of AMPK increased the phosphorylation of GR at serine-211 and reversed GC-induced hepatic steatosis and suppressed GC-mediated stimulation of glucose production in rats[143]. Interestingly, impaired AMPK activity was associated with steatotic graft injury in patients with living donor liver transplantation[144]. Thus, whether AMPK activators can ameliorate the metabolic side effects of GCs in SOT warrants investigation. In conclusion, approaches that enhance GC's selectivity for GR, increase target tissue-specific delivery of GCs, and ameliorating the metabolic side effects of GCs will increase the efficacy and decrease the side effects of GCs in SOT.

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*MINIREVIEWS*

# Exercise training in heart transplantation

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## Abstract

Heart transplantation remains the gold standard in the treatment of end-stage heart failure (HF). Heart transplantation patients present lower exercise capacity due to cardiovascular and musculoskeletal alterations leading thus to poor quality of life and reduction in the ability of daily self-service. Impaired vascular function and diastolic dysfunction cause lower cardiac output while decreased skeletal muscle oxidative fibers, enzymes and capillarity cause arteriovenous oxygen difference, leading thus to decreased peak oxygen uptake in heart transplant recipients. Exercise training improves exercise capacity, cardiac and vascular endothelial function in heart transplant recipients. Pre-rehabilitation regular aerobic or combined exercise is beneficial for patients with end-stage HF awaiting heart transplantation in order to maintain a higher fitness level and reduce complications afterwards like intensive care unit acquired weakness or cardiac cachexia. All hospitalized patients after heart transplantation should be referred to early mobilization of skeletal muscles through kinesiotherapy of the upper and lower limbs and respiratory physiotherapy in order to prevent infections of the respiratory system prior to hospital discharge. Moreover, all heart transplant recipients after hospital discharge who have not already participated in an early cardiac rehabilitation program should be referred to a rehabilitation center by their health care provider. Although high intensity interval training seems to have more benefits than moderate intensity continuous training, especially in stable transplant patients, individualized training based on the abilities and needs of each patient still remains the most appropriate approach. Cardiac rehabilitation appears to be safe in heart transplant patients. However, long-term follow-up data is incomplete and, therefore, further high quality and adequately-powered studies are needed to demonstrate the long-term benefits of exercise training in this population.

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**Core Tip:** Heart transplantation is the gold standard treatment of end-stage heart failure (HF). Heart transplantation patients present lower exercise capacity due to cardiac, vascular and skeletal muscle abnormalities. Exercise training improves exercise capacity, cardiac and vascular endothelial function in heart transplant recipients. Pre-rehabilitation regular aerobic or combined exercise is beneficial for patients with end-stage HF awaiting heart transplantation. All heart transplant recipients either hospitalized or after hospital discharge should be referred to a cardiac rehabilitation program. Individualized training still remains the most applicable approach despite the fact that high intensity interval training seems to have more benefits than moderate intensity continuous training.

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## INTRODUCTION

Heart transplantation is the gold standard treatment of end-stage heart failure (HF), although important advances in the field of mechanical circulatory support and technology have been noticed during the last 30 years. Since the first human-to-human heart transplant operation by a cardiac surgeon called Christiaan Neethling Barnard back in 1967, many adult heart transplants have been performed worldwide, especially in patients with end-stage HF. A continuous improvement in morbidity and mortality of transplanted recipients has been noticed despite the fact that they may be older with higher risk[1]. Heart transplantation remains, however, a difficult operation with significant short-term and long-term post-surgery outcomes including graft-related complications such as early graft dysfunction, acute allograft rejection and cardiac allograft vasculopathy, and non-graft-related complications such as infections, acute and chronic renal injury and malignancies[2]. All these complications usually lead to higher morbidity and mortality[3].

Despite the fact that donor and recipient age and comorbidity are being increased over the last years, heart transplantation survival rates seem to have progressively improved. It is estimated that, worldwide, almost 5000 transplants are being performed each year. The median survival for adult heart transplant recipients varies and ranges from 10.7 to 12.2 years approximately, with 82% one-year survival and 69% at five-years[1]. Survival for women is slightly better compared to men[1]. The highest incidence of mortality most often occurs within the first 6 mo after the transplant[1]. After 12 mo, the mortality rate decreases to 3.4% per year[1].

Heart transplantation patients present lower exercise capacity due to cardiac, vascular and skeletal muscle abnormalities leading thus to poor quality of life and reduction in the ability of daily self-service[4]. Impaired vascular function and diastolic dysfunction cause lower cardiac output (CO) while decreased skeletal muscle oxidative fibers, enzymes and capillarity cause arteriovenous oxygen difference, leading thus to decreased peak oxygen uptake ($VO_2$) in heart transplant recipients which is lower at about 40% to 50% than age, sex, and activity matched healthy controls[4-6]. Exercise has been proven to improve exercise capacity and vascular endothelial function in patients with chronic HF and thus in patients with vascular endothelial impairment[7-10]. Exercise also improves aerobic capacity *via* the suppression of the oxidative stress, the increase of the bioavailability of nitric oxide (NO) and the induction of vasodilation[11,12].

The aim of this narrative review was to demonstrate the existing knowledge on the training protocols and highlight the benefits of exercise training in patients after heart transplantation.

## CARDIOVASCULAR AND MUSCULOSKELETAL ALTERATIONS IN HEART TRANSPLANT RECIPIENTS

### *Cardiovascular alterations*

One possible complication after heart transplantation is that the donor heart is surgically denervated and loses efferent and afferent autonomic connections. As a result, the regulation and function of the cardiovascular system is being affected and its reflex reactions are reduced[13,14] (Figure 1). Hypertension and peripheral vaso-constriction are usually the first signs in heart transplant recipients[14]. A possible explanation could be the permanent denervation of low-pressure cardiopulmonary baroreceptors in the heart and the permanent enhancement of sympathetic vasomotion due to lack of afferent impulses[15,16]. Left ventricular (LV) mass and wall thickness is increased, either within the first 30 d after heart transplantation or secondary as a consequence by immunosuppressive agents which trigger chronic tachycardia, hypertension and multiple rejection episodes[17,18].

Despite the fact that the atrial remnant of the heart transplant recipients is innervated, the suture line causes higher intrinsic rate of the atrium and reduced heart rate variability[19]. Moreover, although some cardiac functions and mechanisms such as Frank-Starling are usually not affected in transplant patients, most heart responses to haemodynamic changes and heart rate variations are impaired[19]. A study by Nygaard *et al*[20], has shown that patients after heart transplantation present altered cardiovascular responses than healthy controls. Most specifically, their blood pressure and total peripheral resistance is higher at supine rest, attenuated during orthostatic challenge and preserved during isometric exercise. Cardiac denervation mediated chronotropic and allograft diastolic dysfunction after heart transplantation results in lower peak exercise CO[21,22]. Peak exercise CO in heart transplant recipients is 30% to 40% lower than age-matched healthy controls[21-23]. Lower CO leads to a higher resting heart rate and slower increase during exercise[24]. However, physical activity status and cardiac allograft reinnervation are important factors of the variety of heart rate impairment[4]. Moreover, diuretics leading to reduced diastolic filling might contribute to lower CO responses[20].

Heart transplant recipients present 20% lower peak exercise end-diastolic volume and stroke volume than healthy people[21,22]. This is another significant pathophysiological alteration. The impaired LV relaxation and the increased LV stiffness could be a possible explanation of this alteration[4,21]. In addition, previous studies have shown the significantly increased pulmonary capillary wedge pressure (PCWP)/end-diastolic volume index ratio during maximal exercise in these patients compared to age-matched sedentary normal controls[21]. This elevated peak exercise mean PCWP results in dysfunction in LV strain and peak systolic velocity of the mitral valve, despite the preserved LV ejection fraction[25]. A possible potential pathway that causes LV diastolic dysfunction may be the decreased adrenergic tone associated with complications after the heart transplantation including denervation of the allograft, injury, myocardial ischemia due to vasculopathy or immunosuppression therapy[4,23].

Endothelial dysfunction is a major cause of disability and lower life expectancy in heart transplant recipients which increases exercise systemic vascular resistance, leading thus to less $O_2$ provided to skeletal muscles[1,4] (Figure 1). As a result, peak $VO_2$ is significantly reduced[1,4]. Several studies have shown that their peak exercise systemic vascular resistance is approximately 50% higher than healthy controls because of the impaired endothelial-dependent vasodilation of peripheral conduit arteries and resistance arterioles[21,22,26,27]. A significant observation is that the severity of the impairment of endothelial function appears to be related to the etiology of HF[28,29]. Most specifically, endothelial function is usually improved in similar levels to healthy age-matched controls in heart transplant recipients of non-ischemic cardiomyopathy compared to ischemic cardiomyopathy due to slower pulmonary $VO_2$ kinetics during ischemia[26,29].

### *Musculoskeletal alterations*

The last significant impairment after heart transplantation concerns abnormalities in skeletal muscles leading in impaired peak $VO_2$ (Figure 1). Heart transplant recipients present lower body and leg lean mass, as well as muscle strength, compared to healthy, sedentary age-matched controls[30].

Before heart transplantation, reduced oxidative muscle fibers (Type I), capillary density, mitochondrial volume and oxidative enzyme capacity are usual abnormalities of the skeletal muscles, directly associated with the syndrome of HF and worsen

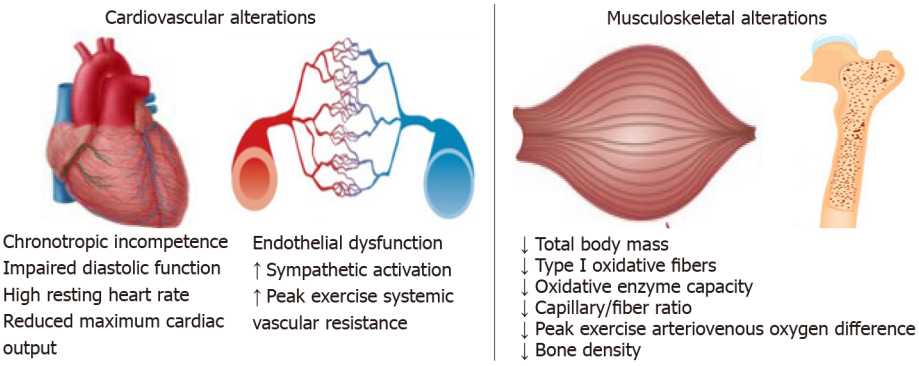


**Figure 1 Cardiovascular and musculoskeletal alterations in recipients after heart transplantation.**

according to its severity[30-32]. More precisely, a reduction in aerobic, Type I and an increase in anaerobic, glycolytic fibers (Type II) is observed in HF patients[33]. Their diaphragm is also metabolically affected with significant atrophy[33-35]. Moreover, reduced levels of enzymes and proteins such as citrate synthase, creatine kinase (CK), MM-CK and lactate dehydrogenase (LDH) prove a major contribution of altered skeletal muscle metabolism to exercise intolerance[36]. As far as muscle metabolism is concerned, electrolyte and phosphocreatine (PCr) disorders, metabolic acidosis and delayed PCr recovery after exercise are common characteristics of patients with HF[33, 34]. Finally, muscle atrophy is caused by a decrease of anabolic mechanisms, increased protein degradation or sometimes both of them[33]. Enhanced protein degradation including impaired function of enzymes ubiquitin-ligases MuRF1 and Atrogin-1, impaired growth factor signaling and protein synthesis including decreased levels of circulating total testosterone, dehydroepiandrosterone and insulin like growth factor-1 and skeletal muscle inflammation including inflammatory mediators released into the circulation such as interleukin 1 (IL-1) and IL-6 and tumor necrosis factor α are the major mechanisms that promote muscle atrophy and skeletal muscle alterations[33,37, 38].

Size of muscle fiber and mitochondrial volume density increases after heart transplantation reaching almost equal levels to healthy age-matched individuals[30,39]. However, reductions in capillary density persist[30,32,39]. Moreover, endurance in exercise performance seems to be impaired by immunosuppression therapy including cyclosporine and corticosteroids[40,41]. A consequence of all these musculoskeletal abnormalities is a decrease in bone density and oxygen utilization, and possible osteoporotic fractures[4,38,42,43].

## THE EFFECT OF EXERCISE TRAINING IN THE CARDIOMYOCYTES, VASCULAR ENDOTHELIAL FUNCTION AND SKELETAL MUSCLES

Exercise training has a beneficial effect in the cardiomyocytes and the function of the vascular endothelial system. As far as the cardiomyocytes are concerned, exercise results in a beneficial form of cardiac remodeling that involves cardiomyocyte growth and proliferation[44,45]. Regular physical exercise has been proven to improve LV contractility, calcium function in the heart and cardiomyocytes size[46,47]. Isometric or static exercises result in mild concentric hypertrophy and usually a normal left atrium while endurance training LV hypertrophy, right ventricular (RV) dilation, and biatrial enlargement[45,48]. In the first case, the increase in cardiac wall thickness is caused by the parallel addition of sarcomeres within cardiomyocytes while in the second case by the addition of cardiomyocyte sarcomeres in series[45,48]. Cardiomyocyte hypertrophy is not the only process in exercise-induced cardiac remodeling. The increased levels of circulating endothelial cells (CECs) and endothelial progenitor cells (EPCs) after acute and long-term exercise seem to play a crucial role in augmentation of vascular density and cardiac repair[49-51].

Exercise training can also contribute to the proliferation of cardiomyocytes, a significant process of cardiomyogenesis[52]. Metabolically, exercise has beneficial effect on LV contractility and increases catabolism of fatty acids and lactate, and therefore of ATP production[53-55]. Circulating metabolites including palmitoleate (C16:1n7), G protein-coupled receptors, Akt, and nuclear receptors are important

regulators of exercise-induced cardiac growth[53,56,57].

Regarding the vascular endothelium, exercise has been proven to suppress the generation of free radicals and oxidative stress and increase the bioavailability of NO [11,12]. As far as the potential mechanisms are concerned, shear stress is a procedure that activates eNOs, increases the concentration of NO and induces vasodilation[11,12, 58,59]. Exercise increases shear stress, and thus, improves aerobic capacity[11,12,58, 59]. Moreover, exercise induces the hypoxic stimuli, as observed by alterations in microcirculation indexes during exercise sessions[59,60]. All these pathophysiological mechanisms may relate to up-regulation of transcriptional factors, including vascular endothelial growth factor (VEGF), matrix metalloproteinases and stromal cell-derived factor 1, and lead to angiogenesis during exercise in healthy controls and patients with comorbidities[60-63]. In healthy subjects, exercise improves peripheral vascular function through the reduction in blood pressure, the endothelin-1 levels and the improvement in vasodilation[64,65].

EPCs and CECs have been shown to restore the dysfunctional or injured endothelium and protect it, regulate vascular homeostasis and promote angiogenesis. Therefore, reflecting the condition of the vascular endothelial function[12,66]. EPCs level is a predicting factor of the occurrence of a cardiovascular event and cardiovascular mortality[67]. Several studies have shown that in both healthy people and population with comorbidities, exercise training increases the number and the function of EPCs[68,69]. We extended previous findings by showing that a single bout of maximal exercise, as well as many bouts organized as an exercise training program, stimulates the mobilization of EPCs and CECs from the bone marrow in patients with chronic HF[8,10]. This beneficial effect of exercise seems to be similar in chronic HF patients of different severity[9].

Physical exercise has the beneficial effect to modify metabolic potential, morphology, and physiology of skeletal muscle[70]. Exercise is a triggering factor for the metabolic and structural skeletal muscle remodeling[70,71]. This remodeling has positive effect in angiogenesis and fatigue[70,71]. Resistance exercise increases muscle mass and strength while endurance training affects mitochondrial function and oxidation[70,72]. Regular exercise mediates molecular and metabolic pathways that are activated by muscle contraction. Intracellular sensors trigger intracellular signaling cascades including several transcription factors[70,72]. These factors are responsible for the remodeling of skeletal muscle *via* upregulation of mitochondrial metabolism and fiber-type transformation[70,72]. Finally, other potential mechanisms for muscle remodeling such as redox signaling seem to be involved in metabolic adaptation to exercise[70,73,74].

## CARDIAC REHABILITATION IN HEART TRANSPLANTATION

Cardiac rehabilitation programs are being implemented all over the world for patients after major cardiovascular disease. A cardiac rehabilitation program is characterized by an interdisciplinary approach and consists of different specialties and health care professionals including cardiologists, physiotherapists, nurses, dieticians, pharmacists, psychologists, physiologists, other specialties such as internists, neurologists, diabetologists and cardiac surgeons, general practitioners and social services experts[75]. One of the most important roles is the role of the program director. A program director could be of any specialty with good organizing and management skills.

Cardiac rehabilitation is a type of secondary prevention in patients with cardiovascular disease. The aim of rehabilitation is to reduce anxiety and depression and instill confidence so that to change lifestyle of patients aimed at preventing further disease[76]. Each patient could benefit from either an in-patient or out-patient cardiac rehabilitation program. The core principles of a cardiac rehabilitation program are patients' medical evaluation, counselling for exercise training and diet, continuous assessment of weight, blood pressure, lipidemic profile, and psychosocial support[75]. The expected outcomes of a cardiac rehabilitation program are improvement of clinical stability and symptom control of patients, reduce of cardiovascular risk, better compliance to medical therapy, and improved quality of life, social integration and prognosis[75].

Another important parameter of a successful cardiac rehabilitation program is the equipment. A cardiac rehabilitation center should provide the appropriate equipment for the assessment of patient's clinical status, LV function, arrhythmias, functional capacity, psychosocial status and equipment for conducting an exercise training program. These include stethoscopes and sphygmomanometers, electrocardiogram,

echocardiography, echocardiography, graded exercise testing on treadmills or cycles, cardiopulmonary exercise testing (CEPT), six-minute walk test (6-MWT), questionnaires about quality of life and psychological status and exercise equipment such as treadmills, cycle ergometers and weight training equipment[75]. Moreover, emergency equipment for complications during exercise is always mandatory.

### Phases of cardiac rehabilitation

Rehabilitation is a complex process, individualized for each patient. Three main phases of rehabilitation can be differentiated according to the updated guidelines about preventive cardiology and rehabilitation of the ESC[75] (Figure 2): (1) Phase 1 is the phase of the in-hospital rehabilitation including early interventions and mobilization immediately after hospital admission[75]; (2) Phase 2 is probably the most critical part in patients with heart transplantation. It is being implemented just after the hospital discharge. It promotes and delivers in-patient and out-patient rehabilitative services for clinical stabilization[75]. In-patient cardiac rehabilitation is being performed to unstable patients in order to stabilize them before the longer-term cardiac rehabilitation program after hospital discharge. Clinically unstable patients after an acute event, with advanced HF under continuous medication or with implantable devices, heart transplant recipients and patients unable to attend a formal outpatient rehabilitation program for any personal reasons are considered as high risk [75]. On the other hand, early out-patient cardiac rehabilitation is being used for independent patients early after hospital discharge, usually within 3 to 6 mo after a cardiovascular event. The mean duration is 8 to 12 wk, most times continuing for one year after the event[75]. Finally, a home-based program is another form of rehabilitation assessed and supported by the rehabilitation group at patient's home. It may include regular visits to the rehabilitation center and contacts with the team. The activities of a home-based program are similar to those of an early outpatient cardiac rehabilitation program[75]; and (3) Phase 3 is the long-term out-patient type of cardiac rehabilitation. The main aim of phase 3 rehabilitation is to promote long-term exercise and rehabilitation in patients out of hospital and the community. Moreover, it usually results in maintenance of the fitness level and better outcomes in heart transplant recipients[75].

Another important phase of rehabilitation is the "pre-rehabilitation" stage. Heart transplant recipients are doing regular aerobic or combined exercise before transplantation in order to maintain a higher fitness level and reduce complications afterwards like intensive care unit (ICU) acquired weakness or cardiac cachexia.

### Significant components of a cardiac rehabilitation program for heart transplant patients

The initial step of the enrollment of a heart transplant recipient in a cardiac rehabilitation program is the risk assessment of the patient by the rehabilitation team. The risk assessment consists of clinical examination including sings such as examination of the wound healing or symptoms of the transplant's rejection, imaging techniques such as chest X ray for infection, pleural effusion or diaphragm paralysis and echocardiography for RV and LV function or pericardial effusion[75]. Moreover, tests for exercise capacity including CPET 30 d after transplantation or bicycle ergometer and modified Bruce protocols and Naughton protocols on treadmill are recommended[75]. Patient education on the risk of acute rejection is also a significant variable of a rehabilitation program. Patients should be instructed to practice self-monitoring during their rehabilitation process. In the case of transplant rejection, usually presented with significant reduce in blood pressure, unexpected variations of heart rate, fever or fatigue, exercise training should be immediately stopped and appropriate interventions are needed[75]. As far as health care professionals are concerned, they need to be aware of all aspects of this condition. For example, physicians should have full knowledge regarding the possible reasons for patients' limited exercise tolerance which could possibly be the immune-suppression therapy side effects, chronotropic incompetence or LV diastolic dysfunction[75]. They should also be aware of all nece-ssary actions to prevent complications which could harm patients and avoid in-fections, and therefore transplant rejection[75].

The second step of a cardiac rehabilitation program is physical activity counselling. Most specifically, heart transplant recipients enrolling a rehabilitation program should perform chronic dynamic and resistance exercises in order to prevent the side-effects of immunosuppressive therapy. In addition, exercise intensity should be increased slowly over time so that patients could reach a score of 12-14 in the Borg scale[75].

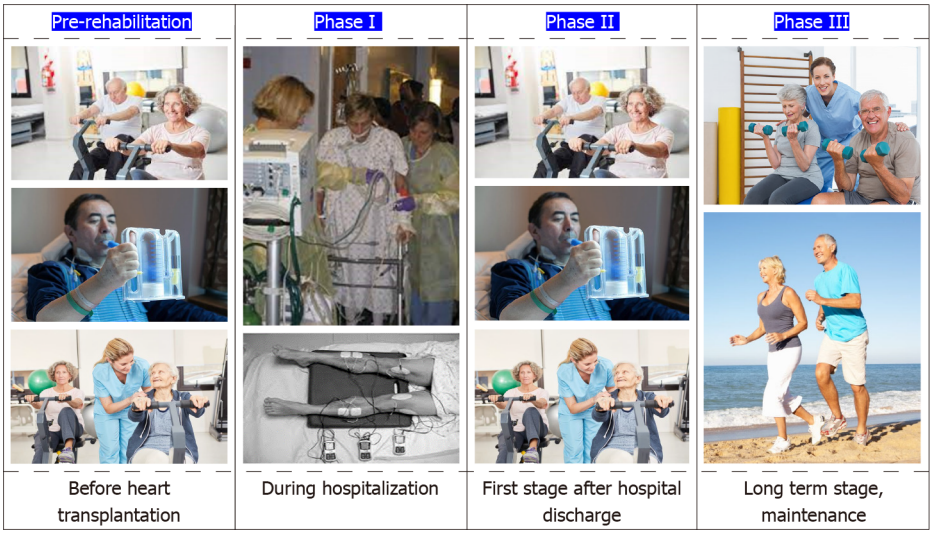


**Figure 2 Stages of a cardiac rehabilitation program.**

Exercise training is the most important aspect of a cardiac rehabilitation program. Early training program could be beneficial in the early and the long-term post-operative period. Early mobilization of heart transplant recipients could be achieved by implementing kinesiotherapy of the upper and lower limbs and prevention of respiratory infections could be achieved by performing respiratory physiotherapy[75]. Supervised exercise programs during the initial phase may be crucial to verify individual responses, tolerability and adaptability to exercise and clinical stability[75]. Aerobic exercise should be performed immediately after CPET for patients' prescription. Specifically, regular aerobic exercise may start in the second or third week after transplantation while resistance exercise should be added after 6 to 8 wk. However, exercise should be discontinued during corticosteroid bolus therapy for rejection[75]. A duration of at least 30-40 min/d of combined aerobic and resistance training at moderate level, slowly progressing warm-up, closed-chain resistive activities and cycling in each exercise training session should be achieved[75]. The intensity of aerobic exercise could be calculated according to peak $VO_2$ (< 50% or 10% below Ventilatory Anaerobic Threshold determined by CEPT) or peak work load (< 50%)[77]. Resistance training should consist of 2-3 sets with 10-12 repetitions per set at 40%-70% of the 1-repetition maximum (RM) test with > 1 min recovery between sets in order to achieve 5 sets of 10 repetitions at 70% of the 1-RM test[75]. Aerobic exercise could be either continuous moderate training (COMT) or high intensity interval training (HIIT) (Figure 3). COMT includes sessions consisted of aerobic exercise of 40 min with a continuous intensity of 55%-75% of peak $VO_2$[75,78]. HIIT may varies between different rehabilitation centers. It could either consist of 40-min exercise of high intensity (blocks of 4 min-2 min-30 s according to 80%, 85% and 90% of peak $VO_2$ with 1 or 2 min recovery)[79] or 16-min interval training (intervals of 4, 2 and 1-min duration at > 80% of peak $VO_2$ with a 2-min active rest period of approximately 60% of peak $VO_2$)[78]. Another very common HIIT protocol consists of 4 min × 4 min exercise bouts at 85%-95% of maximum heart rate, with 3 min recovery between them corresponding to 11-13 on the Borg scale[80]. Duration between COMT and HIIT sessions is similar and a 10-min pre-training warm up above 50% of peak $VO_2$, as well as a 10-min post-training stretching and exercises are included in both protocols. HIIT is suggested for hemodynamic stable heart transplant recipients with beneficial effects for them[75,78-80].

Except for exercise training, there are other important parameters which contribute to the success level of a cardiac rehabilitation program. Patients should be guided by expert nutritionists in order to maintain a balanced diet without sudden weight gain that could increase the risk of cardiac allograft vasculopathy or other classical cardiovascular risk factors[75] and avoid food that could lead to infection such as raw meat or seafood, un-pasteurized milk or cheese and raw eggs. A healthy lifestyle should be adopted by patients in their daily program. Monitoring of blood pressure, lower sodium intake, avoidance of hyperlipidemia and tobacco smoking, and adherence to the suggested medication would increase the beneficial effect of rehabilitation and reduce drug side effects. Appropriate medication with diltiazem, amlodipine and angiotensin-converting enzyme inhibitors, usually completed by diu-

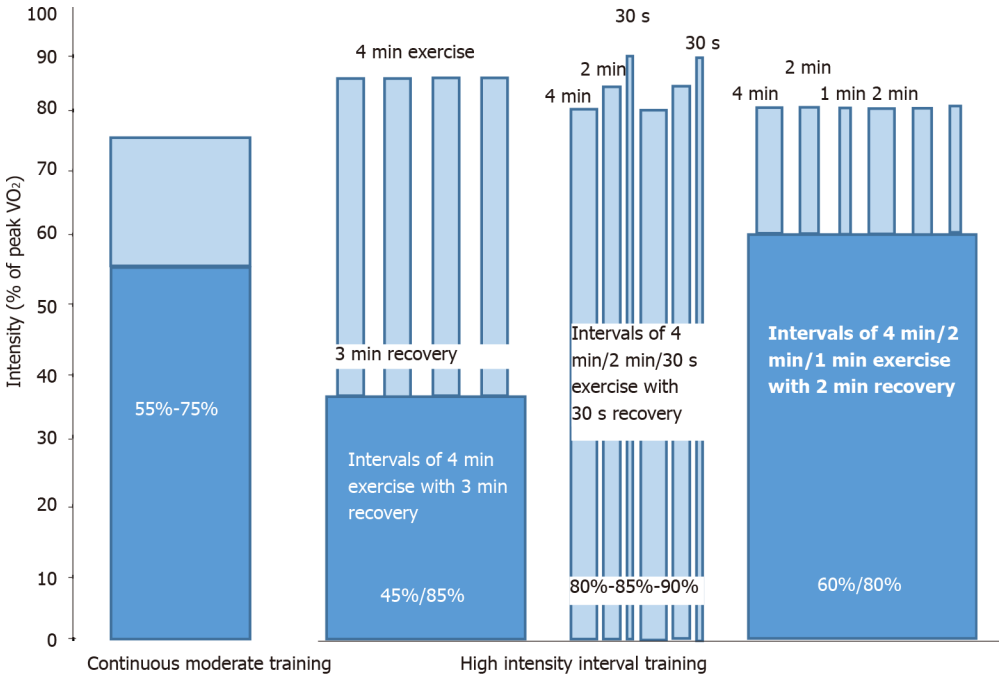


**Figure 3 Different protocols of continuous moderate training and high intensity interval training.** $VO_2$: Oxygen uptake.

retics, is mandatory. Also, statins, daily exercise and healthy diet should be applied in patients with hyperlipidemia in order to reduce the possibility of cardiovascular disease and improve survival[75]. Finally, psychosocial management is being considered as an important element in each cardiac rehabilitation program. Patients usually present high levels of depression, apprehensiveness or anxiety, and therefore support coping strategies should be implemented by expert psychologists[75].

### *Effects of exercise training in heart transplant patients*

As far as pre-rehabilitation stage is concerned, 2 clinical trials were recently conducted in pa-tients awaiting heart transplantation. In the first study[81], 7 end-stage HF patients awaiting heart transplantation while on intravenous inotropic support performed exercise training on a cycle ergometer while 11 patients followed the conventional protocol. 6-MWT assessed exercise capacity and manovacuometry assessed inspiratory muscle strength before and after each protocol. The intergroup comparison revealed significant increase in 6-MWT and inspiratory muscle strength in the intervention group compared to the control ($P < 0.01$)[81]. In the second study[82], 24 HF patients with advanced symptoms awaiting heart transplantation performed HIIT during hospitalization. HIIT was shown to improve skeletal muscle strength, and most specifically knee extensor strength, and decrease brain natriuretic peptide levels in these patients, however, without having any effect on hand grip strength[82].

Exercise training, as early as possible after hospital discharge, is being considered beneficial for the acute and long-term outcomes of heart transplant patients[83-86]. It has been shown to improve endothelial function assessed by brachial artery flow-mediated dilatation (FMD)[79]. In addition, it reduces systolic blood pressure, pro-atrial natriuretic peptide and high sensitive C-reactive protein (CRP)[79]. Two clinical trials investigated the effects of exercise training within the first year of hospital discharge after transplantation. In Braith *et al*[85] study, 8 wk after transplantation, 10 heart transplant recipients performed COMT on a treadmill 3 d/wk for 12 wk and 10 recipients took standard medical care for the same time period. Patients performed warm-up for 5 min, treadmill walking for 30 min and cooldown for 5 min within the first month. After the first month, treadmill walking increased to 35-40 min with an intensity between 11 and 13 or 12 and 14 of the Borg scale. Brachial artery reactivity was assessed using flow-mediated dilation. This randomized clinical trial proved the benefit of aerobic exercise on peripheral artery function in the early period after heart transplantation, demonstrating increase in brachial artery FMD in contrast with the progressive decline in patients who did not undergo rehabilitation. In addition, resting norepinephrine decreased significantly ($P < 0.05$) after exercise in the training group compared to controls and peak $VO_2$ increased 26% in the trained patients but remained unchanged in controls[85]. In another study of the same institution[42], 8 heart

transplant recipients, 2 mo after transplant, underwent a 6-mo resistance training program (2 d/wk, 10-15 repetitions at 50% of 1-RM in the beginning and then increase by 5%-10% in resistance in each set) for upper and lower body while 7 recipients were used as a control group. The aim of the study was to show the shift of type II fibers to type I fibers through biopsy of the right vastus lateralis, and therefore the beneficial effect of resistance training in the reverse of skeletal muscle myopathy even within a few days after heart transplantation[42].

Several studies have shown the effects of exercise training in heart transplant patients who enrolled a cardiac rehabilitation program in more than one year after hospital discharge. Most of these studies examined the effect of HIIT protocol in different functional capacity and vascular endothelial function indices. Nytrøen *et al* [80], included 48 clinically stable heart transplant recipients 1-8 (mean time: 4.1 ± 2.2) years after transplantation. Maximal CPET on a treadmill was performed in both 12-mo HIIT patients (intervention group) and patients who received usual care for the same time period. The HIIT group performed warm up for 10 min, followed by four 4 min exercise bouts at 85% to 95% of their maximum heart rate, with 3 min recovery time between them (intensity 11-13 on the Borg scale). Exercise group presented higher mean peak $VO_2$ and predicted peak $VO_2$ compared to controls ($P < 0.001$). Muscular exercise capacity and general health were also improved. Hermann *et al*[79], examined the effect of HIIT on peak $VO_2$ and FMD of the brachial artery in 14 patients after heart transplantation who performed an 8-wk HIIT program. Each session included a warm up above 50% of peak $VO_2$ and then 42 min of HIIT divided in 4 min-2 min-30 s intervals at 80%, 85% and 90% of peak $VO_2$ (intensity at 18-19 of the Borg scale) with 1- or 2-min recovery between the intervals. There was also a control group of 13 patients after heart transplantation who did not exercise. Blood pressure and several indices were also evaluated at baseline and 8 wk later. There was a significant increase in peak $VO_2$ and FMD in patients performed HIIT compared to controls, but nitroglycerin-induced vasodilation remained unchanged. Moreover, HIIT reduced systolic blood pressure in heart transplant recipients while it remained unchanged in controls, indicating thus the benefits of HIIT in endothelial after transplantation. Monk-Hansen *et al*[87], did not observe improvement of LV function in heart transplant recipients after an 8-wk exercise training program, although an increase in peak $VO_2$ was noticed.

A single study recently examined the effects of COMT on ambulatory blood pressure and arterial stiffness of heart transplant recipients. In this study[88], 40 patients either performed 40 min endurance exercise at 70% of peak $VO_2$ (3 times per week) for 12 wk or did not perform any kind of exercise. All patients underwent CPET, 24-h ambulatory blood pressure monitoring, and carotid-femoral pulse wave velocity assessment in 2 time periods; at baseline and after 12 wk. COMT reduced ambulatory blood pressure but pulse wave velocity remained unchanged, suggesting thus that it could be beneficial for the treatment of hypertension in heart transplant recipients.

Comparing HIIT an COMT, Yardley *et al*[89] showed that heart transplant patients had similar beneficial effect in inflammatory indices such as CRP, blood platelets and angiogenesis, but indices of angiogenesis including VEGF and angiopoietin 2 after HIIT seemed to increase more than COMT.

Finally, combined exercise, including aerobic exercise and muscle strength training, is still under investigation.

### *Limitations and perspectives*

In most studies there are gaps in methodology which could lead to bias. Inclusion criteria, different baseline exercise capacity and fitness level, differentiations in exercise training protocols and small number of samples are some variables that may lead to systemic bias and underpowered conclusions. Taking these factors into consideration, it would be safer to reach a conclusion that HIIT is effective and feasible in heart transplant patients rather than state that it is more beneficial than exercise with moderate intensity. Moreover, patients may drop out of the program either for logistic reasons or for complications of the transplantation caused by transplant rejection, infections and side effects of the immunosuppressive therapy.

Many cases of heart transplant patients could be inspiring examples of the remarkable human exercise capacity. A combination between the conventional post-heart transplantation multi-disciplinary medical therapy with the carefully monitored aerobic or combined endurance exercise training could be a real breakthrough in the field of medicine.

## CONCLUSION

Exercise training improves exercise capacity, cardiac and vascular endothelial function in heart transplant recipients. Pre-rehabilitation regular aerobic or combined exercise is beneficial for patients with end-stage HF awaiting heart transplantation in order to maintain a higher fitness level and reduce complications afterwards like ICU acquired weakness or cardiac cachexia. All hospitalized patients after heart transplantation should be referred to early mobilization of skeletal muscles through kinesiotherapy of the upper and lower limbs and respiratory physiotherapy in order to prevent infections of the respiratory system prior to hospital discharge. Moreover, health care providers should suggest all heart transplant recipients to participate in a rehabilitation program after hospital discharge. Although HIIT seems to have more benefits than COMT especially in stable transplant patients, individualized training based on the abilities and needs of each patient still remains the most appropriate approach. Cardiac rehabilitation appears to be safe in heart transplant patients. However, long-term follow-up data is incomplete and, therefore, further high quality and adequately-powered studies are needed to demonstrate the long-term benefits of exercise training in this population.

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SYSTEMATIC REVIEWS

# Native and transplant kidney histopathological manifestations in association with COVID-19 infection: A systematic review

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## Abstract

### *BACKGROUND*

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can result in clinically significant multi-system disease including involvement in the kidney. The underlying histopathological processes were unknown at the start of the pandemic. As case reports and series have been published describing the underlying renal histopathology from kidney biopsies, we have started to gain an insight into the renal manifestations of this novel disease.

### *AIM*

To provide an overview of the current literature on the renal histopathological features and mechanistic insights described in association with coronavirus disease 2019 (COVID-19) infection.

### *METHODS*

A systematic review was performed by conducting a literature search in the following websites-'PubMed', 'Web of Science', 'Embase' and 'Medline-ProQuest' with the following search terms-"COVID-19 AND kidney biopsy", "COVID-19 AND renal biopsy", "SARS-CoV-2 AND kidney biopsy" and "SARS-CoV-2 AND renal biopsy". We have included published data up until February 15, 2021, which includes kidney biopsies (native, transplant and postmortem) from patients with COVID-19. Data on clinical presentation, histopathological features, management and outcome was extracted from the reported studies.

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*RESULTS*

The total number of biopsies reported on here is 288, of which 189 are postmortem, 84 native and 15 transplants. The results are varied and show underlying pathologies ranging from collapsing glomerulopathy and acute tubular injury (ATI) to anti-nuclear cytoplasmic antibody associated vasculitis and pigment nephropathy. There was variation in the specific treatment used for the various renal conditions, which included steroids, hydroxychloroquine, eculizumab, convalescent plasma, rituximab, anakinra, cyclophosphamide and renal replacement therapy, amongst others. The pathological process which occurs in the kidney following COVID-19 infection and leads to the described biopsy findings has been hypothesized in some conditions but not others (for example, sepsis related hypoperfusion for ATI). It is important to note that this represents a very small minority of the total number of cases of COVID-19 related kidney disease, and as such there may be inherent selection bias in the results described. Further work will be required to determine the pathogenetic link, if any, between COVID-19 and the other renal pathologies.

*CONCLUSION*

This report has clinical relevance as certain renal pathologies have specific management, with the implication that kidney biopsy in the setting of renal disease and COVID-19 should be an early consideration, dependent upon the clinical presentation.

**Key Words:** COVID-19; Histopathology; Kidney biopsy; Transplant; SARS-CoV-2



**Core Tip:** Coronavirus disease 2019 (COVID-19) affects multiple organ systems, including the kidneys resulting in acute kidney injury. Multiple pathologies and different mechanisms have been attributed to the pathogenesis of kidney disease in COVID-19. This systematic review aims to provide an overview of the histopathological findings reported in kidney biopsies associated with COVID-19 infection.

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## INTRODUCTION

The novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes the disease coronavirus disease 2019 (COVID-19), was first identified in Wuhan, China in 2019; it has resulted in a global pandemic. The first cases were reported to the World Health Organization on December 31, 2019[1]. As of February 27, 2021, there were over 112 million cumulative cases and more than 2.5 million deaths worldwide[2]. The initial disease presentation is typically with respiratory symptoms[3], however, the multisystem effects of SARS-CoV-2 infection are now widely acknowledged and include cardiac, gastrointestinal tract, neurological, hematological and renal involvement[4-8]. It is recognized that patients with kidney dysfunction and COVID-19 have an increased risk of adverse outcomes[8,9]. A recent systematic review has shown an estimated incidence of acute kidney injury (AKI) of 10.0% in hospitalized patients with COVID-19[10]. Furthermore, within the United Kingdom, since September 1, 2020 and March 18, 2021, 3981 of 24542 (16.2%) patients with COVID-19 admitted to intensive care have required renal replacement therapy (RRT). Of these, 2633 (66.1%) died[11].

Various mechanisms of AKI secondary to COVID-19 have been proposed–from direct intrarenal infection to dysregulation of the renin-angiotensin-aldosterone system, to altered hemodynamic control, coagulation and cytokine homeostasis[12].

These proposed mechanisms require further validation with pathological correlation. An increasing number of case reports of patients with COVID-19, who have undergone kidney biopsies, are now published. The underlying pathology in these reports is varied and includes acute tubular injury (ATI) and collapsing glomerulopathy (CG) associated with high-risk apolipoprotein L1 (APOL1) alleles. Here, we provide a rapid clinical review of the current literature to help delineate the range of renal histopathological features associated with COVID-19. It is important to note that the case reports and series described in this review only represent a very small minority of the total number of cases of COVID-19 related kidney disease, and as such there may be inherent selection bias in the results described.

## MATERIALS AND METHODS

### *Eligibility criteria*

We included all research articles reporting histopathological findings in kidney biopsies from adult patients (> 18 years) with concurrent COVID-19 infection. These included native, transplant and postmortem kidney biopsies. We only included articles published in the English language. All studies published before February 15, 2021, were included in this review.

### *Search strategy and study selection*

A systematic literature search was conducted by two independent authors (VJ and HW) in the following websites-'PubMed', 'Web of Science', 'Embase' and 'Medline-ProQuest'. The search terms incorporated the following-"COVID-19 AND kidney biopsy", "COVID-19 AND renal biopsy", "SARS-CoV-2 AND kidney biopsy" and "SARS-CoV-2 AND renal biopsy". The articles were screened by three authors (VJ, HW and RC) for relevance and duplicate publications were removed. Duplicate screening and eligibility check was performed by JS. The study selection was carried out as *per* the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guideline (Figure 1).

### *Data extraction*

Data including patient demographics (age, gender, ethnicity), co-morbidities, clinical presentation (COVID-19 and renal manifestations), kidney parameters at baseline (serum creatinine, serum albumin and proteinuria), time from COVID-19 diagnosis to kidney biopsy, management (COVID-19 and renal specific), indication for RRT and outcome (renal specific and all-cause outcomes) were extracted from each article. Data is illustrated as figures and tables.

### *Study registration*

A pre-defined review protocol was registered at the PROSPERO international prospective register of systematic reviews, registration number CRD42020218048. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020218048.

## RESULTS

Our review identified a total of 59 studies reporting COVID-19 related histopathological diagnoses from kidney biopsy. Of these 59 studies, 30 reported on native kidney biopsies, 9 reported on transplant biopsies, 3 reported on a mixture of native and transplant kidney biopsies and 17 reported on post-mortem kidney biopsies (Figure 2). In total, there were 84 native biopsies, 15 transplant biopsies, and 189 post-mortem biopsies. Our review describes the presentation, management, and outcomes of the various pathologies. The various pathologies reported are listed in Supplementary Table 1.

### *Native kidney biopsies*

A list of all histopathological features reported in native kidney biopsy is illustrated in Figure 3.

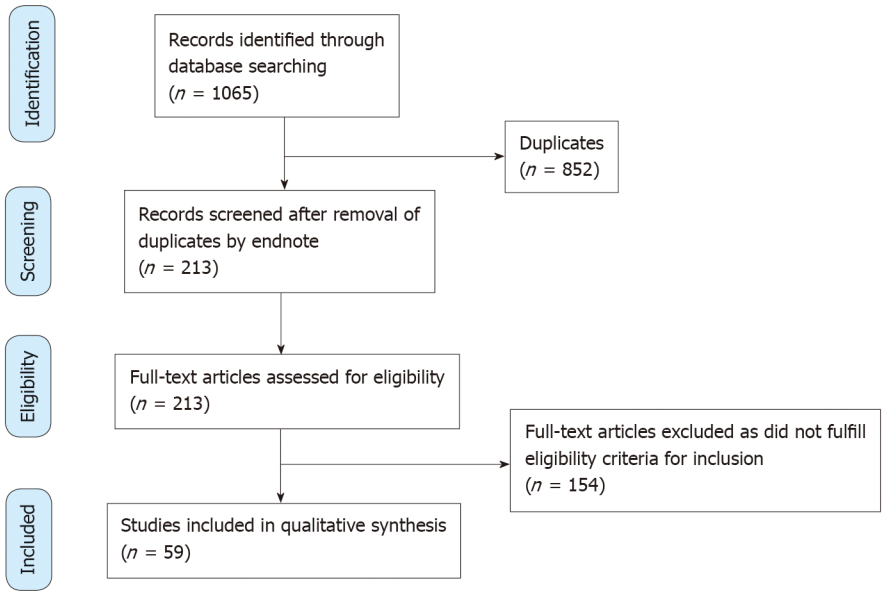


**Figure 1 PRISMA flow diagram.**

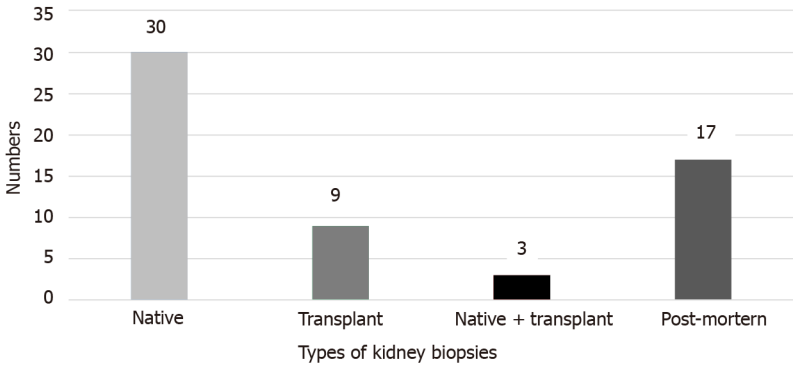


**Figure 2 Number of studies describing the different types of kidney biopsy in patients with coronavirus disease 2019.**

### *Collapsing focal segmental glomerular sclerosis (CG)*

CG was reported in 19 out of 30 native kidney biopsy studies which encompassed a total of 40 patients[13-30]. The median age of this cohort was 55 years with a predominance of males (80%) and black ethnicity (92.5%). A history of hypertension was reported in 30 patients and 11 patients had diabetes mellitus. APOL1 genetic mutation was reported in 10 patients. Non-resolving AKI and nephrotic range proteinuria (NRP) were the most common indications for kidney biopsy. The median time between COVID-19 positivity [as measured by polymerase chain reaction (PCR)] and kidney biopsy was 10 d. The most frequent treatment approach included steroids and hydroxychloroquine. There were 27 patients who needed RRT, of which 8 became dialysis independent on discharge, and 2 died. Table 1 illustrates the studies that demonstrated CG in kidney biopsy and their characteristics.

### *ATI*

ATI was the second most frequent pathological process described in the kidney biopsies of patients with COVID-19 infection (observed in 14 patients over 6 studies) [13,14,17,31-33]. Of these 14 patients, 10 had a history of hypertension and five were diabetic. Nine (64%) were male with a median age of 60.5 years. AKI was the main presenting feature in all of these cases with three patients also reporting NRP. Eleven patients needed dialysis of which four remained dialysis dependent on discharge, and two patients died in hospital. Lenti *et al*[31] reported the presence of viral particles in endothelial and tubuloepithelial cells from the kidney biopsy of one patient[31]; this patient did not require dialysis and was discharged from hospital after 15 d. Table 2 illustrates the studies which describe ATI on kidney biopsy in association with

**Table 1 Native kidney biopsy outcomes of collapsing glomerulopathy in coronavirus disease 2019 cases**

| Ref. | Age | Sex | Ethnicity | Comorbidities | Renal Px | Baseline creatinine (mg/dL) | Presentation creatinine (mg/dL) | Presentation proteinuria (g/day) | Presentation albumin (g/L) | Treatment received | Outcome (renal and survival) | RRT needed | Time to biopsy | Haematuria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kudose *et al* [13] | 46 | M | B | Obesity | AKI, NS | 1.1 | 12.5 | 5.8 | 3.1 | Tocilizumab/Steroids | DD | Yes | - | < 10 |
| Kudose *et al* [13] | 62 | M | B | HTN, prostate cancer, CKD | AKI, NS | 2 | 10.7 | 12.1 | 3.1 | None | DI | No | - | < 10 |
| Kudose *et al* [13] | 62 | M | B | HTN, DM, prostate Cancer | AKI, NRP | 1 | 11.6 | 19 | 2.4 | HCQ, Steroids | DI | No | - | - |
| Kudose *et al* [13] | 57 | M | B | HTN, hepatitis C, CKD | AKI, NRP | 1.1 | 4.9 | 6.2 | 2.5 | None | DI | No | - | < 10 |
| Kudose *et al* [13] | 61 | M | B | HTN, obesity | AKI, NRP | Normal | 15 | 9 | 2.5 | - | DD | Yes | - | - |
| Sharma *et al* [14] | 77 | F | B | HTN | AKI | 1 | 8.15 | 1.5 | - | HCQ, Steroids | DI | Yes | - | No |
| Wu *et al*[16] | 63 | M | B | HTN, DM | - | 1.3 | 4.9 | 12.7 | - | - | DD | Yes | - | < 10 |
| Wu *et al*[16] | 64 | F | B | HTN, DM | - | 1.5 | 4.2 | 4.6 | - | - | DI | No | - | Negative |
| Wu *et al*[16] | 65 | F | B | HTN, DM | - | 1.3 | 2.9 | 13.6 | - | - | Died | Yes | - | Negative |
| Wu *et al*[16] | 44 | M | B | - | - | 1.4 | 11.4 | 25 | - | - | DD | Yes | - | 50-100 |
| Wu *et al*[16] | 37 | M | B | - | - | 1 | 9 | - | - | - | Died | Yes | - | < 10 |
| Wu *et al*[16] | 56 | M | B | HTN | - | 1.2 | 6.7 | 3.6 | - | - | DI | Yes | - | > 100 |
| Akilesh *et al* [17] | 46 | M | B | HTN | AKI, NS | - | 8.7 | 13.7 | - | - | DD | Yes | 2 wk | No |
| Akilesh *et al* [17] | 60 | F | B | HTN | AKI, NRP | - | 5.7 | 21 | - | - | - | - | 4 wk | No |
| Akilesh *et al* [17] | 58 | F | B | HTN | AKI, NS | - | 10.2 | 20 | - | - | DD | Yes | - | - |
| Akilesh *et al* [17] | 44 | M | H | - | AKI, NRP | - | 12 | 11.4 | - | - | DD | Yes | 6 wk | No |
| Akilesh *et al* [17] | 58 | M | B | - | AKI, NRP | - | 11.3 | 4 | - | - | DI | Yes | Day 4 | Yes |
| Akilesh *et al* [17] | 47 | M | B | HTN | AKI, TMA | - | 6.6 | 7.6 | - | - | DD | Yes | Day 25 | Yes |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Akilesh *et al* [17] | 63 | F | B | HTN | AKI, NRP, TMA | - | 6 | 20 | - | - | DD | Yes | Day 10-14 | Yes |
| Gupta *et al* [18] | 71 | M | I | HTN, DM | AKI, NS | 1.19 | 4.49 | 18.46 | 2 | Steroid (Prednisolone 60mg OD) | DD | Yes | 1st-D6, 2nd 2 mo | No |
| Gupta *et al* [18] | 54 | M | B | HTN, DM | AKI, NS | 1.08 | 4.67 | 16 | 1.6 | None | - | No | Day 30 | No |
| Noble *et al* [43] | 54 | M | B | HTN, obesity | AKI, NRP | 125 | 6.54 | 4.08 | - | None | DI | Yes | Day 16 | Yes |
| Kissling *et al* [19] | 63 | M | B | HTN | AKI, NRP | - | 1.2 | 5 | - | None | DI | No | Day 8 | - |
| Magoon *et al* [21] | 28 | M | B | - | AKI | - | 0.99 | 2 | - | None | DI | Yes | Day 7-34 | Yes |
| Magoon *et al* [21] | 56 | M | B | HTN, CKD | AKI, NRP | - | 3.17 | 21 | - | None | DI | Yes | - | Yes |
| Gaillard *et al* [20] | 79 | M | B | HTN, MGUS, CKD | AKI, NRP | - | 2.55 | 11.4 | 2.9 | Dexamethasone, lopinavir/ritonavir, PLEX | DD | Yes | Day 5 | No |
| Sharma *et al* [15] | 67 | M | B | HTN, DM | AKI, NRP | 1 | 2.2 | 3.2 | - | HCQ/steroids | DD | Yes | Day 8-8/52 | < 10 |
| Sharma *et al* [15] | 49 | M | B | HTN | AKI | 0.95 | 4.85 | 2.59 | - | HCQ/steroids | DD | Yes | > Day 4 | < 10 |
| Nlandu *et al* [22] | 48 | M | B | HTN, DM | AKI, NS | 0.72 | 15.9 | 18 | - | Chloroquine, azithromycin, vitamin C | DI | Yes | Day 30 | No |
| Deshmukh *et al*[23] | 42 | M | I | - | NS | - | 1 | 8 | 'hypoalbuminaemia' noted | Ramipril | - | No | Day 24 | Yes |
| Kadosh *et al* [24] | 56 | M | B | CKD | AKI, NRP | - | 1.86 (peak 7.78) | 1.97 (peak 7.35) | - | MMF and steroids stopped, azithromycin, nitozaxonide | DI | No | > Day 7 | - |
| Coutourier *et al*[25] | 53 | M | B | HTN | AKI, NRP | 1.02 | 1.89 (peak 2.20) | 5.64 (peak 18.7) | 1.3 (day 3) | Oseltamivir, HCQ, chloroquine, azithromycin | DI | No | Day 3-11 | No |
| Couturier *et al*[25] | 53 | M | B | HTN, Hepatitis B | AKI, NRP | 1.35 | 5.34 (peak 6.01) | 1.5 (peak 2.65) | - | - | - | No | > Day 7 | No |
| Larsen *et al* [26] | 44 | M | B | HTN, DM, CKD | AKI, NRP | 1.4 | 4 | 3.9 (peak 25) | 2.5 | None | DD | Yes | Day 8 | Yes |
| Malhotra *et al*[27] | 64 | M | B | HTN, DM, CKD, HIV on HAART | AKI, NRP | - | 2.3 | 2.74 | - | Solumedrol, zinc, Vitamin C, Oxitris Filter | DD | Yes | Day 11 | Yes |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Izzedine *et al* [28] | 49 | F | B | CKD, heart transplant, type 2 diabetes, HTN, obesity | AKI, NS | 1.78 | 2.39 | 6.6 | 1.7 | - | DI | Yes | Day 8 | < 10 |
| Izzedine *et al* [28] | 38 | F | B | CKD, SLE, HTN, obesity | AKI, NS | 14.64 | 11.7 | - | 1.9 | - | DI | No | - | < 10 |
| Laboux *et al* [29] | 47 | M | B | HTN | AKI | 0.8 | 30.3 | 1.2 | 2.5 | Dialysis | DI | Yes | Day 30 | - |
| Malik *et al* [30] | 57 | M | B | - | AKI, NS | - | 2.0 then 3.4 | 14.9 | 3.4 | Antibiotics, oseltamivir, oxygen | DD | Yes | - | - |
| **FSGS with podocytopathy** | | | | | | | | | | | | | | |
| Akilesh *et al* [17] | 59 | M | B | HTN, DM | AKI, NRP | - | 11.9 | > 12 | - | Unknown | - | Unknown | Day 11 | - |

AKI: Acute kidney injury; B: Black; CKD: Chronic kidney disease; DM: Diabetes mellitus; DD: Dialysis dependent at hospital discharge; DI: Dialysis independent at hospital discharge; F: Female; H: Hispanic; HAART: Highly active antiretroviral therapy; HCQ: Hydroxychloroquine; HIV: Human immunodeficiency virus; HTN: Hypertension; I: Indian; M: Male; MGUS: Monoclonal gammopathy of undetermined significance; MMF: Mycophenolate mofetil; NRP: Nephrotic range proteinuria; NS: Nephrotic syndrome; PLEX: Plasma exchange; SLE: Systemic lupus erythematosus; TMA: Thrombotic microangiopathic anemia; FSGS: Focal Segmental Glomerulosclerosis.

COVID-19.

### *Thrombotic microangiopathy*

Thrombotic microangiopathy (TMA) was observed in eight patients in three studies. Sharma *et al*[14] reported two cases presenting with TMA and severe AKI requiring dialysis in association with COVID-19 infection[14]. The first patient had a background of gemcitabine treatment for cervical malignancy. She had no COVID-19 respiratory symptoms and was noted to be Coombs immunoglobulin (Ig) G positive. She was managed with steroids and rituximab for suspected Autoimmune Hemolytic Anemia and gemcitabine induced TMA. The second patient had severe COVID-19 respiratory manifestations requiring mechanical ventilation. There were signs of alternative pathway activation (low factor H, raised serum CBb and C5b-9). She was given treatment with tocilizumab, steroids, anakinra, convalescent plasma and eculizumab. Unfortunately, both patients died.

Akilesh *et al*[17] described five patients with histological findings of TMA on light microscopy[17]. All five patients had hypertension and AKI with biochemical features of TMA, prompting a kidney biopsy. Three of these patients also had histopathological features consistent with concurrent collapsing Focal Segmental Glomerulosclerosis (FSGS). Two patients were noted to have had gemcitabine treatment for underlying malignancy. All five required dialysis and only one patient recovered renal function without needing further dialysis. Management was supportive for all except one patient who received plasma exchange and eculizumab, though she remains dialysis dependent (Supplementary Table 2).

**Table 2 Native kidney biopsy outcomes of acute tubular injury and necrosis in coronavirus disease 2019 cases**

| Ref. | Age | Sex | Ethnicity | Comorbidities | Renal presentation | Baseline creatinine (mg/dL) | Presentation Creatinine (mg/dL) | Presentation proteinuria (g/day) | Presentation albumin (g/L) | Treatment received | Outcome (renal and survival) | RRT needed | Time to biopsy | Haematuria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sharma *et al* [14] | 62 | M | Hispanic | T2DM | AKI and proteinuria | - | 1.2 | 3 | - | Steroid, HCQ, anakinra, plasma | Died | Yes | - | Yes |
| Sharma *et al* [14] | 69 | M | Hispanic | HTN | AKI, proteinuria, anti-cardiolipin positive | - | 0.9 | 2.4 | - | Steroid, HCQ, anakinra, plasma | Died | Yes | - | Yes |
| Sharma *et al* [14] | 76 | F | Caucasian | T2DM, HTN | Severe AKI and Proteinuria | - | 1 (peak 4.4) | 0.9 | - | None | DI | No | - | No |
| Sharma *et al* [14] | 59 | M | Black | HTN, CCF | AKI, Proteinuria and raised K:L ratio | - | 4.5 (peak 6) | 2.8 | - | None | DI | No | - | Yes |
| Sharma *et al* [14] | 69 | F | Black | HTN, Hyperlipidaemia | AKI NRP | - | 1.9 | 7.6 | - | Steroids | DD | Yes | - | No |
| Kudose *et al* [13] | 43 | F | Black | T2DM, HLD, streptococcal infection, obesity (BMI 52.5) | AKI | - | 3.5 (peak 6.7) | 1 | - | None | DD | Yes | - | Yes |
| Kudose *et al* [13] | 67 | M | Caucasian | HTN, Gout, Obese | AKI on CKD | - | 5.7 | 0.3 | - | Tocilizumab, HCQ, azithromycin | DD | Yes | - | Yes |
| Kudose *et al* [13] | 51 | M | Black | HTN, AF, HLD, CVA, BPH | AKI on CKD | 1.8 | 4.8 | 0.5 | - | HCQ | DI | No | - | Yes |
| Akilesh *et al* [17] | 34 | F | Caucasian | HTN, T2DM | AKI NS | - | 1.2 | 7 | - | - | DI | No | Day 4 | No |
| Akilesh *et al* [17] | 67 | F | Hispanic | HTN | AKI | - | 1.4 | 1 | - | - | DI | No | Day 5 | Yes |
| Lenti *et al*[31] | 25 | M | Caucasian | - | AKI NS | - | 3.8 | 0.48 | - | - | - | - | - | - |
| Rossi *et al*[32] | 49 | M | Caucasian | Obesity | AKI | - | - | - | - | HCQ, Lopinavir/Ritonavir | DI | Required when in hospital | - | - |
| Papadimitriou *et al*[33] | 52 | M | - | HIV, HTN, coronary artery disease, Factor V deficiency | AKI | Normal | 7.5 | 1.85 | - | - | DD | Yes | Day 10 | - |
| Papadimitriou | 64 | M | - | AF, | AKI | 1 | 1.4 | - | - | I&V, IV heparin then apixaban | DI | Yes | Day 84 | - |

| | | |
|---|---|---|
| *et al*[33] | hyperlipidaemia, gout | (AF), 4 units blood following haematemesis, meropenem (*E. coli* in sputum), RRT day 22 to 33, MRSA > linezolid |

AKI: Acute kidney injury; AF: Atrial fibrillation; BPH: Benign prostatic hypertrophy; CCF: Congestive cardiac failure; CKD: Chronic kidney disease; CVA: Cerebrovascular accident; DD: Dialysis dependent at hospital discharge; DI: Dialysis independent at hospital discharge; DSA: Donor specific antibodies; HCQ: Hydroxychloroquine; HIV: Human immunodeficiency virus; HLD: Hyperlipidaemia; HTN: Hypertension; I&V: Intubated and ventilated; K:L ratio: Kappa:lambda light chain ratio; RRT: Renal replacement therapy; T2DM: Type 2 diabetes mellitus.

### *Antinuclear cytoplasmic antibody associated vasculitis*

In a case series of 10 COVID-19 positive patients who underwent kidney biopsy for AKI, Sharma *et al*[14] reported one patient (64-year-old Black male) with a positive myeloperoxidase (MPO) antibody in which his kidney biopsy demonstrated crescentic glomerulonephritis (GN), supporting a diagnosis of antinuclear cytoplasmic antibody (ANCA) associated vasculitis[14]. Electron microscopy features and immunostaining were negative for viral RNA particles. The same patient was reported as one of two cases by Uppal *et al*[34] in which COVID-19 was managed with oxygen support, tocilizumab, and convalescent plasma[34]. When his COVID-19 re-test became negative, the patient was initiated on methylprednisolone and rituximab; his renal function recovered back to baseline and further dialysis was not required.

A second case reported by Uppal *et al*[34] presenting with AKI, hematuria and proteinuria with concomitant COVID-19 infection, had proteinase 3 (PR3) ANCA positivity[34]. Kidney biopsy features were consistent with crescentic or focal segmental necrotizing GN. A skin biopsy of this patient, who had a new-onset skin rash, revealed leukocytoclastic vasculitis. The patient received hydroxychloroquine treatment alongside methylprednisolone and rituximab, achieving good outcomes: Reduction in PR3 from 57.3 units/mL to 28.8 units/mL and improvement in serum creatinine from 4.0 mg/dL to 2.0 mg/dL. Moeinzadeh *et al*[35] described another case of a 25-year-old male diagnosed with PR3 ANCA vasculitis who presented with AKI and pulmonary hemorrhage[35]. He was managed with methylprednisolone, plasma exchange, cyclophosphamide and hydroxychloroquine. The patient's renal function stabilized on these treatments, and he avoided the need for acute dialysis.

Jalalzadeh *et al*[36] described a 46 year old female with a background of scleroderma and type 2 diabetes, who presented with respiratory and abdominal symptoms[36]. She had been diagnosed with COVID-19 six months previously. She had a significant AKI with proteinuria and was found to have a raised MPO titer at 161.8 units. She was managed with captopril (concern for potential scleroderma renal crisis), and methylprednisolone for 3 d. She did not require RRT and was discharged home. Kidney biopsy revealed a crescentic GN with 45 out of 48 glomeruli globally sclerosed.

### *Anti-glomerular basement membrane (anti-GBM) disease*

Kudose *et al*[13] reported a case of anti-GBM disease in a COVID-19 positive patient

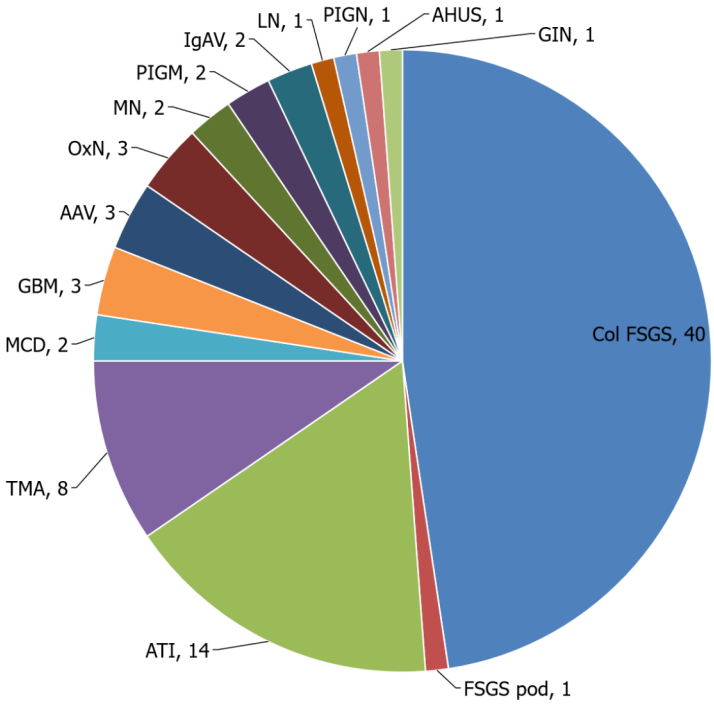


**Figure 3 Native kidney biopsy histopathological features reported in association with coronavirus disease 2019.**

who presented with pulmonary infiltrates on chest X-ray and severe AKI[13]. Kidney biopsy revealed crescentic GN alongside ATI with microcyst formation and interstitial infiltrates. The patient was managed with steroids, cyclophosphamide, and plasma exchange without an improvement in renal function; he was initiated on dialysis therapy.

Prendecki *et al*[37] described eight patients who presented with positive anti-GBM serology[37]. Though none of these patients had positive results for COVID-19 PCR, four patients tested positive for SARS-CoV-2 IgM. All eight patients reported non-specific prodromal symptoms although only five reported respiratory symptoms and/or diarrhea. None of the patients had pulmonary manifestations. Of the four patients with positive findings for SARS-CoV-2 IgM, crescentic linear IgG was reported in the kidney biopsy for two patients. With a confirmed histological diagnosis of anti-GBM disease, these two patients were treated with steroids, cyclophosphamide, rituximab and plasma exchange. One patient achieved complete recovery of renal function.

### *IgA vasculitis*

Suso *et al*[38] described a case of a 78-year-old man who had COVID-19 associated respiratory failure along with extremely high IL-6 levels (177 pg/mL)[38]. He received treatment with hydroxychloroquine, lopinavir/ritonavir, dexamethasone, ceftriaxone, azithromycin, and tocilizumab. The patient presented three weeks later with a triad of arthralgia, cutaneous vasculitis and haematoproteinuria. Kidney biopsy was performed and showed crescentic manifestations in two of the seven glomeruli and mesangial IgA deposits, raising the possibility of IgA vasculitis as a result of COVID-19. The patient was treated with methylprednisolone followed by rituximab. He improved clinically with a reduction in proteinuria, and on discharge his creatinine improved to 1.4 mg/dL (baseline 0.78 mg/dL).

Huang *et al*[39] described a 65-year-old Chinese female who presented with headache, myalgia, fatigue, dark colored urine and flank pain[39]. She had haematoproteinuria. Kidney biopsy showed 16 glomeruli, 5 of which were globally sclerosed, with 2+ IgA staining on immunofluorescence. Electron microscopy showed mesangial electron dense deposits. She was treated with methylprednisolone for 3 d and oseltamivir for 5 d. Dialysis was not required, and she was discharged home.

### *Lupus nephritis*

Kudose *et al*[13] described a case of a 27-year-old African female with a previous diagnosis of class II lupus nephritis who presented with COVID-19 associated res-

piratory failure[13]. On presentation, she displayed clinical features of nephrotic syndrome and AKI. Kidney biopsy revealed histopathological features of Class IV/Class V lupus nephritis. The patient was managed with steroids following kidney biopsy. She deteriorated clinically and died from multi-organ failure on her 6$^{th}$ day of hospital admission.

### Minimal change disease

Kudose *et al*[13] described a single case of minimal change disease (MCD) in a young African-Caribbean patient with a homozygous G1 APOL1 variant presenting to hospital with nephrotic syndrome[13]. This patient went into partial remission following treatment with steroids in addition to azithromycin and hydroxychloroquine for COVID-19. Akilesh *et al*[17] presented another case of MCD in an elderly Caucasian female who presented with nephrotic syndrome[17]. The patient had a kidney biopsy six weeks after a positive COVID-19 PCR test. A full remission was achieved within four weeks after receiving high-dose steroid management.

### Membranous nephropathy

Two reported cases of membranous nephropathy (MN) in association with COVID-19 infection were identified[13]. In these cases, both patients had NRP. The first patient had immunohistochemistry positive for phospholipase A2 receptor (PLA2R) on kidney biopsy staining and was treated with tacrolimus. He remained COVID-19 positive, although a reduction in proteinuria was noted. The second patient had previous cervical neoplasm and did not have PLA2R antibodies but had positive serum anti-dsDNA and antinuclear antibody were identified. The patient was not initiated on any active treatment and is currently under nephrology follow-up without the need for dialysis.

### Oxalate nephropathy

Three cases of oxalate nephropathy in patients with positive COVID-19 status were identified in our review[27,40]. All three patients presented with AKI and received vitamin C in high doses as management for sepsis-related acute respiratory distress syndrome. Kidney biopsy showed calcium oxalate monohydrate crystals on hematoxylin and eosin staining, which were birefringent under polarized light. The scanning electron microscope and X-ray spectrometry analyses confirmed the presence of calcium oxalate monohydrate crystals. None of the patients required dialysis treatment and all three were discharged after clinical recovery.

### Post infectious GN

Akilesh *et al*[17] reported a case of post infectious GN in a 69-year-old Caucasian female presenting with AKI and NRP[17]. She had a background history of diabetes mellitus and recurrent *E. coli* urinary tract infection. Kidney biopsy revealed the presence of subepithelial deposits, granular C3 staining, advanced changes related to diabetic nephropathy and severe ATI. The patient improved clinically but remained dialysis dependent.

### Pigment nephropathy

Pigment nephropathy was reported in two case reports[13,14]. In both cases, the patients presented with ATI, with raised creatinine kinase levels and myoglobinuria secondary to rhabdomyolysis. The kidney histopathology showed pigment cast and was positive for myoglobin immunohistochemistry. Both patients required dialysis; one patient achieved complete recovery whilst the other deteriorated and died during hospitalization.

### Atypical hemolytic uremic syndrome

There was one case report of atypical hemolytic uremic syndrome (aHUS) that reactivated post COVID-19 infection[41]. A 28-year-old Caucasian female who had previously been diagnosed with aHUS aged 3 presented with fever, dysphagia and headache. She had an AKI along with proteinuria. She was managed with eculizumab, did not require RRT and was discharged with a creatinine of 2 mg/dL.

### Granulomatous interstitial nephritis

A 62-year-old Caucasian male presented with cough, fever and myalgia[42]. He had an AKI with non-NRP. He required critical care admission and was treated with hydroxychloroquine and continuous veno-venous hemofiltration for 38 d. Kidney biopsy was performed 32 d post admission and showed 34 mostly normal glomeruli with multiple

non-caseating granulomas consistent with granulomatous interstitial nephritis. He survived to discharge and remained dialysis independent.

### *Transplant biopsies*

We have also identified case reports highlighting histopathological changes amongst transplant recipients in the setting of COVID-19 infection[13,17,43-51] (Figure 4 and Table 3). Two cases of CG have been reported in transplant biopsies in addition to severe ATI changes, both in patients of African-Caribbean origin and presenting with AKI and NRP[43,47]. The antiproliferative agent (mycophenolate mofetil) was withheld in both cases. Whilst one patient recovered renal function, the other remained dialysis dependent. In one case the donor was found to have low risk APOL1 variant with G2 heterozygosity[47], a risk factor for CG, whilst the other case did not have genetic testing but on in-situ hybridization, viral RNA was detected in the tubulo-epithelial cell[43].

Recurrence of FSGS was reported in two cases in association with COVID-19 infection. The first case report describes a patient who had a second recurrence of FSGS (16 wk post-transplant) in the setting of COVID-19 infection and resolved spontaneously with viral clearance[45]. The second case presented with AKI and nephrotic syndrome five weeks post-transplant in a patient with high risk homozygous G2 APOL1 variant[48]. This patient was treated with steroids and renin-angiotensin-aldosterone system (RAAS) inhibition with improvement of renal parameters.

Yamada *et al*[51] describe a case in which the renal presentation was with AKI and NRP. The biopsy showed minimal change disease[51]. The patient was treated with high dose steroids and partial remission was achieved. Both the recipient and donor were homozygous for high risk G1 APOL1 variant and biopsy was taken five days after admission for COVID-19 infection.

There were 2 cases of isolated ATI in patients presenting with AKI[13,17]. These patients did not receive any specific treatment and were discharged with good renal outcomes, with the creatinine of one returning to baseline (around 1.3 mg/dL) shortly after biopsy[17].

Kudose *et al*[13] describe one case of a patient with grade 2A T-cell mediated rejection (TCMR) one-month post-transplant[13]. The patient had positive donor specific antibodies (DSA) and was treated with steroids, tocilizumab and thymoglobulin. Her creatinine stabilized and she was discharged. In the same case series, there was a case of transplant cortical infarction with the patient remaining dialysis dependent. A further case of transplant infarction was described by Webb *et al*[49]. A 49-year-old male presented with respiratory symptoms and AKI. He was managed with oxygen, steroids, low molecular weight heparin and ertapenem. He required dialysis and were subsequently discharged home. Kidney biopsy showed almost complete infarction of the renal cortical parenchyma with no viable glomeruli seen.

A case of de-novo DSA positivity was reported by Akilesh *et al*[17] in a patient presenting with AKI six weeks post COVID-19 infection[17]. The patient had active antibody mediated rejection (AMR) in the biopsy and was managed with steroids, plasma exchange, intravenous immunoglobulin, and rituximab. Another case of chronic active AMR was described in a patient who developed AKI and proteinuria on a background of known transplant glomerulopathy[17]. The biopsy showed signs of activity with C4 complement component (C4d) positivity and TMA. There were also mesangial changes with IgA deposition, which may indicate concurrent IgA changes. The primary kidney disease was unknown. Abuzeineh *et al*[44] reported a case of a 54-year-old male with a renal transplant from 2015 who presented with AKI and was managed with fluids, oxygen, antibiotics, antifungals and tocilizumab[44]. Subsequent transplant biopsy revealed AMR which was managed with intravenous immunoglobulin.

Jespersen *et al*[46] describe one patient who underwent a transplant kidney biopsy which showed TMA[46]. The patient presented with abdominal pain without any respiratory symptoms. Computerized tomography (CT) scan confirmed acute pancreatitis and they developed hemolytic anemia with worsening kidney function. Management was supportive; RRT was not needed, and they were discharged home.

Westhoff *et al*[50] described a case of kidney allograft infiltration with SARS-CoV-2. The patient had received a pancreas-kidney transplant 13 years prior and presented with SARS-CoV-2-pneumonitis, new insulin requirement, renal transplant AKI and high tacrolimus levels likely secondary to diarrhoea. Immunosuppression was rationalised to steroid monotherapy. Kidney transplant biopsy revealed mild ATI and mononuclear cell inflammation, in addition to SARS-CoV-2 spike protein RNA present in the interstitium and tubular epithelial cells, demonstrated *via* in-situ hybridisation.

**Table 3 Transplant kidney biopsy findings in coronavirus disease 2019 cases**

| Ref. | Age | Sex | Ethnicity | Comorbidities | Renal Presentation | Baseline creatinine (mg/dL) | Presentation creatinine (mg/dL) | Presentation proteinuria (g/day) | Presentation albumin (g/L) | Treatment received | Outcome (renal and survival) | RRT needed | Time to biopsy | Haematuria |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **T-cell mediated rejection** | | | | | | | | | | | | | | |
| Kudose *et al* [13] | 54 | F | Caucasian | IgA Nephropathy, Donor Specific Ab +ve, HTN, obesity | AKI | 1.7 | 2.6 | 0.2 | - | Steroids, Tocilizumab, thymoglobulin, IVIG | DI | No | - | Yes |
| **ABMR** | | | | | | | | | | | | | | |
| Akilesh *et al* [17] | 47 | F | Black | HIV-associated Nephropathy, Deceased Donor Tx 2015, Vascular Rejection Post-Tx, HTN | AKI | - | 1.63 | 2 | - | Renal transplantation, 5-MTP, PLEX IVIG | - | - | 6 wk | No |
| Akilesh *et al* [17] | 54 | M | Asian | Chronic Transplant Glomerulopathy, C4d –ve, HTN, T2DM | AKI with Proteinuria | 1.9 | 5.2 | 3 | - | Regular MMF withheld, regular tacrolimus dose reduced, steroids | DI | No | 6 wk | No |
| Abuzeineh *et al*[44] | 54 | M | Black | Diabetic nephropathy, Tx, HTN | AKI | 1.4 | 2.6 | - | - | IVF, MMF discontinued, NHF oxygen, antibiotics, antifungals, tocilizumab | DI | No | 73 d | - |
| **Acute tubular injury** | | | | | | | | | | | | | | |
| Akilesh *et al* [17] | 42 | M | Hispanic | Live Donor Tx 2019, HTN | AKI | 1.27 | 1.53 | 0.15 | - | - | DI | No | 7 wk | No |
| Kudose *et al* [13] | 54 | F | Hispanic | ADPKD, Deceased Donor Tx 2020, HTN | AKI | 2.5 | 2.9 | 0.2 | - | None | DI | No | - | - |
| Westhoff *et al*[50] | 69 | M | - | Diabetic nephropathy | AKI | 1.1 | 2.2 | - | - | IV hydrocortisone, tacrolimus and MMF held, HCQ, levetiracetam | DI | No | 14 d | - |
| **FSGS** | | | | | | | | | | | | | | |
| Doevelaar *et al*[45] | 35 | M | Black | Deceased donor Tx 2019 | AKI, Normothermic Regional Perfusion | - | 1.7 | 3.29 | - | Steroids (Hydrocortisone 200 mg/d) | DI | No | 34 d | - |
| Oniszczuk *et al*[48] | 49 | M | Black | Renovascular disease, deceased donor Tx 2020 | AKI, Nephrotic Syndrome | 1.47 | 2.17 | 3.27 | 2.7 | Steroids, ACE Inhibitor | DI | No | 2 wk | - |
| Yamada *et al* [51] | 49 | F | Black | Pre-eclampsia, Live donor Tx 1995 (from | AKI, Normothermic | 1.6 | 3.4 | 6.3 | 3.8 at diagnosis with COVID-19 | ACE Inhibitor, Steroids (Prednisolone 60 mg | DI | No | 5 d | - |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | sibling) | Regional Perfusion | | | | | with quick wean due to side effects) | | | | |
| **Collapsing FSGS** | | | | | | | | | | | | | | |
| Noble *et al* [43] | 45 | M | Black | Malignant HTN, Obesity (BMI 42.6), Live Donor Tx 2016 | AKI, Nephrotic syndrome | 3.22 | 4.69 | 1.09 | - | MMR withheld on admission, restarted after 14 d. Steroid (Prednisolone dose doubled from 10 mg OD to 20mg OD) | DD | Yes | 12 d | Yes |
| Lazareth *et al*[47] | 29 | M | Black | Urinary Schistosomiasis, Deceased Donor Tx 2015, Previous ABMR in Jan 2020 | AKI, Nephrotic Syndrome | 3.18 | 6.06 | 0.49 | 2.8 | MMF withheld temporarily | DI | No | 2 d | - |
| **Transplant infarction** | | | | | | | | | | | | | | |
| Kudose *et al* [13] | 22 | M | Black | Membranous Nephropathy PLA2R +ve, Deceased Donor Tx 2018, HTN | AKI | - | 9.4 | - | - | Tocilizumab, HCQ, Azithromycin | DD | Yes | - | - |
| Webb *et al* [49] | 49 | M | - | Chronic glomerulonephritis, HTN, DCD renal transplant 2001 with subsequent ABMR, CMV | AKI | 0 | 2.03 | - | - | Nasal high flow oxygen, prednisolone, enoxaparin, ertapenem | DD | Yes | 27 d | - |
| **TMA** | | | | | | | | | | | | | | |
| Jespersen *et al*[46] | 49 | F | - | FSGS | AKI | - | 2.81 | - | - | Supportive | DI | No | > 22 d | - |

5-MTP: 5-methoxytryptophan; Ab: Antibody; ABMR: Antibody mediated rejection; ADPKD: Autosomal dominant polycystic kidney disease; AKI: Acute kidney injury; CMV: Cytomegalovirus; DCD: Donor after circulatory death; DD: Dialysis dependent at hospital discharge; DI: Dialysis independent at hospital discharge; FSGS: Focal and segmental glomerulosclerosis; HCQ: Hydroxychloroquine; HIV: Human immunodeficiency virus; HTN: Hypertension; IVF: Intravenous fluids; IVIG: Intravenous immunoglobulin; MMF: Mycophenolate mofetil; NHF: Nasal high flow; PLA2R: Phospholipase 2 receptor antibody; PLEX: Plasma exchange; T2DM: Type 2 diabetes mellitus; Tx: Transplant.

However, serum RT-PCR remained negative. This patient later developed neurological complications with cerebrospinal fluid positive for SARS-CoV-2 PCR requiring admission to intensive care. The patient made an excellent recovery and was discharged with complete resolution of renal transplant AKI and partial pancreatic graft recovery. Post-mortem studies have suggested that kidney viral tropism likely occurs due to viraemia and perfusion of the kidney with infected blood. However, kidney infiltration despite negative serum testing suggests a possible alternative pathophysiological mechanism.

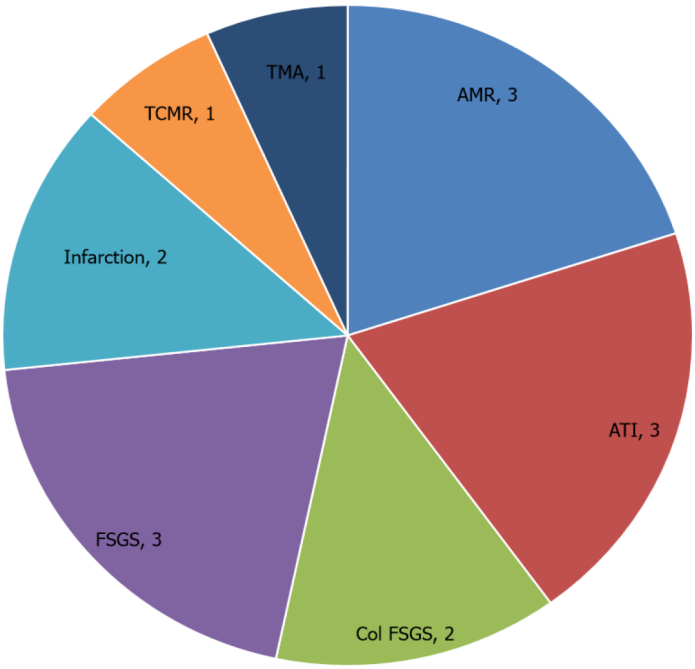


**Figure 4 Transplant kidney biopsy histopathological features reported in association with coronavirus disease 2019.**

### *Post-mortem biopsies*

We identified 17 reports describing post-mortem kidney biopsies[52-68]. The most common findings were ATI, arterionephrosclerosis[64] and FSGS[52,55,67], with other findings including renal vein thrombus[52], pigment cast nephropathy[67], IgA staining[64,67], IgG humps on EM consistent with post-infectious GN[67], chronic interstitial nephritis[52,54,60], nodular diabetic glomerulosclerosis[57] and oxalosis[56, 59] (Figure 5). The findings are summarized in Table 4.

Farkash *et al*[55] reported isometric tubular vacuolization on light microscopy, these corresponded to coronavirus like particles in the tubular epithelial cells noted in electron microscopy[55]. Remmelink *et al*[63] have reported positive viral RNA on PCR from renal samples of 10 of their 14 cases[63]. In the cases series by Su *et al*[67] three patients showed nucleocapsid SARS-CoV-2 positivity on in situ hybridization in tubuloepithelial cells[67].

Treatments received varied and included steroids, azithromycin, tocilizumab, hydroxychloroquine and anakinra. One of the significant limitations of the postmortem series is autolysis which often occurs resulting in many samples being excluded.

## DISCUSSION

A wide range of histopathological findings were reported in the kidney biopsies of patients in association with COVID-19 infection. CG appears as the dominant histopathology amongst glomerular diseases, being observed in 40 out of 84 native kidney biopsies. In non-COVID-19 patients, CG is a distinct and aggressive variant of FSGS more commonly observed in African-Caribbean ethnic groups. It is characterized by glomerular tuft collapse in segmental or global distributions, where there is concurrent hypertrophy and hyperplasia of the overlying podocytes[69-71]. Recent reports highlighted the significance of podocytopathy as the major histopathological manifestation of COVID-19 induced glomerular disease[72]. CG is commonly associated with various infections and inflammatory conditions, such as human immunodeficiency virus (HIV) and systemic lupus erythematous[73]. Current opinion on COVID-19 associated CG suggests its pathogenesis as a multifactorial process. Direct viral podocyte invasion is supported by electron microscopy findings of coronavirus particles within the cytoplasm of podocytes in native and post-mortem biopsies. Suggestions of CG secondary to cytokine release from systemic COVID-19 manifestations have been proposed, particularly in those with APOL1 high risk genotype and African-Caribbean ethnicity[13-22,24-29]. Basic-science studies have shown viral infections stimulating interferon production which in turn encourages APOL1 gene

**Table 4 Post-mortem kidney biopsy findings in coronavirus disease 2019 cases**

| Ref. | Number in series | Number with kidney histology | Age-median (range) | Gender (male), *n* (%) | Comorbidities, *n* (%) | AKI, *n* (%) | RRT, *n* (%) | Covid treatment, *n* (%) | Pathological findings, *n* (%) |
|---|---|---|---|---|---|---|---|---|---|
| Bradley *et al* [52] | 14 | 14 | 73.5 (42-84) | 6 | Diabetes 5, HTN 9, CKD 5 | 6 (1 at presentation) | | - | ATI 11, FSGS 1, chronic inflammation 1, renal vein thrombus 1 |
| Su *et al*[67] | 26 | 26 | 69 (39-87) | 19 | Diabetes 3, HTN 11, CKD 2 | - | 5 (6 no record) | Arbidol 10, Ribavirin 2, Lopinavir/ritonavir 5, steroids 15 | ATI 26, TMA 1, FSGS 2, pigment nephropathy 3, IgA 1, pyelonephritis 2, PIGN 1 |
| Santoriello *et al*[64] | 42 | 31 (11 excluded due to autolysis) | 71.5 (38-97) | 29 | Diabetes 17, HTN 30, CKD 8 | 31 (94)-stage (38.1) | 8 (36) | Plaquenil 36, steroids 22 (61% combination), tocilizumab 6 (17%) | ATI 31, TMA 6, collapsing FSGS 1, chronic inflammation 27, IgA 1 |
| Farkash *et al* [55] | 1 | 1 | 53 | - | - | 1 | 1 | HCQ, IL-6 blinded trial | ATI 1 |
| Werion *et al* [68] | 49 | 6 | 64 (54-74) | 34 | Diabetes 10, HTN 23, CKD 7 | 11 (22) | 2 (4) | HCQ 48 (98%), azi 7 (14%), steroids 7 14%), IL-7: 8 (16.5%), tocilizumab 1 (2%) | ATI 5, FSGS 1, chronic inflammation 2 |
| Lax *et al*[60] | 11 | 11 | N/A | 8 | Diabetes 5, HTN 8 | 6 (54.5) | - | Azi/HCQ 2 | ATI 11, chronic inflammation 2 |
| Golmai *et al* [56] | 12 | 12 | 75 (49-92) | 10 | Diabetes 4, HTN 9, CKD 1 | 9 | 8 | Tocilizumab/HCQ/steroids 7, HCQ/steroids 4 | ATI 9, oxalosis 1 |
| Falasca *et al* [54] | 18 | 9 | 76.5 (27-92) | 12 | Diabetes 4, HTN 4 , CKD 2 | - | - | | Chronic inflammation 12 |
| Schurink *et al*[65] | 21 | 21 | 68 (41-78) | 16 | Diabetes 1 | 15 (71); 10 stage 3 | 5 | Chloroquine 10 (48%), antiviral 4 (19%), steroids 5 (24%) | ATI 12, TMA 1 |
| Hanley *et al* [58] | 10 | 9 | 73 (IQR 52-79) | 7 | HTN 4 | - | - | - | ATI 9, TMA 5 |
| Rapkiewicz *et al*[62] | 7 | 7 | 60 (44-65) | 3 | Diabetes 5, HTN 6, CKD 1 | - | - | Azi/HCQ 2, Azi/HCQ/Tocilizumab 2, Azi/HCQ/Anakinra | ATI 7, TMA 1 |
| González Pessolani *et al*[57] | 4 | 2 | 78 | 2 | Diabetes 1, HTN 1 | 2 | | - | ATI 2, TMA 1 |
| Jacobs *et al* [59] | 1 | 1 | 78 | 1 | HTN 1 | 1 | 1 | Azi/HCQ/steroids | ATI 1, Oxalosis 1 |
| Sekulic *et al* [66] | 2 | 2 | (54-81) | 2 | Diabetes 2, HTN 2, CKD 1 | 2 | - | Remdesivir 1 | ATI 2 |
| Remmelink *et al*[63] | 17 | 17 | 72 (62-77) | 12 | Diabetes 9, HTN 10, CKD 3 | 15 | - | HCQ 15, Steroids 2, Lopinavir/ritonavir 2, Remdesivir 2, Oseltamivir 1 | - |
| Brook *et al* [53] | 5 | 3 | 75 (58-82) | 1 | Diabetes 2, HTN 3, CKD 1 | - | - | - | ATI 3 |
| Menter *et al* [61] | 21 | 17 | 76 (53-96) | 17 | Diabetes 7, HTN 21, CKD 4 | - | - | - | ATI 14, TMA 2 |

AKI: Acute kidney injury; ATI: Acute tubular injury; Azi: Azithromycin; CKD: Chronic kidney disease; FSGS: Focal and segmental glomerulosclerosis; HCQ: Hydroxychloroquine; HTN: Hypertension; IgA: Immunoglobulin A; IL-6: Interleukin-6; PIGN: Post infectious glomerulonephritis; RRT: Renal replacement therapy; TMA: Thrombotic microangiopathy.

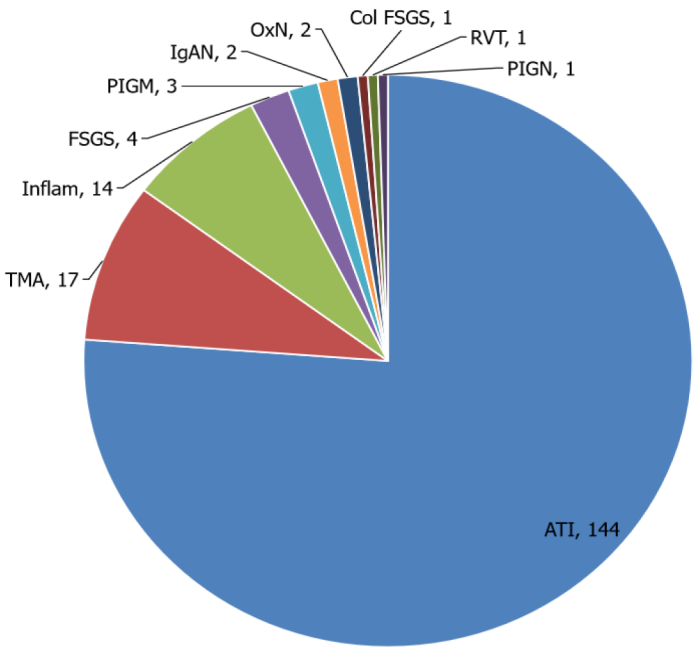


**Figure 5 Postmortem kidney biopsy histopathological features reported in association with coronavirus disease 2019.**

expression[74].

Izzedine *et al*[28] argue in favor of a direct causal link between SARS-CoV-2 infection and the occurrence of CG and have suggested using the term COVIDAN (in a similar way to HIVAN for HIV associated nephropathy)[28]. Homozygosity for APOL1 risk alleles (G1/G2) confers significantly increase risk for CG[16]. This suggests kidney injury caused by SARS-CoV-2 is likely to manifest in different ways in different individuals depending on genetic risk (for example CG or direct viral mediated ATI).

ATI is another frequently reported pathological finding in the kidney biopsies described in this review. It most frequently causes frank epithelial necrosis with cellular debris in the tubular lumen[75]. Unsurprisingly, the hemodynamic compromise associated with COVID-19 related sepsis syndrome is thought to be the primary contributing factor to the development of ATI. ATI has also been reported to manifest through direct invasion of SARS-CoV-2 particles in renal tubular epithelium and podocytes *via* the angiotensin-converting enzyme 2 (ACE2) inhibitor pathway, causing AKI[12]. Intrarenal injury through the ACE2 pathway leads to mitochondrial dysfunction and progresses to acute tubular necrosis[12]. It should be recognized that biopsy findings of ATI are common even when there are other intrarenal pathologies, given the effects of SARS-CoV-2 particles on direct tubular injury.

A hypercoagulable state has been observed involving various organ complications in patients with COVID-19, of which there were several presentations of TMA. However, whether TMA is directly caused by COVID-19 in the majority of published cases remains uncertain. Many of the patients described have multiple co-morbidities, increasing their risk of coagulopathy. Increasing evidence supports the role of COVID-19 in contributing to procoagulatory interactions with the endothelial system[76]. TMA occurs where endothelial dysfunction and destruction is caused by pathological stimulation of immune cells, which leads to activation of the micro-thrombotic pathway and complement activity[75].

There have been reports of anti-GBM disease in patients with COVID-19. It has been hypothesized that respiratory insults from COVID-19 may expose the cryptic target of the Goodpasture antigen, leading to widespread pulmonary injury in the alveolar capillary membranes and glomerular basement membrane injury seen in anti-GBM nephritis[13,37]. However, coincidental associations remain a distinct possibility.

As with the other histopathologies described in COVID-19-associated kidney biopsies, vasculitis often presents with AKI. The pathophysiological mechanism of vasculitis induced by the SARS-CoV-2 virus remains elusive due to the scarce number of available kidney biopsies, though AKI within this context is believed to have been caused by glomerular hypoperfusion and tubular necrosis leading to fibrinoid necrosis in the arterial wall of small intrarenal vessels[38,39,77]. Neutrophil extracellular trap

(NET) formation is well known to be part of the innate inflammatory process of SARS-CoV-2 infection. The inflammatory state of SARS-CoV-2 may in turn affect immunotolerance and lead to ANCA antibody formation. It is postulated that NET formation could be the source of presentation of MPO or PR3 antigen[34]. There is also the possibility that vasculitis in association with COVID-19 is a co-incidental finding, given the tens of millions of people who have acquired COVID-19.

Toxic nephropathies such as oxalate and pigment nephropathy have surprisingly had multiple descriptions in patients with COVID-19 disease (given the relative rarity of these presentations in non-COVID-19 disease). The mechanisms for how SARS-CoV-2 infection directly causes these conditions are unclear, and the authors of the original reports attribute these cases to their conventional pathophysiology[13,14,27,40].

Other forms of GN associated with COVID-19 are mainly reported as individual cases at present and will require further corroboratory reports to help establish if there is indeed an association with COVID-19 and to explain what the pathophysiological mechanism may be.

The findings from post-mortem biopsies are consistent with live patient biopsy reports in that there is a wide range of histopathological processes observed in patients with COVID-19. Whilst ATI was seen in all post-mortem series, there were also a number of other pathologies observed. This provides additional support to the hypothesis that a kidney biopsy should be considered in more patients with COVID-19 associated AKI.

As this review draws on case reports and case series, we have been limited in only being able to perform a qualitative analysis. In addition, whilst this data provides useful insights, we must remember that the vast majority of patients with AKI do not undergo a kidney biopsy and so there may be inherent selection bias in those cases presented here. Furthermore, there was significant autolysis observed in the post-mortem series resulting in a lot of the data being excluded from analysis.

It is also likely that some of the rarer glomerulonephritidies, such as lupus nephritis and ANCA associated vasculitis, are coincidental and simply occur concomitantly with COVID-19 infection rather than as a direct consequence of it.

Nevertheless, we believe this provides an up-to-date, substantial insight into the underlying renal histopathological processes occurring in patients with COVID-19, given the number and range of case reports and series[78,79]. This has clinical relevance as for many of these conditions the AKI may not recover with standard management. As such, clinicians should pay careful attention to features of GN, and ensure that patients are followed up in the outpatient setting. In view of the significant number of histopathological findings reported in association with COVID-19 infection, we would recommend an early kidney biopsy where appropriate (*e.g.* unresolved AKI, proteinuria, positive immunology tests) at the safest possible time which can guide the management approach.

## CONCLUSION

This review summarizes 59 published case reports and series which describe the histopathology of native, transplant and post-mortem kidney biopsies in patients with COVID-19. In addition to expected ATI, there were many other histopathological processes observed in association with COVID-19, with CG being prominent. There was significant variation in ethnicity, presentation creatinine and proteinuria, requirement for RRT and outcomes. This suggests that COVID-19 may cause multiple different effects in the kidney. Whilst the underlying pathological processes of ATI and CG resulting from COVID-19 can be hypothesized based on our current understanding of kidney disease, further work is required to determine what, if any, is the link between COVID-19 and some of the other processes described. It is a distinct possibility that many of the rarer glomerulopathies occurred coincidentally with COVID-19 infection. The need for kidney biopsy should be carefully considered in patients presenting with COVID-19 and kidney disease.

## ARTICLE HIGHLIGHTS

### *Research background*

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can result in clinically

significant multi-system disease, including involvement in the kidney. A wide range of histopathological findings have been reported in kidney biopsies in association with coronavirus disease 2019 (COVID-19) infection.

### Research motivation

Renal dysfunction in COVID-19 infection is reported in association with multiple pathologies. However, the mechanism behind these pathologies is not well understood.

### Research objectives

This systematic review was conducted to provide an overview of the current literature on the renal histopathological features and mechanistic insights described in association with COVID-19 infection.

### Research methods

A systematic review was performed by conducting a literature search in the following websites-'PubMed', 'Web of Science', 'Embase' and 'Medline-ProQuest' with the following search terms- "COVID-19 AND kidney biopsy", "COVID-19 AND renal biopsy", "SARS-CoV-2 AND kidney biopsy" and "SARS-CoV-2 AND renal biopsy". Data on presentation, histological features, management and outcome was extracted from the reported studies.

### Research results

Our review identified a total of 59 studies reporting COVID-19 related histopathological diagnoses from kidney biopsy. Of these 59 studies, 30 reported on native kidney biopsies, nine reported on transplant biopsies, three reported on a mixture of native and transplant kidney biopsies and 17 reported on postmortem kidney biopsies. In total, there were 84 native biopsies, 15 transplant biopsies, and 189 postmortem biopsies. Many histopathological features were described, including acute tubular injury (ATI), collapsing focal segmental glomerular sclerosis, thrombotic microangiopathy and vasculitis.

### Research conclusions

Many other histopathological processes were observed in association with COVID-19 in addition to the expected ATI, highlighting the need for an early kidney biopsy.

### Research perspectives

Whilst the underlying pathological processes of a few conditions developing due to COVID-19 infection can be hypothesized based on our current understanding of kidney disease, further work is required to determine what, if any, is the link between COVID-19 and some of the other processes described.

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