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Growing challenge of post-liver transplantation non-alcoholic fatty liver disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is one of the leading causes of chronic liver disease, cirrhosis, and hepatocellular carcinoma worldwide, with an estimated prevalence of 25%. Post-liver transplantation (LT) recurrent or *de novo* hepatic steatosis is a common complication in recipients, irrespective of transplantation indication. Risk factors for graft steatosis mainly include obesity, immunosuppression, donor steatosis, and genetic factors. Liver transplant recipients are at high risk of developing insulin resistance, new-onset diabetes, and post-transplantation metabolic syndrome that is highly associated with immunosuppressive treatment. Post-LT NAFLD is often underdiagnosed due to the poor sensitivity of most routine imaging methods. The gold standard for the diagnosis of hepatic steatosis is liver biopsy, which is, however, limited to more complex cases due to its invasive nature. There is no approved pharmacotherapy in NAFLD. Lifestyle modification remains the cornerstone in NAFLD treatment. Other treatment strategies in post-LT NAFLD include lifestyle modifications, pharmacotherapy, bariatric surgery, and tailored immunosuppression. However, these approaches originate from recommendations in the general population, as there is scarce data regarding the safety and efficacy of current management strategies for NAFLD in liver transplant patients. Future prospective studies are required to achieve tailored treatment for these patients.

Key Words: Non-alcoholic fatty liver disease; Steatohepatitis; Hepatic steatosis; Liver transplantation; Cirrhosis; Metabolic syndrome

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Core Tip: Non-alcoholic fatty liver disease (NAFLD) is a common complication in liver transplant recipients. Despite the rising prevalence and potentially progressive nature of this entity, there are currently no recommendations regarding NAFLD diagnosis and management in the post-transplant setting. Future studies are urgently needed to fill this knowledge gap and define optimal diagnostic and treatment approaches in this patient population.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is characterized by the presence of steatosis in at least 5% of hepatocytes in the absence of any secondary causes, such as excessive alcohol consumption or other chronic liver diseases[1]. NAFLD encompasses a wide spectrum of histological findings, ranging from simple steatosis (non-alcoholic fatty liver, NAFL) to non-alcoholic steatohepatitis (NASH), the latter of which is additionally characterized by lobular inflammation and hepatocyte ballooning[2]. NAFL is generally considered a slowly progressive or non-progressive condition, while NASH is associated with an increased risk of disease progression to cirrhosis and hepatocellular carcinoma[3].

EPIDEMIOLOGY

NAFLD has become the leading cause of chronic liver disease worldwide, with an estimated prevalence of 25%, which is constantly rising in parallel to the worldwide obesity pandemic[4]. NAFLD is often considered the hepatic component of the metabolic syndrome and is associated with other metabolic disorders, such as obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and insulin resistance (IR)[5]. Due to the increasing prevalence and high risk of progression, NASH has become the second most common indication for liver transplantation (LT) in the United States, reporting a 170% increase from 2004 to 2013[6,7]. LT leads to the resolution of NASH-related complications; however, the underlying metabolic risk factors remain, and are even exacerbated following LT, resulting in a high rate of post-LT NAFLD recurrence[8]. In addition, many recipients are prone to develop a post-LT metabolic syndrome (PTMS), mainly due to the reversal of the cirrhosis-related catabolic state and immunosuppression side effects, leading to *de novo* NAFLD[9].

Recurrent NAFLD

Recurrence of steatosis and steatohepatitis in recipients with a pre-transplant diagnosis of NASH is more common compared to *de novo* NAFLD, with a prevalence ranging between 8% and 100% in a follow-up period of 1-10 years[10]. Yalamanchili *et al*[11] studied 257 patients transplanted for NASH or cryptogenic cirrhosis. Post-LT steatosis was reported in 31% of patients; however, bridging fibrosis or cirrhosis was only found in 5% and 10% of recipients after 5 years and 10 years, respectively[11]. In a recent retrospective study of 275 NASH recipients, the prevalence of NAFLD and NASH recurrence was 22% and 11%, respectively[12]. However, it should be underlined that most studies have important heterogeneity regarding NAFLD diagnosis and patient selection. Recipients with cryptogenic cirrhosis as an indication for LT were included in most of these studies, resulting in a possible NAFLD recurrence overdiagnosis[11,13,14].

De novo NAFLD

De novo NAFLD is defined as the presence of steatosis or steatohepatitis in patients who underwent LT for indications other than NASH[15]. Up to one-third of liver transplant recipients develop *de novo* NAFLD depending on a combination of host and graft factors[16,17]. Dumortier *et al*[16] studied 599 non-NASH liver transplant recipients and reported a prevalence of *de novo* NAFLD of 31%[16]. The authors demonstrated several independent risk factors for the occurrence of post-LT *de novo* steatosis, such as post-LT obesity, tacrolimus-based immunosuppression therapy, diabetes mellitus, and pre-transplant liver graft steatosis, demonstrating a dose-dependent relationship between the number of these risk factors and the risk of developing *de novo* NAFLD. In a recent meta-analysis by Losurdo *et al* [15] the pooled prevalence of *de novo* NAFLD and NASH was 26% and 2%, respectively, at a follow-up period of 6 mo to 10 years[15]. The highest prevalences were observed in patients transplanted for either alcoholic (37%) or cryptogenic cirrhosis (35%), or those receiving tacrolimus (26%). Data remain,

however, scarce regarding these entities, while the retrospective design and small sample size of most studies represent important limitations.

RISK FACTORS

Several risk factors have been associated with post-LT NAFLD occurrence (Table 1). As mentioned above, the pre-transplant metabolic risk factors persist following LT, despite the resolution of liver disease. In addition, the commonly used maintenance immunosuppressive regimens, namely corticosteroids, calcineurin inhibitors (CNIs), and mammalian targets of rapamycin (mTOR) inhibitors are directly linked to obesity, hypertension, dyslipidemia, and hyperglycemia, exacerbating the existing metabolic profile of transplanted patients or leading to a new-onset PTMS. Recipients are at high risk of developing PTMS, irrespective of LT indication, with an estimated prevalence ranging from 44%-58% at 6 mo following LT[17]. The presence of PTMS has been associated with both recurrent and *de novo* NAFLD[16,18,19]. Pre-transplant graft-steatosis, genetics, and other recipient-related risk factors appear to contribute to the development of both recurrent and *de novo* NAFLD in the transplanted population [20]. In a recent observational study of 108 recipients, it was concluded that recipient-related factors are more important than donor-related factors in the development of NAFLD, following LT[21].

Genetic factors

Several studies have attempted to reveal the role of genetic predisposition in the development of post-LT NAFLD. Both recipient and donor genetics have been associated with an increased risk of graft steatosis. The role of patatin-like phospholipase domain-containing protein 3 (PNPLA3) in the development of NAFLD is well established. Finkenshtedt *et al*[22] showed that LT recipients who carry rs738409-GG in PNPLA3 are at increased risk of post-LT NAFLD[22]. In another study of 176 liver transplant patients, Trunečka *et al*[23] demonstrated that the expression of PNPLA3 p.148M variant in donors represents an independent risk factor for graft steatosis[23]. The donor transmembrane 6 superfamily member 2 c.499A allele was also associated with a higher risk of steatosis in recipients[24]. John *et al*[25] found that recipient, but not donor, adiponectin polymorphisms rs1501299 G/G and rs17300539 G/G were related to a higher prevalence of post-LT graft steatosis[25].

Immunosuppression

The maintenance immunosuppressive agents used after LT can exacerbate a preexisting metabolic syndrome in recipients, or lead to a new-onset PTMS, thereby contributing to the development of recurrent and *de novo* NAFLD[26]. Corticosteroids are widely used in the immediate post-operative period against allograft rejection. They increase the hepatic output of glucose and decrease insulin production and peripheral glucose uptake, inducing IR. Corticosteroid use has been associated with an increased risk of T2DM, dyslipidemia, hypertension, and rapid weight gain in recipients following LT [27]. CNI therapy (cyclosporine and tacrolimus) is also recognized as a risk factor for metabolic syndrome and consequent post-LT NAFLD. They are linked to hypertension, dyslipidemia, new-onset T2DM, and chronic renal disease, with tacrolimus having a more prominent diabetogenic effect compared to cyclosporine, which is mainly associated with post-transplant hypertension[26,28,29]. However, studies investigating the direct association between CNI therapy and post-LT NAFLD seem to provide conflicting results[16,30,31]. Another commonly used class of immunosuppressive drugs, mTOR inhibitors, appear to have metabolic adverse effects, being associated with significant dyslipidemia and IR[26]. Sirolimus increases adipose tissue lipase activity and decreases lipoprotein lipase activity, resulting in hypertriglyceridemia, especially with concomitant cyclosporine therapy[32,33]. In a retrospective study of 430 post-LT biopsies, Galvin *et al*[31] reported that sirolimus use was predictive of *de novo* NAFLD following LT[31].

Donor graft steatosis

Donor steatosis has also been suggested as a potential risk factor for post-LT *de novo* and recurrent NAFLD. While microvesicular steatosis does not affect graft function or survival, donor livers with severe macrovesicular steatosis have been associated with an increased risk of primary graft dysfunction, inferior graft survival, and requirement for retransplantation[34]. However, there is not enough evidence to support the predictive role of donor steatosis in the development of post-LT NAFLD. Three studies have indicated an association between pre-existing donor graft steatosis and post-LT NAFLD, whereas findings in a meta-analysis by Saeed *et al*[35] did not support this association [16,35-37].

Pre-transplant liver disease

Aside from NASH, specific other LT indications have been associated with an increased risk of *de novo* NAFLD. Recipients with a pre-transplant diagnosis of alcoholic liver disease (ALD) are at higher risk of developing *de novo* post-LT steatosis[16,30]. Hepatitis C virus infection was also reported as a risk factor for post-LT NAFLD[31,38]. In a meta-analysis by Losurdo *et al*[15], the authors reported the highest

Table 1 Risk factors associated with post-transplantation non-alcoholic fatty liver disease

Recipient factors	Donor factors
Obesity/post-LT weight gain	Macrovesicular graft steatosis
T2DM	Genetics
Dyslipidemia	
Genetics	
Immunosuppression	
LT indication: NASH, HCV, ALD	

ALD: Alcoholic liver disease; HCV: Hepatitis C virus; LT: Liver transplantation; NASH: Non-alcoholic steatohepatitis; T2DM: Type 2 diabetes mellitus.

prevalence of *de novo* NAFLD in patients that underwent an LT for ALD and cryptogenic cirrhosis (37% and 35%, respectively)[15].

PROGNOSIS

Despite the high prevalence of recurrent and *de novo* NAFLD following LT, progression to NASH and advanced fibrosis is less frequent in these patients. Dumortier *et al*[16] reported recurrent steatosis in 31% of recipients; however, NASH and advanced fibrosis/cirrhosis were only observed in 3.8% and 2.25% of patients[16]. Yalamanchili *et al*[11] confirmed these findings, reporting similarly low incidence rates of NASH and cirrhosis in patients with post-LT NAFLD (4% and 10%, respectively)[11]. However, in the meta-analysis by Saeed *et al*[35], the authors reported significantly higher rates of recurrent and *de novo* NASH (38% and 17%, respectively)[35]. Overall survival of patients transplanted for NASH-related cirrhosis is comparable to those with non-NASH indications in most studies[39–41]. In a recent retrospective analysis of 68950 patients that underwent LT for end-stage liver disease of various indications, Halder *et al*[42] confirmed the aforementioned findings and demonstrated a patient survival at 1, 5, and 10 years post-LT of 84.1%, 73.4%, and 62.1%, respectively, for NASH patients that underwent LT[42]. Overall graft survival was also reported similar between NASH recipients *vs* those with non-NASH LT indications. Mortality in patients transplanted for NASH was mainly attributed to cardio/cerebrovascular disease and infection rather than liver-related complications. However, the true impact of recurrent or *de novo* NAFLD on overall and graft survival has not been largely investigated. Dureja *et al*[43] studied 88 liver transplant recipients and found no difference in post-LT survival between patients with NAFLD recurrence and those without in a follow-up period of 5 years[43]. More relevant studies with longer follow-up time are necessary to clarify whether post-LT NAFLD *per se* is associated with increased mortality in the post-transplant setting.

MANAGEMENT

There are scarce data regarding the treatment of NAFLD in liver transplant patients. Main treatment strategies include lifestyle modifications, pharmacotherapy, bariatric surgery, and alteration in immunosuppression therapy[44]. The first approach in the management of post-LT NAFLD is lifestyle modification including adequate physical activity, weight loss, and calorie restriction. No drugs have been approved for the treatment of NAFLD and none of the proposed pharmacotherapies has been studied in the post-transplant population. In the latest American Association for the Study of Liver Diseases and European Association for the Study of the Liver guidelines, pioglitazone, and vitamin E, either as monotherapy or as combination therapy, have been proposed as a potential treatment approach in biopsy-proven NASH patients[45]. However, there are concerns about the safety of long-term use of vitamin E, as it has been associated with an increased risk of prostate cancer and hemorrhagic stroke[46,47]. Pioglitazone has been associated with weight gain and should be, therefore, cautiously recommended in transplanted patients, for fear of exacerbating post-LT obesity and PTMS [48]. Bariatric surgery is recommended in cases where obese patients cannot achieve weight reduction following LT; however, there are concerns regarding the potential malabsorption and altered pharmacokinetics of immunosuppressive drugs[49,50]. Optimization of immunosuppression is of vital importance to reduce drug-induced metabolic risks and subsequent NAFLD in the post-LT period. Early steroid withdrawal, minimization, and alterations of immunosuppressive regimens based on patient's metabolic complications are common approaches in the management of PTMS. More specifically, in cases where hypertension is the major metabolic complication, conversion from

cyclosporine to tacrolimus has been shown to have a beneficial effect on blood pressure[51]. Similarly, reducing tacrolimus dosage or switching to another immunosuppression regimen has been associated with better glycemic control in recipients with new-onset T2DM[52]. mTOR inhibitors, on the other hand, should be avoided in cases of severe uncontrolled dyslipidemia[32,33].

CONCLUSION

Post-LT NAFLD remains a great challenge for hepatologists and transplant surgeons. Early detection of modifiable risk factors plays a crucial role in preventing disease occurrence. There is an unmet need for specific recommendations regarding both NAFLD screening and management in the post-transplant setting. Post-LT diagnosis tends to be underdiagnosed due to poor sensitivity of routine imaging modalities, whereas liver biopsy is not routinely used for NAFLD diagnosis, due to its invasive nature and possible complications. Regarding disease management, while numerous studies have investigated potential treatment approaches for NAFLD in non-transplant patients, there are scarce data on liver-transplant recipients, with most treatment strategies being extrapolated from recommendations in the general population. However, certain limitations in transplanted patients, such as reduced physical activity, immunosuppressive therapy, and drug-drug interactions with NAFLD treatment regimens, as well as treatment dilemmas regarding minimization or alteration of immunosuppression therapy in the setting of PTMS remain major problems for hepatologists. Prospective, longitudinal studies in liver transplant recipients are necessary to optimize screening, disease monitoring, and treatment in this special patient population.

FOOTNOTES

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Liver transplantation during COVID-19: Adaptive measures with future significance

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Abstract

Following the outbreak of coronavirus disease 2019 (COVID-19), a disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the field of liver transplantation, along with many other aspects of healthcare, underwent drastic changes. Despite an initial increase in waitlist mortality and a decrease in both living and deceased donor liver transplantation rates, through the implementation of a series of new measures, the transplant community was able to recover by the summer of 2020. Changes in waitlist prioritization, the gradual implementation of telehealth, and immunosuppressive regimen alterations amidst concerns regarding more severe disease in immunocompromised patients, were among the changes implemented in an attempt by the transplant community to adapt to the pandemic. More recently, with the advent of the Pfizer BNT162b2 vaccine, a powerful new preventative tool against infection, the pandemic is slowly beginning to subside. The pandemic has certainly brought transplant centers around the world to their limits. Despite the unspeakable tragedy, COVID-19 constitutes a valuable lesson for health systems to be more prepared for potential future health crises and for life-saving transplantation not to fall behind.

Key Words: Liver transplantation; COVID-19; SARS-CoV-2; Vaccine; Immunosuppression; Telehealth

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Core Tip: Several articles in the bibliography report on the state of liver transplantation during coronavirus disease 2019 (COVID-19). To our knowledge, this is the first review to retrospectively investigate the various changes that occurred throughout the pandemic, but also recognize which interventions, and to what extent, are possibly going to help the transplant community improve beyond the end of COVID-19; in the event of a major health crisis in the future, transplant programs should be able to adapt even faster to the rapidly changing landscape, in order for life-saving transplantation not to fall behind.

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INTRODUCTION

Since December 2019, the coronavirus disease 2019 (COVID-19) pandemic has changed the landscape for transplant programs across the United States[1]. Although helpful, the experience gained from previous outbreaks, like the middle eastern respiratory syndrome coronavirus, could not quite compare to the full-scale pandemic of the last two years. Therefore, transplant programs were largely unprepared for the challenges of the current pandemic, as evidenced by the complex moral decision of temporarily holding life-saving transplantation for fear of COVID-19 transmission amongst immunocompromised patients, the healthcare personnel, and the community[2]. Despite primarily being a respiratory pathogen, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) impacts liver biochemistry and many other organs[3,4]. The S protein on the surface of SARS-CoV-2 binds the angiotensin-converting enzyme 2 receptor on the surface of hepatocytes, injecting its viral genome inside liver cells [5]. Aside from its direct cytotoxic effect, SARS-CoV-2 may adversely affect the liver through its systemic inflammatory response and, indirectly, through many potentially hepatotoxic medications employed to combat COVID-19[6]. At the same time, the effect of COVID-19 on cirrhotic patients can be especially severe due to their baseline immunosuppression in the setting of chronic liver disease[7]. However, it is not uncommon for SARS-CoV-2 to cause only mild elevations in hepatic enzymes, with patients otherwise remaining asymptomatic, either due to the virus' minor hepatotoxicity or through COVID-19-related inflammation of the muscles, with little direct injury to the liver[8].

Because of the significant health risks the new coronavirus poses to patients with chronic liver disease and liver transplant recipients, the transplant community had to adapt to the pandemic. In the spring of 2020, and in the states most severely affected by COVID-19, new listings were 11% lower than anticipated, there were 59% more deaths in patients waiting for a transplant than expected, and 34% fewer deceased donor liver transplantations. Fear of transmission amongst patients and healthcare workers has led to a series of new measures, such as regular testing, mandatory protective equipment against the virus, and telehealth to replace in-person visits during the pandemic[9]. At the same time, the race to develop new vaccines against SARS-CoV-2 has given hope that the end of the pandemic is slowly approaching. COVID-19 accelerated the implementation of measures already in motion in the transplant community, albeit at a slower pace.

This review aims to retrospectively evaluate the status of liver transplantation during the pandemic, the effectiveness of multiple vaccine doses in liver transplant recipients, the recent change in the waitlist prioritization policy, potential alterations in immunosuppressive regimens for COVID-19 positive recipients, and explore the benefits and drawbacks of telehealth during and after the pandemic.

LIVER TRANSPLANTATION IN THE COVID-19 ERA

As the pandemic is slowly getting better controlled, the scientific community has a chance to evaluate how COVID-19 has affected liver transplantation programs during this unforeseen worldwide health crisis by tracing changes regarding vaccination protocols, waitlist prioritization, immunosuppression regimens, and the implementation of telehealth. These adaptive mechanisms may prove to be an invaluable lesson in the face of future health threats so that the rate of liver transplants will not descend again.

A query of the United Network for Organ Sharing database showed that, throughout the pandemic, whenever the number of new coronavirus cases peaked, primarily during the winter months, the number of transplants showed a concurrent decrease (Figure 1). In early 2020, from mid-March to mid-April, in states most severely affected by COVID-19, there were 11% fewer new listings, 49% fewer living donor transplantations, 9% fewer deceased donor liver transplantations, and 59% more deaths while waiting for a transplant than anticipated[10]. Despite every successive COVID-19 wave inherently

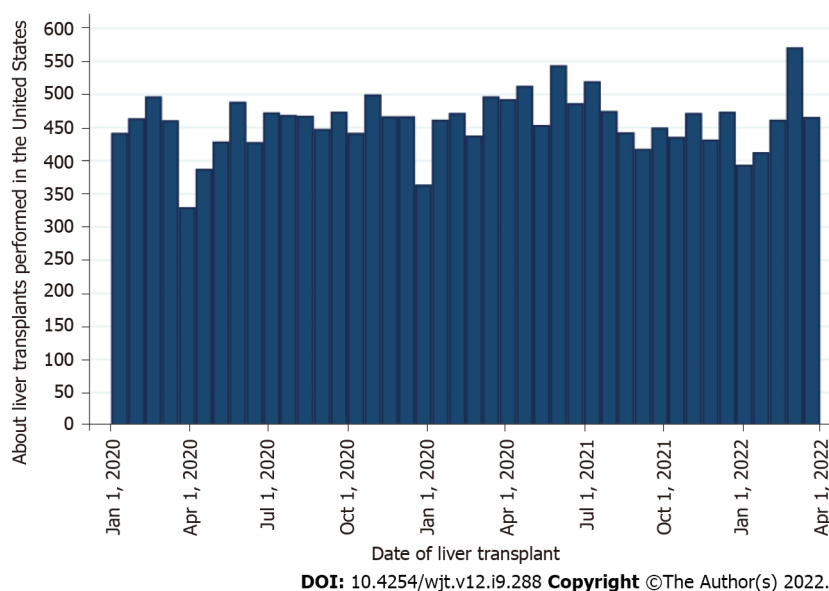


Figure 1 Number of adult liver transplants performed in the United States between January 1, 2020, and April 1, 2022 (data from the United Network for Organ Sharing database). The number of liver transplants performed during the course of the coronavirus disease 2019 pandemic. An initial decrease in the Spring of 2020 was countered with a series of measures, that restored the number of transplants by the Summer of 2020. With each consecutive wave, primarily during the winter months, there were fewer adult liver transplants.

carrying different epidemiologic outcomes than those of the first wave, transplant programs seemed to adapt to the changing landscape, as by August of the same year, except for deceased donor liver transplants, rates were within the expected range[11]. The increased waitlist mortality, particularly during the first few months of 2020, can be explained by a multitude of factors, including deaths from end-stage liver disease while waiting for transplantation, the inability to admit patients facing complications of chronic liver disease, and the particularly severe impact of SARS-CoV-2 on obese patients with concurrent non-alcoholic steatohepatitis listed for transplantation[12]. While SARS-CoV-2 has a direct toxic effect on the liver, the extent to which it can affect patients with chronic liver disease has not been definitively established; only mild elevations in liver enzymes are known to occur, with patients remaining otherwise asymptomatic[13,14].

Observing how the transplant community managed to adapt relatively quickly by the summer of 2020, following a brief period of increased waitlist mortality and decreased living and deceased liver transplantation rates during the spring of 2020, it would be of great interest to investigate how the new liver transplant allocation policy change influenced that result. In December 2018, United Network for Organ Sharing approved a new allocation policy called the “acuity circle policy”, eventually implemented on February 4, 2020, coinciding with the beginning of the COVID-19 pandemic in late 2019 [15]. The new model would replace the “donation service area” distribution system, whereby one area was served by only one specific organ procurement organization. Under the new policy, the distance between donor and recipient was the primary determinant of organ allocation. Inevitably, states with lower COVID-19 incidence, where transplant centers were still active, received a larger volume of transplant patients from other, more heavily infested areas.

However, it is difficult to know the degree to which the changes that occurred after the acuity circle allocation policy resulted from the implementation of the new model or the concurrent outbreak of the coronavirus pandemic shifting the landscape for liver transplant allocation across the United States. By some preliminary estimates, under the new allocation system, adult patients with lower model for end-stage liver disease (MELD) scores have received fewer transplants, while at high MELDs, transplantation rates were actually increased[10]. According to Radhakrishnan and Goldberg, the new allocation policy has led to delays in procurement times due to the logistics involving procurement team travel, the challenges in working with new centers, and the increased number of possible local recipients [16]. On the other hand, pediatric liver transplant recipients, median MELD/pediatric end-stage liver disease scores decreased under the new system, indicating that they were now receiving transplants earlier, thus avoiding the life-threatening risk of being diagnosed with late-stage disease by the time of transplantation[17]. As the acuity circle allocation policy is relatively new, future studies may retrospectively prove its value during the outbreak of COVID-19 and may even display its usefulness after accounting for the drastic changes brought on by the pandemic. Regardless, seeing how the transplant community was able to adapt during the current pandemic, the acuity circle policy may prove to be a valuable tool, guiding efforts to improve waitlist mortality and deceased and living donor transplantation rates in the face of potential health crises in the future[9,13].

IMMUNOSUPPRESSION AND COVID-19 IN LIVER TRANSPLANT RECIPIENTS

At the beginning of the pandemic, it was postulated that the use of immunosuppressive regimens in liver transplant recipients would predispose them to a higher risk for severe disease following COVID-19 infection. In a study of 39 solid organ transplant recipients, reported mortality following COVID-19 was 37.5% in the liver group[18]. Despite the limited number of patients, mortality was significantly higher in immunosuppressed patients than in other studies. In a nationwide Korean study by Baek *et al* [19] that included a total of 6435, both immune-competent and immunocompromised subjects, mortality in the immunocompromised group was 9.6% - including patients who had undergone transplantation in the last three years, were taking steroids or other immunosuppressants, were diagnosed with human immunodeficiency virus/acquired immunodeficiency syndrome or had a known malignancy[19]. The potential risk of post-transplant immunosuppression regimens contributing to a more severe clinical course in SARS-CoV-2 infected patients had to be balanced against the inevitable risk of rejection following reduction of the treatment. An individualized approach to immunosuppressive regimen alteration in the setting of COVID-19 was stressed by Giannis *et al*[20], whereby not all transplant recipients, and certainly not all COVID-19 positive patients, are the same; in other words, COVID-19 complicated the already individualized approach to transplant regimen selection and therapeutic-range dose regulation even further[20]. An Iranian study recruiting 265 liver transplant recipients with a median time since transplantation of 68 mo identified 25 patients who contracted COVID-19, four of whom eventually died. For fear of organ rejection, the patients' immunosuppressive regimens were only slightly modified, with mycophenolate mofetil (MMF) dose being reduced to limit liver enzyme level elevation. While previous studies have argued in favor of lowering immunosuppression during COVID-19, Sheikhalipour *et al*[21], among others, have shown that despite minimal alterations in the patients' immunosuppressive regimen, most participants fully recovered from COVID-19[22]. Ethical considerations regarding the risk of acute rejection following a significant reduction in the immunosuppressive regimen make randomized control trials investigating the role of immunosuppression discontinuation or decrease in the setting of COVID-19 inherently challenging.

The choice of immunosuppression has proven to variably affect postoperative mortality for coronavirus-positive liver transplant recipients. Tovikkai *et al*[23] conducted a large retrospective study including 3837 liver transplant recipients from the United Kingdom. They showed cardiovascular disease and non-hepatic malignancy amongst transplant recipients were the primary determinants of mortality within 10 years after transplantation[23]. Interestingly, in a study by Becchetti *et al*[24], coronavirus-positive liver transplant recipients did not necessarily have worse outcomes than other solid transplant recipients, while only active extra-hepatic cancer was associated with increased mortality from SARS-CoV-2 infection, but cardiovascular disease did not predispose to a worse outcome. Immunosuppression was reduced in 39% of patients and discontinued in 7% - primarily in patients taking MMF[24]. Importantly, patients who did not require hospitalization due to COVID-19-related complications had no change in their immunosuppressive regimen, arguing that maintaining the immunosuppressant dose stable may not negatively impact outcomes in liver transplant recipients infected with SARS-CoV-2[20]. Colmenero *et al*[25] conducted a cohort study including 111 liver transplant recipients who tested positive for COVID-19, whom they followed for 23 d. Out of the 96 patients requiring admission, there was an 18% mortality rate, which was actually lower than that of the general population (28% and 42% in patients requiring high-dependency unit and intensive care unit admission, respectively), pointing towards a potential anti-viral effect of immunosuppressive therapy, with the exception of MMF[26]. Although immunosuppressive regimen modification is a complex decision, one to be made by the transplant center regarding each individual patient, MMF has been associated with increased rates of severe COVID-19 at doses greater than 1000 mg per day, perhaps explained by the peripheral CD4⁺ depleting effect of MMF acting in synergy with the cytotoxic T-cell effect of SARS-CoV-2[25]. On the contrary, mammalian target of rapamycin inhibitors have memory T-cell boosting effects, while calcineurin inhibitors are postulated by *in vitro* studies to tone down the cytokine storm responsible for acute respiratory distress syndrome in patients with COVID-19[27,28].

COVID-19 VACCINATION IN LIVER TRANSPLANT RECIPIENTS

With the advent of the BNT162b2 vaccine, a safe and effective preventive strategy against COVID-19 was made available to transplant recipients. In a study by Hardgrave *et al*[29], amongst 103 unvaccinated liver transplant recipients, before vaccination had been made widely available, 90-d mortality was 10%, with age > 60, use of belatacept and cyclosporin being associated with an increased risk, and tacrolimus acting as a protective factor. Interestingly, comorbidities (hypertension, diabetes, obesity) were not significantly associated with high mortality rates amongst unvaccinated individuals[29]. Prior studies have demonstrated the safety and efficacy of inactivated and subunit vaccines against various pathogens in solid transplant recipients[30]. It is not unlikely, however, for immunocompromised patients to be unable to mount an adequate immune response following vaccination. Interestingly, liver transplant recipients have shown better immune response rates to SARS-CoV-2 vaccination than other

solid organ recipients. Out of the 43 liver transplant recipients who received the second dose of the BNT162b2 vaccine, 79% developed antibodies, compared to 100% of immunocompetent individuals, but their response was reportedly superior to that of other solid organ recipients in the bibliography[31]. According to the recent Global Hepatology Society Statement and the European Association for the Study of the Liver, liver transplant recipients are strongly encouraged to get vaccinated with any approved COVID-19 vaccine, as the benefits outweigh the risks of SARS-CoV-2 infection[32-34].

The BNT162b2 vaccine is an mRNA vaccine that has proven to be safe, albeit with low immunogenicity, particularly following its second dose, in specific categories of liver transplant patients[35]. In a group of 107 patients, just 76% achieved immunity six months following their second vaccine. However, after receiving their third dose, 91% of patients had sufficient antibody titers against SARS-CoV-2[36]. Various factors have been reported to affect the degree of immunogenicity following vaccination in liver transplant patients (Figure 2). Combined immunosuppression with a calcineurin inhibitor and another agent, either MMF, steroids, or mammalian target of rapamycin inhibitors (double or triple regimen), were risk factors for a reduced immune response after the second dose of the BNT162b2 vaccine[37,38]. Renal impairment was also associated with lower vaccine responses following the second dose, with a mean estimated glomerular filtration rate of 56 mL/min amongst patients who were unable to mount an adequate immune response *vs* 75 mL/min amongst patients who had a positive immunoglobulin G spike[35]. Interestingly, renal toxicity is one of the key side effects of calcineurin inhibitors - the predominant immune suppressive agents used post-transplantation, which have even been shown to harbor a protective effect against severe COVID-19 disease[39]. Older age is another significant risk factor for lower immunogenicity, with one study showing a mean age of 63 years in liver transplant recipients with a negative immune response, compared to 58 years in positive vaccine responders[35]. Furthermore, in a group of 365 patients, a higher body mass index (mean 27.7 in seronegative recipients *vs* 26.7 in positive vaccine responders, $P = 0.031$) and a shorter time since liver transplantation (11.9 years in seronegative recipients *vs* 14.7 years in seropositive transplant patients, $P = 0.031$) were also significant risk factors for attenuated vaccine response, according to Guarino *et al*[40]. Mazzola *et al*[41] identified diabetes as an additional risk factor for a negative response after the second dose of the SARS-CoV-2 BNT162b2 vaccine in a study that included 133 liver transplant recipients, with 46 out of 55 diabetic patients in the study group not mounting an adequate immune response following the second dose.

The variable effectiveness following each dose of the COVID-19 vaccine may reflect a different effect on T and B cell populations after every booster, with each cell type playing a different role in the immune system's defense against SARS-CoV-2. Despite the importance of humoral immunity in preventing infection following vaccination, the role of T-cell-mediated immunity has not been established[42]. Although T cells (CD4, CD8) are theoretically implicated in the defense against SARS-CoV-2, a recent study by Ruether *et al*[43] showed decreased rates of cellular immunity in liver transplant recipients following the second BNT162b2 vaccine dose[38]. On the contrary, in 74 patients treated with rituximab, only 39% of patients seroconverted, indicating that CD19⁺ B cells seem primarily responsible for the immune response generated following the second vaccine dose. Interestingly, according to Davidov *et al*[44], after receiving the third dose, 98% of patients seroconverted, compared to only 56% following the second dose. At the same time, T-cell counts increased significantly in all 12 liver transplant recipients who were evaluated[44]. A similar T-cell amplifying effect was demonstrated by Schrezenmeier *et al*[45] in a study of 25 kidney transplant recipients who had been unable to mount an adequate humoral response after their second dose. Thirty-six percent of those patients eventually generated humoral immunity, with CD4⁺ T-cell levels significantly increased in the same patients[45]. In recipients with lower humoral titers following vaccination, a T-cell response may instead protect against the virus. Fernández-Ruiz *et al*[46] demonstrated that 22% of liver transplant recipients had an adequate T-cell spike response following their third vaccine dose. The role of T-cell mediated cellular immunity against SARS-CoV-2 as a complementary or second-line defense mechanism against the virus is yet to be investigated by future studies.

TELEHEALTH IN LIVER TRANSPLANTATION

SARS-CoV-2 has had a profound effect on nearly all aspects of medicine. Liver transplant centers, among others, have had to adjust their practices to the new landscape[47]. High-volume centers were notably affected the most; the number of transplants performed had decreased initially, and the time spent on the waitlist had shortened. With approximately 15% of organs originating from coronavirus-positive donors, protocols and treatment regimens had to change. Notably, telemedicine emerged as a solution to the consecutive lockdowns and the unavoidable halt to in-person patient visits[25]. While it is not without its downsides, there is a clear consensus on the benefits telehealth can have in liver transplant programs during the pandemic. As new protocols are implemented, telehealth is proving to be an effective alternative to in-person visits even after the end of the pandemic.

Proper follow-up, along with improvements in perioperative care, surgical technique, and immunosuppression, is largely responsible for the improved outcomes in liver transplant recipients

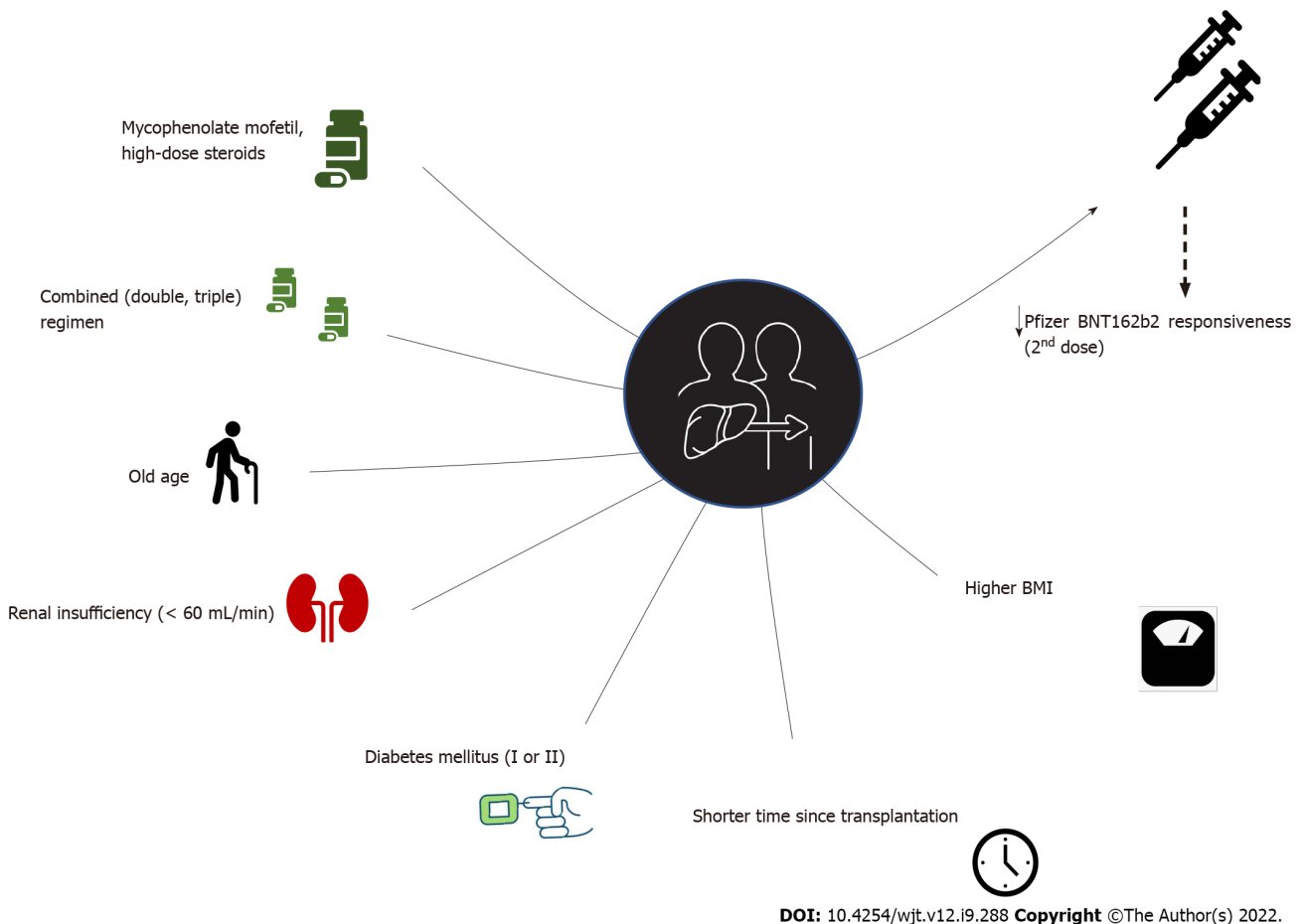


Figure 2 Factors contributing to decreased response rate following the second dose of the BNT162b2 vaccine in liver transplant recipients. BMI: Body mass index.

over the last decades[48]. Survival after transplantation is slowly approaching that of the general population, but at the same time, there is an increasing number of patients requiring postoperative follow-up. In the first five years following transplantation, major causes of mortality include cardiovascular disease and infection, while death after that time is usually attributed to malignancy, renal failure, and cardiovascular disease[49]. Therefore, the importance of regular follow-up to ensure compliance with treatment, proper imaging, and biochemical studies cannot be understated. While cooperation between primary care providers, transplantation centers, and liver clinics is crucial, especially for patients living further away from the transplant hospital, telehealth may offer another option[50].

Prior studies have demonstrated the usefulness of telehealth in heart failure and diabetic glucose regulation, exhibiting similar results to telephone follow-up and in-patient visits[51]. With regards to liver transplantation, one study showed that long-term follow-up *via* telehealth had comparable outcomes to in-person follow-up, with the only drawback of requiring stricter control over tacrolimus levels[52]. Importantly, 75% of physically stable transplant patients expressed interest in telemonitoring, with distance from the hospital being a major contributing factor. A different study by Le *et al*[53] involving a small number of matched patients followed *via* telehealth underlined the increased satisfaction from shorter wait times and complete absence of travel, with 90% of patients stating they would opt for telemedicine again. In an interesting approach toward new technologies, Levine *et al*[54] had 108 patients assigned to regular in-person follow-up, app-assisted follow-up in the form of tacrolimus level monitoring, and app-plus-smartwatch groups (mean ages 53, 52, and 50, respectively), demonstrating no significant difference in tacrolimus levels overall. Moreover, telehealth can impact multiple constituents of post-transplant patient care, from immunosuppression to lifestyle modification, as demonstrated by Barnett *et al*[55] in a group of 19 liver transplant recipients, in whom telemedicine effectively promoted adherence to dietary and exercise recommendations.

Despite all the benefits telemedicine has to offer, especially amidst a pandemic, there are undeniable downsides to its use (Table 1). One study involving 98 young adults (*i.e.*, individuals acquainted with new technologies), who had undergone liver transplantation in childhood, showed that during the COVID-19 pandemic, of the 12 patients who were followed up *via* video calls, nine had experienced rejection episodes and were using telehealth as an adjunct to in-person visits[56]. Delman *et al*[57] also

Table 1 Telehealth in liver transplantation - benefits and possible drawbacks/areas of improvement

Benefits	Drawbacks
Ease of follow-up (lack of travel)	Lack of a physical exam
Fewer costs	
Saves time	
Preferred by patients living in remote areas	
As effective as in-person follow-up (stricter drug level control may be required)	Few studies demonstrated increased readmissions associated with telehealth follow-ups[56]
Ease of access (smartphone, smartwatch apps)	Lack of access to technology (hardware)
	Institution-level
	Patient-level
Multiple aspects of postop patient care (immunosuppression, diet, exercise, <i>etc.</i>)	Communities/homes with limited internet access (software)
	Technical problems (hardware)
	Lack of a private setting in shared living environments
	Limited English proficiency, need for an interpreter
	Auditory/visual impairment, additional need for aids
	Concerns regarding adherence of younger patients

pointed out a rather concerning drawback regarding increased readmissions following telemonitoring. Despite not being statistically significant (41.9% *vs* 61.5% 30-d readmission rate in patients followed by telehealth), the exhibited difference could be partly explained by the lack of a physical exam; still, hospital length-of-stay was significantly shorter in the telemedicine group. Another possible drawback of new technologies is the relative lack of access, as not all centers and not all patients can afford newer computer systems. At the same time, the learning curve may also prove to be a challenge for healthcare professionals and patients alike, who are not acquainted with the new technologies[57]. Despite being more adept at embracing emerging technologies, young people may actually be the ones more challenged regarding adherence, therefore constantly being at risk of rejection[58]. Lower socioeconomic status may further contribute to inequalities in the use of new technologies; namely, internet access is not always available; many patients may lack an appropriately private setting for the physician-patient encounter to take place; they may have limited English proficiency, or limiting visual or hearing impairment that may hinder proper physician-patient communication[59]. Furthermore, technical problems often arise, as demonstrated by a recent randomized control trial recruiting 54 patients; only 17% of patients could attend all appointments without technical issues. Regardless, patients agreed that video appointments saved them time and money, were easier to attend, and limited the exposure of immunocompromised individuals to COVID-19 during the peak of the pandemic[60]. All in all, the ideal use of new technologies may entail their co-implementation with the classic processes (*i.e.*, outpatient visits), especially as pandemic-related restrictions are slowly being lifted, contrary to telehealth replacing in-person appointments entirely. An interesting point could be made regarding the need for general physicians “closer to home” to be more deeply involved in the care of transplant recipients, complementing the role of telehealth and perhaps aiding the transplant community to overcome certain limitations associated with its use (*i.e.*, lack of a physical exam, software and hardware-related issues, accessibility difficulties)[61].

CONCLUSION

Overall, during the last two-and-a-half years, the COVID-19 pandemic has significantly changed liver transplant programs worldwide. It is fair to say that certain changes, such as updated vaccination protocols or immunosuppressive regimen modifications, would never have happened had it not been to ameliorate the effect of COVID-19 on transplant recipients. Other changes, however, such as the reformed waitlist prioritization policy and the implementation of telehealth, were accelerated by the pandemic. It is up to the scientific community to assess the outcome of these measures now that the pandemic is slowly subsiding; what was initially viewed as a “necessary evil” by many physicians could be a unique opportunity to overcome limitations and address pitfalls in the current system. In addition to the already existing problems, such as liver donor shortage, future health crises are now becoming a pressing concern, threatening to make the work of transplant centers even more challenging

than it already is. The COVID-19 pandemic could be an invaluable lesson as, despite its terrible implications, perhaps it catalyzed significant changes in the transplant community that will help surgeons adapt in the face of significant health crises in the future.

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FOOTNOTES

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Retrospective Cohort Study

Vitamin D deficiency may predispose patients to increased risk of kidney transplant rejection

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Abstract

BACKGROUND

Vitamin D deficiency occurs in more than 80% of kidney transplant recipients. Its immunomodulatory effects can predispose transplant recipients to rejection and chronic allograft nephropathy (CAN). This study determined the association between serum 25 (OH) vitamin D, biopsy-proven allograft rejection, and CAN rates.

AIM

To determine the relationship between serum 25 (OH) vitamin D level and biopsy-proven allograft rejection and CAN rate in renal transplant recipients.

METHODS

Adult renal transplant recipients followed at the clinic between January 2013 and 2018 were included. Recipients requiring graft biopsy due to declined function, hematuria, and proteinuria were reviewed. The two groups were compared regarding collected data, including the biopsy results, immunologic parameters, vitamin D, parathyroid hormone (PTH), phosphorus, albumin levels, and graft function tests.

RESULTS

Fifty-two recipients who underwent graft biopsy met the inclusion criteria. In all,

14 recipients had a vitamin D level > 15 ng/mL (group 1) *vs* ≤ 15 ng/mL (group 2) in 38. In total, 27 patients had biopsy-proven rejection, and 19 had CAN. There was only 1 recipient with biopsy-proven rejection in group 1, whereas there were 24 patients with rejection in group 2. The rejection rate was significantly higher in group 2 than in group 1 ($P < 0.001$). Four patients were diagnosed with CAN in group 1 *vs* fifteen in group 2. There was no significant difference in the CAN rate between the two groups. PTH was higher at the time of graft biopsy ($P = 0.009$, $P = 0.022$) in group 1 with a mean of 268 pg/mL. Donor-specific antibodies were detected in 14 (56.0%) of the recipients with rejection. Vitamin D level was 9.7 ± 3.4 ng/mL in the rejection group *vs* 14.7 ± 7.2 in the non-rejection group; this difference was statistically significant ($P = 0.003$). The albumin levels were significantly lower in patients with rejection than in those without rejection ($P = 0.001$). In univariate regression analysis of risk factors affecting rejection, sex, serum vitamin D, phosphorus and albumin were found to have an impact ($P = 0.027$, $P = 0.007$, $P = 0.023$, $P = 0.008$). In multivariate regression analysis, the same factors did not affect rejection.

CONCLUSION

The serum 25 (OH) vitamin D level in kidney transplant recipients remained low. Although low serum vitamin D level emerged as a risk factor for rejection in univariate analysis, this finding was not confirmed by multivariate analysis. Prospective studies are required to determine the effect of serum vitamin D levels on allograft rejection.

Key Words: Kidney transplantation; Rejection; 25 (OH) vitamin D; Vitamin D; Chronic allograft nephropathy

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Core Tip: This study analyzed the results of 130 kidney transplant recipients. Of the 52 recipients who underwent graft biopsy and met the study inclusion criteria, 14 had a vitamin D level > 15 ng/mL *vs* ≤ 15 ng/mL in 38. Although low serum vitamin D level emerged as a risk factor for rejection in univariate analysis, this finding was not confirmed by multivariate analysis. Nonetheless, diagnostic and predictive accuracy is limited when a single test is used, and larger-scale prospective clinical studies are needed to clearly discern the effects of serum vitamin D level on the renal allograft rejection rate.

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INTRODUCTION

Kidney transplantation is the best treatment option for patients with terminal kidney failure. Successful transplantation prolongs longevity and significantly improves quality of life. In addition, following kidney transplantation, 75% of recipients return to work, and approximately 1 in 50 females can get pregnant[1]. For recipients to experience these benefits, close follow-up and optimization of modifiable risk factors are crucial. One of the modifiable risk factors is the serum vitamin D level[2].

It is known that 25 (OH) vitamin D plays a significant role in calcium and phosphate balance. Furthermore, a low vitamin D level can have deleterious effects on renal allografts[3,4]. A large prospective clinical study on kidney transplant recipients reported that a low 25 (OH) vitamin D level was associated with a reduced glomerular filtration rate (GFR) at 9 mo post-transplantation[5]. Moreover, vitamin D has a wide range of effects on the immune, renal, and cardiovascular systems[6]. The vitamin D receptor (VDR) is found in almost every immune cell including macrophages, CD4+/CD8+ T lymphocytes, and dendritic cells. VDR induces allograft tolerance by directing naive T lymphocytes to transform into T helper type 2 cells phenotypically; this process is defined as vitamin D-influenced immunomodulation[7].

The immunomodulatory features of vitamin D have been observed in autoimmune diseases such as psoriasis and rheumatoid arthritis and in experimental transplant models showing that vitamin D analogs amplified cyclosporin A's inhibitory effects on acute and chronic allograft rejection[8,9]. Likewise, vitamin D analogs inhibit adventitial inflammation and intimal hyperplasia in rat aortic allografts [10]; however, the effect of the vitamin D level on the allograft rejection and chronic allograft nephropathy (CAN) rates have not been studied in detail in kidney transplant recipients. Therefore, this study

determined the relationship between serum 25 (OH) vitamin D level and biopsy-proven allograft rejection and CAN rate in renal transplant recipients.

MATERIALS AND METHODS

Study design and population

This single-center retrospective cohort study was performed at the Health Sciences University of Turkey, Diskapi Research and Training Hospital, Department of Nephrology and Transplantation, Ankara, Turkey. All adult renal transplant recipients followed at the transplant clinic between January 2013, and July 2018 were reviewed. Among these patients, recipients requiring allograft biopsy due to progressive graft function decline, new-onset hematuria, and proteinuria were included in the study.

Allograft biopsies were performed as per Kidney Disease Improving Global Outcomes (KDIGO) practice guidelines[11]. Banff 97 criteria were used to evaluate biopsy specimens[12]. Biopsy specimens were considered adequate if they had ≥ 10 glomeruli and two arteries; patients with inadequate biopsy specimens were excluded from the study. Additionally, patients with post-transplant follow-up < 1 year were excluded from the study to establish a homogeneous cohort. The serum vitamin D level was measured every 3 mo, as per the KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder. All recipients received vitamin D replacement therapy considering their serum vitamin D levels, as per KDIGO guidelines[13].

Demographic characteristics, medical history, prior type and duration of dialysis, donor type, human leukocyte antigen (HLA) mismatches, maintenance immunosuppression, biopsy results, and serum vitamin D level at the time of graft biopsy were obtained from hospital records by a research nurse. In addition, as this study determined the relationship between serum vitamin D level and allograft biopsy results, other biochemical parameters associated with rejection and CAN, such as the GFR, and serum creatinine, albumin, calcium, phosphate, and parathyroid hormone (PTH) levels at the time of graft biopsy, were also recorded. The study protocol was approved by the hospital's ethical review committee (06.08.2018-no. 53/20) and was carried out in accordance with the Declaration of Helsinki and the Declaration of Istanbul. All patients provided written informed consent.

Immunosuppression

Recipients of live donor kidneys were induced with interleukin 2 receptor blockers and steroids, whereas recipients of deceased donor kidneys were induced with anti-thymocyte globulin and steroids. Maintenance immunosuppression was based on mycophenolate mofetil (MMF), prednisone, and calcineurin, or mammalian target of rapamycin inhibitors.

Vitamin D status

The serum vitamin D level was measured using the chemiluminescence method (Kit No: A98856; Beckman Coulter Inc., Sykesville, MD, United States). A serum vitamin D level > 30 ng/mL (*i.e.*, > 75 nmol/L) was considered adequate. Concentrations between 15 and 30 ng/mL (40-75 nmol/L) were considered vitamin D insufficiency, whereas < 15 ng/mL (< 37.5 nmol/L) was considered vitamin D deficiency according to KDIGO guidelines[13].

Biochemistry

The serum PTH concentration was measured *via* immunochemiluminescent assay (Kit No: A16972; Beckman Coulter). Total calcium, phosphate, glucose, blood cell count, albumin, uric acid, total cholesterol, triglyceride, C-reactive protein (CRP), and creatinine levels were measured using standard methods (Kit Nos: OSR61117, OSR6222, OSR 6221, DW20180105, OSR6202, OSR 6298, OSR 6116, OSR6199, and OSR6178, respectively; Beckman Coulter). The GFR was calculated using the modification of diet in renal disease formula.

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, United States). The distribution of data was analyzed using the Kolmogorov-Smirnov test. Mean \pm SD was used for descriptive analysis of parametric quantitative data, whereas number and percentage were used to analyze the qualitative data. The student's *t*-test was used for parametric data analysis, and the Mann-Whitney *U* test was used for non-parametric data analysis. Pearson's chi-square test was used to analyze qualitative data. The level of statistical significance was set at $P < 0.05$. Binary logistic regression analysis was used to determine the independent factors related to rejection. After excluding multicollinear variables, clinically relevant variables and parameters presenting statistical significance were subject to the binary logistic regression analysis. The odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were used to show the factors affecting the outcomes.

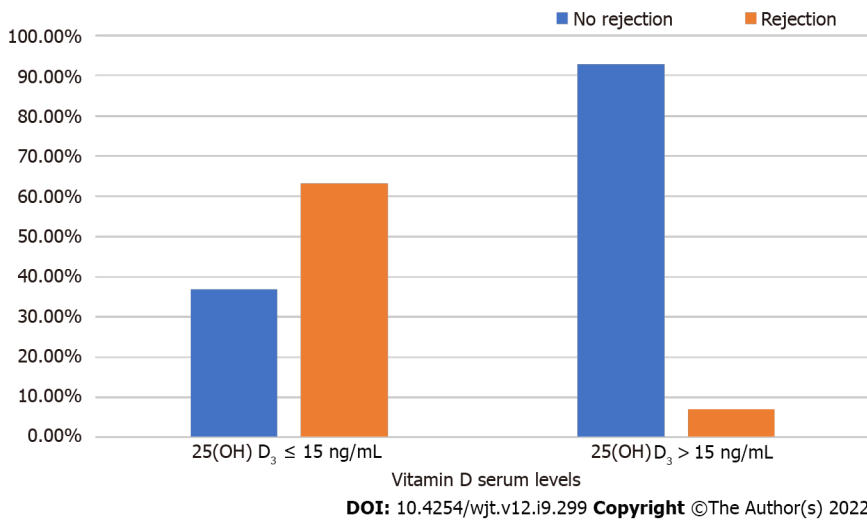


Figure 1 Baseline vitamin D levels at the time of biopsy, and the rejection rate in the low and high vitamin D level groups ($P < 0.001$).

RESULTS

Among 130 kidney transplant recipients, 52 met the study inclusion criteria. The mean age of the recipients was 41 ± 11.9 years, of which 38 (73.1%) were male and 14 (26.9%) were female. During the post-transplantation period, 25 (48.1%) patients had hypertension and 15 (28.8%) had diabetes mellitus. Pre-transplantation duration of dialysis was 5.8 ± 4.71 years, and hemodialysis was the most common therapy (82.7%). The majority (65.4%) of the study population received live donor kidney transplants, of which 3 (5.8%) were transplanted preemptively. Of the 34 live donors, 20 were spousal donations, 10 were first-degree relatives, and 4 were second-degree relatives.

The average age of the donors was 49.6 ± 9.7 years, and the majority of them were 29 (55.8%) male. The mean post-transplant duration of follow-up was 5.91 ± 1.83 years. The mean number of HLA mismatches was 3 ± 1 . Delayed graft function developed in 9 (17.6%) patients. Fourteen (27.5%) patients were donor-specific antibody (DSA)-positive at the time of renal biopsy. Kidney failure had occurred due to hypertension in 25 (48.1%), diabetes mellitus in 15 (28.8%), glomerulonephritis in 7 (13.5%), post-renal kidney disease in 3 (5.8%), and unknown reasons in 2 (3.8%) of the recipients (Table 1).

Maintenance immunosuppressive regimens at the time of graft biopsy were as follows: 38 (73.4%) patients were on a combination of MMF, tacrolimus, and prednisone, whereas 11 (20.9%) were receiving a combination of MMF, cyclosporine, and prednisone. Only 3 (5.7%) of the recipients used mechanistic target of rapamycin inhibitor-based regimens. At the time of allograft biopsy, the average serum trough calcineurin level was 4.8 ± 0.8 , cyclosporine serum level ng/mL was 545 ± 89 , and the mean daily intake of MMF was 1.7 ± 0.3 gr/d. Within the study cohort 20 patients were receiving vitamin D treatments according to the KDIGO guidelines. Among the 52 allograft biopsies, 25 (48%) showed rejection. Acute T cell-mediated rejection, acute antibody-mediated rejection (ABMR), and chronic active ABMR were observed in 6 (11.5%), 10 (19.2%), and 9 (17.3%) of the recipients, respectively. CAN was noted in 19 (36.5%) of the recipients. Calcineurin toxicity was observed in 3 (5.8%) patients, whereas BK virus nephropathy and recurrent nephritis were noted in 4 (7.7%) and 1 (1.9%), respectively.

The study population was divided into two groups based on the serum vitamin D level (Table 2). Patients with a vitamin D level > 15 ng/mL constituted group 1, and those with a level ≤ 15 ng/mL constituted group 2. The two groups were compared concerning graft function, HLA mismatches, biochemical parameters, GFR, and rejection status. Group 1 included 14 (27%) patients, and group 2 included 38 (73%). There were no significant differences concerning age, comorbidities, or HLA mismatches between the groups ($P > 0.05$). Males were predominant in group 2 ($P = 0.035$). Four (28.6%) recipients in group 1 and 15 (39.5%) recipients in group 2 were diagnosed with CAN. There was no significant difference in the CAN rate between the two groups ($P > 0.05$). Only 1 (7.1%) recipient was diagnosed with rejection in group 1 and 24 (63.2%) recipients in group 2. The biopsy-proven rejection rate was significantly higher in group 2 compared to group 1 ($P < 0.001$) (Figure 1).

The estimated GFR (eGFR) was 38 ± 18.3 in group 1 and 41 ± 19.7 in group 2. There was no significant difference between these groups regarding eGFR ($P > 0.05$). In addition, hemoglobin, serum glucose, albumin, CRP, calcium, phosphate, uric acid, total cholesterol, triglyceride, blood urea nitrogen, and creatinine did not significantly differ between the two groups ($P > 0.05$). The mean PTH level was 205 pg/mL in group 1 and 268 pg/mL in group 2. PTH level was higher in group 2 than in group 1 ($P = 0.007$).

Table 1 Demographic characteristics of the kidney recipients at the time of graft biopsy

Parameter	Patients, <i>n</i> = 52
Mean age, yr	41 ± 11.9
Male, <i>n</i> (%) / female, <i>n</i> (%)	38 (73.1) / 14 (26.9)
DM, <i>n</i> (%) / HT, <i>n</i> (%)	15 (28.8) / 25 (48.1)
Hemodialysis, <i>n</i> (%) / peritoneal dialysis, <i>n</i> (%)	43 (82.7) / 6 (11.5)
Mean dialysis duration, yr	5.8 ± 4.71
Pre-emptive, <i>n</i> (%)	3 (5.8)
Donor type: Living, <i>n</i> (%) / Cadaver, <i>n</i> (%)	34 (65.4) / 18 (34.6)
Donor sex: Male / female	29 (55.8) / 23 (44.2)
Donor age in yr	49.6 ± 9.7
Time since transplantation, yr	5.91 ± 1.83
Number of HLA mismatches	3 ± 1
DGF, <i>n</i> (%)	9 (17.6)
DSA, <i>n</i> (%)	14 (27.5)
Cyclosporine/tacrolimus serum levels, ng/mL	545 ± 89 / 4.8 ± 0.8
MMF, gr/d	1.7 ± 0.3
Pre-transplant kidney failure etiology	
DM, <i>n</i> (%)	15 (28.8)
HT, <i>n</i> (%)	25 (48.1)
Glomerulonephritis, <i>n</i> (%)	7 (13.5)
Post-renal kidney failure, <i>n</i> (%)	3 (5.8)
Unknown, <i>n</i> (%)	2 (3.8)

CSA: Cyclosporine A; DM: Diabetes mellitus; DGF: Delayed graft function; DSA: Donor-specific antibody; HLA: Human leukocyte antigen; HT: Hypertension; MMF: Mofetil mycophenolate; TAC: Tacrolimus.

The study cohort was also divided into two groups based on the presence or absence of biopsy-proven rejection (Table 3). The mean age was 39 ± 12.9 in the rejection group and 42 ± 10.9 in the no-rejection group. In the rejection group females were predominant [22 (88%) *vs* 16 (59.3%); *P* = 0.020]. The comorbid status, previous dialysis vintage, and donor characteristics did not differ between these two groups (*P* > 0.05). Hemoglobin, glucose, CRP, calcium, uric acid, lipid profile, and the number of HLA mismatches did not differ between groups (*P* > 0.05). Nevertheless, there were significant differences in the serum albumin, phosphorus, PTH, vitamin D, and DSA levels. The albumin was 4.0 ± 0.5 g/dL in the no-rejection group *vs* 3.5 ± 0.6 g/dL in the rejection group (*P* = 0.001). Phosphorus, PTH, and vitamin D levels in the no-rejection group were 3.9 ± 1.52 mg/dL, 197 pg/mL, and 17.4 ± 7.2 ng/mL, respectively. The results of these parameters in the rejection group were 5.3 ± 1.96 mg/dL for phosphorus, 310 pg/mL for PTH, and 9.7 ± 3.4 ng/dL for vitamin D serum levels. The *P* values of these comparisons showed a statistically significant difference between the two groups (*P* = 0.009, *P* = 0.022, and *P* = 0.003, respectively). DSA positivity was present in 14 (56%) of those with rejection (56%), whereas no patients in the non-rejection group had DSA positivity (*P* < 0.001). There was no significant difference between the two groups regarding serum cutaneous neurogenic inflammation levels and daily MMF dose (*P* > 0.05). Kidney failure with a GFR < 15 mL/min was observed in 5 (18.5%) patients in the non-rejection group and 12 (48%) in the rejection group. The kidney failure rate was significantly higher in the rejection group (*P* = 0.024); patients in the rejection group had lower GFRs and higher serum creatinine levels (*P* = 0.012 and *P* = 0.016, respectively). The serum vitamin D level was significantly lower, and the PTH level was significantly higher in the rejection group than in the non-rejection group (*P* = 0.003 and *P* = 0.022). A regression analysis was performed using rejection risk factors (Table 4). In univariate regression analysis, female sex, serum vitamin D level, phosphorus, and albumin were found to be effective in the development of rejection (*P* = 0.027, *P* = 0.007, *P* = 0.023, *P* = 0.008). However, these risk factors did not demonstrate a significant effect (*P* > 0.05).

Table 2 Comparison of demographic characteristics and laboratory findings in the low and high vitamin D level groups at the time of graft biopsy

Vitamin D level	Group 1 (> 15 ng/mL), n = 14	Group 2 (≤ 15 ng/mL), n = 38	P value
Age, yr	40 ± 11.9	41 ± 12.0	0.856
Male, n (%)	7 (50)	31 (81.6)	0.035
DM/HT, n (%)	2 (14.3)/6 (42.9)	13 (34.2)/19 (50)	0.300/0.759
Hemodialysis/peritoneal dialysis	12 (92.3)/1 (7.7)	31 (86.1)/5 (13.9)	1.00
Mean dialysis duration, yr	5.9 ± 4.5	5.6 ± 3.7	0.839
Preemptive, n (%)	1 (7.1)	2 (5.3)	1.00
Rejection, n (%)	1 (7.1)	24 (63.2)	< 0.001
CAN, n (%)	4 (28.6)	15 (39.5)	0.534
Number of HLA mismatches	3 ± 1	3 ± 1	1.00
ESRD actual, n (%)	7 (58.3)	10 (27)	0.80
Hemoglobin, g/dL	11.5 ± 2.0	10.7 ± 2.4	0.266
Glucose, mg/dL	106 ± 60.7	98 ± 33.9	0.433
Albumin, g/dL	4.0 ± 0.4	3.7 ± 0.6	0.063
Uric acid, mg/dL	7.1 ± 1.8	7.7 ± 1.5	0.276
Urea, mg/dL	68 ± 35.3	77 ± 38.6	0.416
Creatinine, mg/dL	2.08 ± 0.61	2.21 ± 1.22	0.702
eGFR, mL/min/1.73 m ²	38 ± 18.3	41 ± 19.7	0.609
Proteinuria, g/d	1.0 ± 0.9	2.5 ± 3.1	0.261
Cholesterol, mg/dL	186 ± 36.9	177 ± 46.2	0.515
Triglyceride, mg/dL	178 ± 82.9	191 ± 110.1	0.877
Calcium, mg/dL	8.9 ± 0.99	8.7 ± 0.80	0.400
Phosphorus, mg/dL	4.8 ± 1.84	4.5 ± 1.86	0.657
PTH, pg/mL (range)	205 (78-927)	268 (59-955)	0.007
CRP, mg/dL	24 ± 48.2	21 ± 29.9	0.483

CAN: Chronic allograft nephropathy; CRP: C-reactive protein; DM: Diabetes mellitus; eGFR: Estimation glomerular filtration rate; ESRD: End-stage renal disease; HLA: Human leukocyte antigen; HT: Hypertension; PTH: Parathyroid hormone.

DISCUSSION

Vitamin D deficiency is associated with a broad spectrum of diseases, including autoimmune conditions such as inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, and type 1 diabetes. In addition, vitamin D deficiency is associated with a severe decrease in the GFR and shorter life expectancy in patients with chronic kidney diseases[14-16].

Epidemiological studies conducted with kidney transplant recipients reported that the prevalence of vitamin D deficiency is as high as 90%, possibly due to the side effects of immunosuppressive regimens and a reduction in sun exposure related to the recommendation that these patients avoid sunlight[2,3,17, 18]. Falkiewicz *et al*[19] reported severe 1.25-dihydroxyvitamin D deficiency in 83% of kidney transplant recipients and that these patients had a high graft failure rate, which is in agreement with the present finding that the mean serum vitamin D level was 12.3 ± 6.2 ng/mL, indicating severe vitamin D deficiency. Findings regarding the relationship between vitamin D and organ rejection are inconsistent. For example, Zimmerman *et al*[5] reported no relationship between the vitamin D level and acute allograft rejection. By contrast, Kim *et al*[20] who conducted a prospective clinical trial that considered 25 nmol/L as the threshold for vitamin D deficiency, observed a correlation between a low vitamin D level and the acute rejection rate. Similarly, Lee *et al*[21] reported that kidney transplant recipients with a vitamin D level < 50 nmol/L within 30 d of transplantation had a higher risk of acute rejection during the 1st year post-transplant. Additionally, Bienaimé *et al*[22] showed that vitamin D deficiency led to interstitial fibrosis and tubular atrophy within the kidney parenchyma in kidney transplant recipients.

Table 3 Demographic characteristics and laboratory findings according to rejection status at the time of graft biopsy

Rejection	No	Yes	P value
Patients, <i>n</i>	27	25	
Mean age, yr	42 ± 10.9	39 ± 12.9	0.316
Female, <i>n</i> (%)	16 (59.3)	22 (88.0)	0.020
DM, <i>n</i> (%) / HT, <i>n</i> (%)	7 (25.9) / 13 (48)	8 (32.0) / 12 (48)	0.629 / 0.991
Donor type Cadaver, <i>n</i> (%)	7 (25.9)	11 (44.0)	0.171
Donor age, yr	47.7 ± 9.6	51.8 ± 9.6	0.133
Time since transplantation, yr	4.4 ± 1.4	5.3 ± 3.1	0.236
Number of HLA mismatches	2.2 ± 1.2	2.6 ± 1.2	0.263
DSA, <i>n</i> (%)	0	14 (56.0)	< 0.001
Cyclosporine / tacrolimus serum levels, ng / mL	576 ± 98 / 4.7 ± 0.9	490 ± 29 / 4.9 ± 0.7	0.063 / 0.352
MMF, gr / d	1.7 ± 0.3	1.7 ± 0.3	0.601
ESRD actual, <i>n</i> (%)	5 (18.5)	12 (48)	0.024
Hemoglobin, g / dL	11.5 ± 2.2	10.4 ± 2.3	0.095
Glucose, mg / dL	95 ± 37.7	107 ± 46.7	0.399
Albumin, g / dL	4.0 ± 0.5	3.5 ± 0.6	0.001
Uric acid, mg / dL	7.3 ± 1.6	7.7 ± 1.6	0.364
Creatinine, mg / dL	1.78 ± 0.44	2.59 ± 1.40	0.016
eGFR, mL / min / 1.73 m ²	45 ± 19.3	36 ± 18.3	0.012
Cholesterol, mg / dL	177 ± 37.2	181 ± 49.8	0.810
Triglyceride, mg / dL	180 ± 103.4	196 ± 104.1	0.379
Calcium, mg / dL	8.8 ± 0.79	8.7 ± 0.92	0.562
Phosphorus, mg / dL	3.9 ± 1.51	5.3 ± 1.96	0.009
PTH, pg / mL (range)	197 (59-440)	310 (106-955)	0.022
Vitamin D, ng / mL	14.7 ± 7.2	9.7 ± 3.4	0.003
CRP, mg / mL	20 ± 24.9	23 ± 43.2	0.05

CRP: C-reactive protein; DM: Diabetes mellitus; DSA: Donor-specific antibody; eGFR: Estimation glomerular filtration rate; ESRD: End-stage renal disease; HLA: Human leukocyte antigen; HT: Hypertension; MMF: Mofetil mycophenolate; PTH: Parathyroid hormone.

Vitamin D deficiency is associated with glomerular disease in native and transplanted kidneys, and this finding has been attributed to endothelial cell dysfunction. Therefore, it was proposed that a low serum vitamin D level and an elevated fibroblast growth factor-23 level hinder endothelial cell function and lead to endothelial injury[23-25]. Although normal endothelium expresses major histocompatibility complex (MHC) class I antigens only, in endothelial injury and inflammation cases, MHC class II antigens are also expressed on the cell surface. These MHC class II antigens increase the recruitment and adhesion of CD4⁺ T cells and initiate allorecognition. Alloantigen recognition subsequently triggers the production of inflammatory mediators and activates the complement cascade[26-28]. The present study could not evaluate endothelial dysfunction or MHC class II antigen expression due to its retrospective design; however, a correlation between a low serum vitamin D level and the kidney rejection rate was observed ($P < 0.001$).

On the other hand, as graft rejection and CAN share some immunological pathways, we suggest that the serum vitamin D level might play a role in CAN risk[29]. To the best of our knowledge, the present study is the first to examine the relationship between vitamin D deficiency and CAN. In the present study, the CAN rate did not differ according to the vitamin D level ($P = 0.534$).

The present findings indicate that the long-term graft survival rate remains moderate, even with meticulous management of risk factors, including vitamin D replacement. In this study, patients with rejection had higher phosphorus and PTH measurements at the time of graft biopsy ($P = 0.009$, $P = 0.022$), and vitamin D and albumin levels were significantly lower in this group ($P = 0.003$, $P = 0.001$). Univariate regression analysis elucidated that female sex, serum vitamin D, phosphorus, and albumin

Table 4 Univariate and multivariate regression analyses for rejection

	Univariate regressions				Multivariate regression			
	B	OR	95%CI	P value	B	OR	95%CI	P value
Age	-0.02	0.97	0.93-1.02	0.381	-0.04	0.95	0.87-1.03	0.265
Sex, female	1.61	5.04	1.20-21.06	0.027	1.12	3.08	0.31-30.45	0.336
Donor type Cadaver, <i>n</i> (%)	0.46	1.58	0.50-5.00	0.434	1.52	4.60	0.71-29.77	0.109
Donor sex, female, <i>n</i> (%)	-0.33	0.71	0.23-2.15	0.555	0.40	1.50	0.26-8.38	0.643
Donor age, yr	0.03	1.04	0.98-1.10	0.192	0.40	1.04	0.95-1.13	0.340
DGF, <i>n</i> (%)	-0.22	0.80	0.18-3.40	0.763	-1.41	0.24	0.01-4.36	0.337
MMF, gr/d	0.78	2.19	0.69-6.97	0.183	0.84	2.32	0.33-16.37	0.397
Serum fosfor (mg/dL)	0.43	1.53	1.06-2.22	0.023	0.63	1.87	1.01-3.48	0.05
Vitamin D, ng/mL	-0.153	0.85	0.76-0.96	0.007	-0.12	0.88	0.72-1.06	0.196
PTH	0.01	1.00	1.00-1.01	0.052	0.01	1.00	0.99-1.00	0.516
Albumin (g/dL)	-1.49	0.22	0.07-0.68	0.008	-1.17	0.30	0.05-1.69	0.177
CSA serum level, ng/mL	-0.01	0.99	0.99-1.00	0.265	0.01	1.00	0.99-1.00	0.983
TAC serum level, ng/mL	0.167	1.18	0.92-1.51	0.189	0.02	1.01	0.54-1.89	0.955

CI: Confidence interval; CSA: Cyclosporine A; DGF: Delayed graft function; MMF: Mofetil mycophenolate; OR: Odds ratio; PTH: Parathyroid hormone; TAC: Tacrolimus.

were significant risk factors affecting rejection. However, in the multivariate regression analysis, these risk factors did not affect the rejection status ($P > 0.05$).

The present study had some limitations, including a retrospective single-center design; the retrospective design might have led to selection and recall biases, and its single-center nature precludes generalization of the findings. In addition, the study population was small and might have been insufficient for establishing the existence of cause and effect relations.

CONCLUSION

In conclusion, the serum 25 (OH) vitamin D level of kidney transplant recipients remained low despite vitamin D replacement recommended by KDIGO guidelines. However, the multivariate regression analysis did not find the same variables effective on rejection. Nonetheless, diagnostic and predictive accuracy is limited when a single test is used, and larger-scale prospective clinical studies are needed to more clearly discern the effects of the serum vitamin D level on the renal allograft rejection rate.

ARTICLE HIGHLIGHTS

Research background

Vitamin D deficiency is commonly diagnosed in patients with kidney transplantation. Deficiency rate remains high despite replacement therapies as per the Kidney Disease Improving Global Outcomes guidelines.

Research motivation

Vitamin D has immunomodulatory effects and vitamin D receptors can be found in various types of cells including T cells and dendritic cells. Its deficiency may predispose transplant recipients to rejection and chronic allograft nephropathy (CAN).

Research objectives

This study determined the association between the serum 25 (OH) vitamin D, biopsy-proven allograft rejection, and CAN rates.

Research methods

Retrospective clinical study involving adult kidney transplant recipients requiring graft biopsy due to declined function, hematuria, and proteinuria.

Research results

Vitamin D level was 9.7 ± 3.4 ng/mL in the rejection group *vs* 14.7 ± 7.2 in the non-rejection group; this difference was statistically significant ($P = 0.003$). In univariate regression analysis of risk factors affecting rejection, sex, serum vitamin D, phosphorus and albumin were found to have impact ($P = 0.027$, $P = 0.007$, $P = 0.023$, $P = 0.008$). In multivariate regression analysis, the same factors did not affect rejection.

Research conclusions

The serum 25 (OH) vitamin D level in kidney transplant recipients remained low. Although low serum vitamin D level emerged as a risk factor for rejection in univariate analysis, this finding was not confirmed by multivariate analysis. Prospective studies are required to appreciate the effect of serum vitamin D levels on allograft rejection.

Research perspectives

Kidney transplantation is the best treatment option for patients with terminal kidney failure. Successful transplantation prolongs longevity and significantly improves the quality of life. However, the long term success of kidney transplantation depends on preventing the chronic allograft dysfunction. Chronic allograft dysfunction is secondary to various immunological, infectious and drug related insults to the graft. Its prevention depends on close clinical follow-up and optimization of controllable variables, such as serum vitamin D levels.

FOOTNOTES

Author contributions: This study was conducted at Ankara Diskapi Research and Training Hospital, affiliated with the Health Sciences University of Turkey; the Departments of Internal Medicine, Nephrology, Urology, and General Surgery were involved in conducting the study; Oguz EG and Ayli MD designed the research; Buyukdemirci S and Cimen SG performed the research; Sahin H collected the data; Cimen S analyzed the data; Cimen SG wrote the paper.

Institutional review board statement: The study protocol was approved by the hospital's ethical review committee (06.08.2018-no. 53/20) and was carried out in accordance with the Declaration of Helsinki and the Declaration of Istanbul.

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Simultaneous kidney transplantation and ipsilateral native nephrectomy in patients with autosomal dominant polycystic kidney disease

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Abstract

The simultaneous kidney transplantation and ipsilateral native nephrectomy for autosomal dominant polycystic kidney disease does not seem to be associated with increased rates of comorbidity and complications. This outcome can efficiently be achieved when the indication and surgical approach of native nephrectomy are properly justified.

Key Words: Autosomal dominant polycystic kidney disease; Kidney transplantation; Native nephrectomy; Retroperitoneal approach; Surgical complications

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Core Tip: The current results showed that simultaneous kidney transplantation (KT) and ipsilateral native nephrectomy for autosomal dominant polycystic kidney disease is not associated with higher rates of comorbidity and complications. However, the indications should be justified to include forming a sufficient surgical space, such as with huge kidneys, alleviating symptoms, such as with infected cysts and accessing preemptive KT. On the other hand, the retroperitoneal surgical approach of the native nephrectomy should be employed, despite the anatomical challenges of approaching the native kidney from the same approach as the transplantation procedure.

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TO THE EDITOR

We read with interest the article by Darius *et al*[1], who studied the effect of the simultaneous ipsilateral native nephrectomy and kidney transplantation (KTIN) in a cohort of 154 patients with autosomal dominant polycystic kidney disease (ADPKD). This procedure was performed in 77 patients who were compared with another 77 patients who had KT alone. The authors addressed certain points in this issue such as the indications, preoperative and perioperative variables and complications. They concluded that KTIN is a safe strategy without a negative impact on the rates of surgical comorbidity, complications and graft survival.

We agree with the authors' conclusions that generally KTIN for ADPKD may not increase the rates of comorbidity and complications of KT. Also, we believe that this surgical strategy has very important practical implications on the field of KT, proving the surgical feasibility and safety of one-stage surgery, non-affected graft survival and a high patient satisfaction. Despite the numerous studies that have reported these outcomes, there are many unresolved controversies that still warrant further studying due to the insufficient evidence-based proofs in the literature[2-5].

In light of the results of this study, relevant literature status and our own experience, we will address some practical points that are crucially relevant to this subject. These points may contribute to the verification of the advantageous implications of KTIN on the KT practice, especially the living donor KT. Although our routine policy is to perform KTIN for ADPKD patients, we have encountered a few serious comorbidities and complications in those patients. We present this brief experience in the purpose of strengthening the focus and attention to the unfavorable sequels of KTIN to avoid them, but not to argue against the results reported by the authors or the growing evidence of the advantages of this strategy in the literature[5].

The authors addressed the common indications of KTIN in the symptomatic patients and they were similar to those indications reviewed and mentioned in the literature without much controversy. They included creating a surgical space for the graft as a cardinal indication, intractable renal pain, significant hematuria, intra cyst infections and hemorrhage, gastrointestinal symptoms such as early satiety, recurrent kidney stones, risk of malignancy and preemptive KT strategy[1,2,5]. Similarly, the current results revealed that the rate of KTIN was higher in patients who had preemptive KT[1]. The latter KT strategy is now an important issue in the literature representing a prominent indication of KTIN in patients with ADPKD, especially with the living donor KT. In regards to the asymptomatic patients who have a possibility of accessing preemptive KT, the number of surgeries can be reduced and the residual kidney functions and diuresis can be preserved until the time of KT surgery[4].

As the authors stated in their methods, the retroperitoneal surgical approach should be used to avoid the involvement of the peritoneal cavity and its contents. In the case of transperitoneal nephrectomy, lymphorrhea and hypoalbuminemia may represent serious complications, threatening the graft and patient survival. We had a serious experience with 2 cases of transperitoneal bilateral KTIN for ADPKD. The indications of the transperitoneal approach were the need of bilateral native nephrectomy and a history of previous surgery on the native kidneys. Prolonged lymphorrhea and hypoalbuminemia represented serious challenges in the management of one of our patients. Also, a very rare incident of pathology in the form of concomitant ADPKD and primary oxalosis was confirmed in the other patient. Both patients died with septicemia after a consecutive series of comorbidity and complications that were empowered by the transperitoneal approach. Hence, we may mention that the safety of KTIN is not absolute, especially when another major pathology coexists. In concordance, many drawbacks have been reported, including the prolongation of the time of surgery, increased need of blood transfusion and increased rates of early urinary tract infections[3]. On the other hand, bilateral native nephrectomy may have advantages when approached *via* the laparoscopic and robotic-assisted techniques in these cases, but the challenges and outcomes of these techniques are still controversial[6-8]. In any case, all of these unfavorable effects warrant proper surgical planning and prompt management of the medical and surgical sequels evolving during the perioperative period which may have a great effect on the whole of KT outcomes.

A recent systematic review by Xu *et al*[5] reached similar conclusions in regards to the vascular complications and safety of KTIN. This meta-analysis revealed that there was no evidence to support that the KTIN procedure increases the rates of the perioperative mortality and complications[5]. Finally, we believe that this study can be considered a step forward in providing cumulative strong evidence for the superiority of KTIN against the staged surgery. Accordingly, we should recommend a critical justification of the indications and timing of the native nephrectomy in patients with ADPKD

undergoing KT. Also, the retroperitoneal approach should be strictly used in these cases. Finally, efficient and meticulous hemostasis and ligation of the renal lymphatics should be performed.

FOOTNOTES

Author contributions: Gadelkareem RA searched and collected the data; Abdelgawad AM contributed in scientific review and revision of the letter; Gadelkareem RA, Abdelgawad AM and Mohammed N wrote and revised the letter; and all authors revised and approved the letter for submission.

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