EVALUATION OF TACROLIMUS, ASSOCIATED ADVERSE EFFECTS, QUALITY OF LIFE, AND TREATMENT SATISFACTION AMONG KIDNEY TRANSPLANT PATIENTS IN RIYADH, SAUDI ARABIA

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by

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Dedicated to my beloved parents and husband for their unconditional love and unwavering support

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ACR	Acute Cellular Rejection
AE	Adverse Events
AKI	Acute Kidney Injury
ALAT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
ANOVA	Analysis Of Variance
Apo	Apolipoprotein
ASAT	Aspartate Aminotransferase
BKD	Burden Of Kidney Disease
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
Ca	Calcium
CK	Creatine Kinase
CKD	Chronic Kidney Disease
CMV	Cytomegalovirus
CNIs	Calcineurin Inhibitors
CRP	C-Reactive Protein
Cr Cl	Creatinine Clearance
CS	Corticosteroids
CsA	Cyclosporine
CVD	Cardiovascular Disease
DD	Deceased-Donor
DM	Diabetes Mellitus
EKD	Effects of Kidney Disease

ESKD	End-Stage Kidney Disease
ESRD	End-Stage Renal Disease
FDA	Food and Drug Administration
GFR	Glomerulus Filtration Rate
eGFR	Estimated Glomerulus Filtration Rate
HCV	Hepatitis C Virus
HD	Hemodialysis
HDL	High Density Lipoprotein Cholesterol
HgA1C	Glycosylated Hemoglobin
HRQoL	Health-Related Quality of Life
IMS	Intercontinental Marketing Statistics
K	Potassium
KDIGO	Kidney Disease Improving Global Outcomes
KDQOL	Kidney Disease Quality of Life
KT	Kidney Transplantation
KSA	Kingdom of Saudi Arabia
LD	Living-Donor
LDL	Low Density Lipoprotein Cholesterol
LPL	Lipoprotein Lipase
MCS	Mental Component Score
Mg	Magnesium
MMF	Mycophenolate Mofetil
Na	Sodium
NICE	National institute for health and care excellence
NODAT	New-Onset Diabetes Mellitus After Transplantation

PCS	Physical Component Score
PD	Peritoneal Dialysis
PK	Pharmacokinetics
PMP	Per Million Population
PTDM	Post-Transplant Diabetes Mellites
PTH	Parathyroid Hormone
QoL	Quality of Life
RCT	Randomized Controlled Trial
RRT	Renal Replacement Therapy
RTP	Renal Transplantation
rUTIs	Recurrent Urinary Tract Infections
SCOT	Saudi Center for Organ Transplantation
SF36	Short Form 36
TAC	Tacrolimus
TG	Triglyceride
TS	Treatment Satisfaction
TSQM	Treatment Satisfaction Questionnaire for Medication
VLDL	Very Low-Density Lipoproteins

PENILAIAN TACROLIMUS, KESAN ADVERS YANG BERKAITAN, KUALITI HIDUP, DAN KEPUASAN RAWATAN DALAM KALANGAN PESAKIT PEMINDAHAN BUAH PINGGANG DI RIYADH, ARAB SAUDI

ABSTRAK

Bilangan pesakit pemindahan buah pinggang di Arab Saudi meningkat secara signifikan. Tacrolimus adalah ubat imunosupresif yang terkenal digunakan untuk mencegah penolakan alograf. Disebabkan oleh tacrolimus- kesan buruk yang tidak diingini, indeks terapeutik yang sempit, interaksi ubat-ubat, dan kebolehubahan antara individu yang ketara dalam farmakokinetik, ia memerlukan pemantauan ubat terapeutik yang berterusan. Tujuan kajian ini adalah untuk mengenal pasti kesan advers berkaitan tacrolimus dan faktor yang berkaitan dengan kejadiannya, penolakan selular akut, dan kehilangan graf. Juga, untuk menilai hubungan antara tahap kepekatan terendah tacrolimus (FK506-C0) dengan semua pembolehubah ini. Akhirnya, kesan faktor demografi, klinikal dan sosial terhadap kualiti hidup berkaitan kesihatan (HRQoL) dan kepuasan rawatan dalam pemindahan pasca-renal (RTP) pesakit yang dirawat tacrolimus dalam populasi Saudi telah disiasat. Ia merupakan reka bentuk kajian pra-eksperimen yang dijalankan di Hospital Security Forces di Riyadh, Arab Saudi. Kajian itu termasuk semua pesakit berumur 18 tahun ke atas yang menerima pemindahan buah pinggang antara Januari 2006 dan Januari 2019 dan telah dirawat dengan tacrolimus, mycophenolate mofetil, dan prednisolone (322 pesakit). Pesakit dipantau pada setiap lawatan klinik dan disusuli sehingga September 2019. Maklumat sosial-demografi serta pembolehubah klinikal seperti tahap FK506-C0 telah dikumpulkan. Alat penilaian kualiti hidup penyakit buah pinggang (KDQOL F-36 v1) dan soal selidik kepuasan rawatan untuk ubat (TSQM1.4) digunakan untuk pesakit

yang menerima pemindahan buah pinggang dari Januari 2017 hingga Januari 2019 (100/322 pesakit) untuk menilai HRQoL dan kepuasan rawatan sebulan dan 6 bulan selepas RTP. Dalam kajian ini, 78.3% pesakit adalah lelaki. Hipertensi post-RTP (40.6%), dislipidemia (38.8%), diabetes (34.4%), nefrotoksisiti (25.2%), neurotoksisiti (gegaran (65.2%)), penolakan selular akut (17%), penolakan graf (9.9%) dan kehilangan pesakit (3.1%) semua diperhatikan. Selepas RTP, dalam analisis bivariat, banyak faktor dikaitkan secara signifikan dengan kesan advers tacrolimus, seperti umur, jantina, BMI, jenis dialisis, tempoh dialisis, hepatitis C, penolakan selular akut, dan penyakit kardiovaskular. Selain itu, dalam analisis multifaktorial dan selepas membenarkan semua faktor yang mengelirukan, didapati peningkatan paras FK506-C0 secara signifikan dikaitkan dengan peningkatan kepekatan glukosa darah puasa 180 hari selepas RTP (ß= 0.133, P<0.017), nefrotoksisiti pada tahun 4 selepas - RTP (OR: 2.066; 95% CI: 1.035, 4.124, P<0.040) dan hipomagnesemia 1-14 hari selepas RTP (ß= -0.003, P<0.011). Selepas 15-28 hari pemindahan buah pinggang, didapati bahawa pesakit dengan penurunan paras FK506-C0 adalah 0.9 kali lebih berkemungkinan untuk mengalami penolakan akut daripada pesakit dengan peningkatan tahap kepekatan melalui tacrolimus (OR: 0.869; 95% CI: 0.774, 0.975, P<0.017). Peningkatan tahap FK506-C0 tidak berkaitan dengan peningkatan tekanan darah, dislipidemia, dan gegaran sehingga 14 tahun selepas RTP (P>0.05). Pada masa yang sama, tahap FK506-C0 tidak berkaitan dengan penolakan graf dalam pasca RTP tahun pertama. Selepas 6 bulan RTP, HRQoL dan kepuasan rawatan bertambah baik. Kualiti Hidup (QoL) dikaitkan dengan umur, jantina, dan tahap pendidikan. Skor min KDQoL adalah jauh lebih rendah (P<0.05) pada pesakit dengan dislipidemia dan diabetes. Di samping itu, skor min TSQM 1.4 (kesan sampingan rawatan) dan KDQoL pada pesakit dengan penolakan selular akut adalah jauh lebih rendah daripada mereka

tanpa penolakan buah pinggang ($P<0.05$). Kesimpulannya, pemantauan berterusan tahap FK506-C0 dan mengubah suai faktor risiko (contohnya obesiti, tekanan darah tinggi, hiperlipidemia) adalah penting untuk meminimumkan kesan advers tacrolimus. Doktor harus mempertimbangkan risiko kardiovaskular dan jangkitan virus hepatitis C sebelum pemindahan buah pinggang untuk mengelakkan penolakan selular akut, kehilangan graf, dan kehilangan pesakit (kematian). HRQoL dan kepuasan rawatan pesakit yang dirawat tacrolimus bertambah baik selepas 6 bulan pemindahan buah pinggang.

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ABSTRACT

The number of renal transplanted patients in Saudi Arabia is markedly increased. Tacrolimus is a well-known immunosuppressive drug used to prevent allograft rejection. Due to tacrolimus- unwanted adverse effects, narrow therapeutic index, drug-drug interactions, and significant inter-individual variability in pharmacokinetics, it requires constant therapeutic drug monitoring. This study aims to determine the tacrolimus-associated adverse effects and the factors associated with their occurrence, acute cellular rejection, and graft loss. Also, to evaluate the relationship between tacrolimus trough concentration (FK506-C0) levels with all of these variables. Finally, the effect of demographic, clinical, and social factors on health-related quality of life (HRQoL) and treatment satisfaction in tacrolimus-treated patients' post-renal transplantation (RTP) in Saudi population was investigated. It is a pre-experimental study design conducted at the Security Forces Hospital in Riyadh, Saudi Arabia. The study included all patients over the age of 18 who received a kidney transplant between January 2006 and January 2019 and were treated with tacrolimus, mycophenolate mofetil, and prednisolone (322 patients). Patients were monitored at each clinic visit and followed up until September 2019. Social-demographic information as well as clinical variables such as FK506-C0 levels were collected. The kidney disease quality of life (KDQOL F-36 v1) assessment tool and the questionnaire treatment satisfaction questionnaire for medication (TSQM1.4) were used for patients who received a kidney transplant from January 2017 to January 2019 (100 /322

patients) to evaluate HRQoL and treatment satisfaction one month and 6 months post-RTP. In this study, 78.3% of patients were men. Post-RTP hypertension (40.6%), dyslipidemia (38.8%), diabetes (34.4%), nephrotoxicity (25.2%), neurotoxicity (tremors (65.2%)), acute cellular rejection (17%), graft loss (9.9%) and patient loss (3.1%) were all observed. After RTP, in bivariate analysis, many factors were associated significantly with tacrolimus adverse effects, such as age, gender, BMI, type of dialysis, dialysis duration, hepatitis C, acute cellular rejection, and cardiovascular disease. Moreover, in multifactorial analysis and after allowing for all confounding factors, it was found that increased FK506-C0 level was significantly associated with increased fasting blood glucose concentration 180 days after RTP (ß= 0.133, P<0.017), nephrotoxicity at year 4 post-RTP (OR: 2.066; 95% CI: 1.035, 4.124, P<0.040) and hypomagnesemia 1-14 days post-RTP (ß= -0.003, P<0.011). After 15-28 days of renal transplantation, patients with lower FK506-C0 levels were found to be 0.9 times more likely to develop acute rejection than patients with higher tacrolimus trough concentration levels (OR:0.869; 95% CI: 0.774,0.975, P<0.017). Increased FK506-C0 levels were irrelevant to increased blood pressure, dyslipidemia, and tremors up to 14 years post-RTP (P>0.05). At the same time, FK506-C0 levels were unrelated to graft loss in the first-year post-RTP. After 6-months of transplantation, HRQoL, and treatment satisfaction improved. Quality of life (QoL) was correlated with age, gender, and educational level. KDQoL mean scores were significantly lower in patients with dyslipidemia and diabetes (P<0.05). In addition, the mean scores of TSQM 1.4 (side effects of the treatment) and KDQoL in patients with acute cellular rejection were significantly lower than in those without renal rejection (P<0.05). In conclusion, constant monitoring of FK506-C0 levels and modifying risk factors (obesity, high blood pressure, and hyperlipidemia) are crucial to minimizing

tacrolimus adverse effects. The clinicians should consider the cardiovascular risk and hepatitis C viral infection before renal transplantation to prevent acute rejection, graft loss, and patient loss (death). HRQoL and treatment satisfaction of tacrolimus-treated patients improved after 6 months of renal transplantation.

CHAPTER 1

INTRODUCTION

1.1 Overview of Chronic Kidney Disease

Chronic kidney disease (CKD) definition and classification have evolved over time. The Kidney Disease Improving Global Outcomes (KDIGO) organization defined CKD in 2020 as kidney structure or function abnormalities that have been present for more than 3 months and have health implications. CKD is based on cause, Glomerular Filtration Rate (GFR) category (G1–G5), and albuminuria category (A1–A3), abbreviated as (CGA) (Coates et al., 2020). There are five stages in this classification. Estimated Glomerular Filtration Rate (eGFR) and three levels of albuminuria are used to diagnose renal dysfunction. A person with a normal or mildly reduced eGFR (G1 or G2) and minimal or no albuminuria (A1) is therefore considered to be at low risk. Patients with eGFR < 60 mL/min/1.73 m^2 and moderate albuminuria are believed to be at a greater risk. The prognosis of CKD by GFR and albuminuria category is shown in **Figure 1.1** (KDIGO, 2012).

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				≥30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73m²) description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Figure 1.1Prognosis of chronic kidney disease by glomerular filtration rate and albuminuria category (KDIGO, 2012)

Among the clinical manifestations of CKD are fatigue, physical weakness, headache, dizziness, nausea, vomiting, diarrhea, skin itching, and muscle cramps (Haynes & Winearls, 2010). CKD patients also experience appetite loss, weight reduction, hypertension, peripheral edema, dyspnea, proteinuria, hematuria, and cognitive impairment (Webster, 2017). Due to hyperkalemia, CKD patients frequently experience abnormal heart rhythm and muscle paralysis (Yamada & Inaba, 2021).

The most important measures to identify CKD in clinical practice are eGFR estimated from serum creatinine and albumin: creatinine ratio derived from a urine sample in primary care. The National Institute for Health and Care Excellence (NICE) recommends that specific populations who have risk factors (diabetes, hypertension, acute kidney injury, cardiovascular disease, structural kidney disease, multisystem disorders that may impact the kidney, family history of ESKD, hematuria) be advised to screen for kidney function using eGFR and albumin: creatinine ratio to diagnose CKD (NICE, 2021).

1.2 Risk Factors of Chronic Kidney Disease

Because the majority of CKD patients are asymptomatic, screening may be required for early disease detection (Inker et al., 2014). The majority of clinical research guidelines encourage risk-based screening. Screening is recommended for adults over the age of 60, as well as patients with a history of diabetes mellitus (DM) or hypertension (HTN) (Farrington et al., 2016). The clinical, socio-demographic, and genetic risk factors for CKD are presented in **Table 1.1**.

Table 1.1 Clinical, Socio-Demographic, and Genetic Risk Factors for Chronic Kidney Disease (Chen et al., 2019)

Clinical	Socio-demographic	Genetic
DM	Age > 60 years	Sickle cell trait and disease
Hypertension	Non-white race	Polycystic kidney disease
Obesity	Low income	APOL1 risk alleles
Smoking	Low education	Alport syndrome
Autoimmune diseases		Congenital abnormalities of the kidney
Systemic infections		
Malignancy		Other familial causes
Nephrotoxic drugs		
IV drug use like heroin		
rUTI		
Kidney stones		
Urinary tract obstruction		
Reduced kidney mass		
History of AKI		
Family history of kidney disease		

DM: Diabetes Mellitus; rUTI: recurrent Urinary Tract Infections; AKI: Acute Kidney Injury; IV: Intravenous; APOL1: Apolipoprotein L 1.

Progressive CKD is associated with several more common and severe complications, including decreased renal function and interaction with one another (Fox et al., 2012). These complications result in a high morbidity and mortality rate, as well as poor quality of life (Bello et al., 2017). Some of these consequences are quantifiable and need a unique therapeutic strategy, such as cardiovascular diseases (Fujii et al., 2017), atherosclerosis (Mathew et al., 2017), hypertension, anemia, mineral bone disorders, volume overload, electrolytes, and acid-base abnormalities. Other consequences with less well-defined pathophysiology, such as anorexia, insomnia, lethargy, cachexia, pruritus, nausea, and sexual dysfunction, may present as complicated symptoms typically associated with severe CKD (Bello et al., 2017).

1.3 Global Perspective (Burden) of Chronic Kidney Disease

Chronic kidney disease (CKD) is a major public health issue, and the tide is rising. End-Stage Kidney Disease (ESKD) incidence and prevalence vary by country

and are difficult to assess accurately because CKD is typically asymptomatic (Haynes & Winearls, 2010). In high-income countries such as the United States (USA) and Australia, the prevalence of CKD is typically around 11%. Within countries, the incidence, prevalence, and progression of CKD vary by ethnicity and socioeconomic status. People in the lowest socioeconomic quartile are 60% more likely to have progressive CKD than those in the highest quartile. Black and Asian people in the United Kingdom (UK), Hispanics in the US, and Indigenous people in Australia, New Zealand, and Canada are more likely to develop CKD and disease progression (Morton et al., 2016).

The two most common causes of CKD are diabetes mellitus and hypertension. DM accounts for 30-50% of all CKD and affects 285 million (6.4%) of the global population. However, by 2030, this figure is expected to increase by 69% in high-income countries and 20% in low- and middle-income countries (Webster et al., 2017).

According to the Global Burden of Disease study, renal disease was the 12th leading cause of mortality in 2015, accounting for 1.1 million deaths worldwide. Overall, CKD mortality has increased by 31.7% in the last decade, making it one of the fastest-growing primary causes of death, alongside diabetes and dementia (Wang et al., 2016).

In recent decades, CKD has emerged as a serious public health issue in Saudi Arabia (SA) (Al-Sayyari & Shaheen, 2011; Mousa et al., 2021). It is unknown how many patients are in each stage of CKD (Assady, S., Ramadan, R., & Rubinger, 2011; James, Hemmelgarn, & Tonelli, 2010; Muneer, Al Nusairat, & Kabir, 2004). The incidence and prevalence of ESKD have been steadily increasing over the last three decades (Al-Sayyari & Shaheen, 2011; Alghythan Abdullah Khader, 2012). Relatives

from all regions of Saudi Arabia were examined for CKD: 23.2% from the central region, 20.7% from the eastern region, 28.9% from the western region, and 27.2% from the southern region (Mousa et al., 2021). In 2019, there were 21,068 patients receiving Renal Replacement Therapy (RRT) (Hemodialysis (HD), and Peritoneal Dialysis (PD), with 19,522 receiving HD and 1,546 receiving PD, for a 631 per million population (PMP) prevalence rate. The majority of dialysis patients were between the ages of 26 and 65, accounting for (67%) of the overall HD population. This percentage is growing at a rate of about 6% each year (Saudi Center for Organ Transplantation Annual Data, 2019). This demonstrates that Saudi Arabia is facing a number of challenges as a result of increased demand for kidney replacement therapy and the significant morbidity associated with ESKD.

The current study was carried out in Riyadh. Riyadh is widely recognized as the capital and central region of the Kingdom of Saudi Arabia. It has 20 governorates (Alfaqeeh et al., 2017). Riyadh's population accounts for three-quarters of the Saudi nationality in the Kingdom. It has several renal transplantation centers (Saudi Center for Organ Transplantation, 2018). The central region has 31% of the dialysis centers in the Kingdom of Saudi Arabia (AlGhonaim et al., 2020). The topographical nature and societal culture, such as relative marriage, contribute to the inheritance of diabetes and kidney disease. (Mousa et al., 2021). The two leading causes of end-stage renal disease among HD patients in Saudi Arabia were diabetic nephropathy 43% and hypertensive nephropathy 34% of the total of 19522 HD patients in 2019. (Saudi Center for Organ Transplantation Annual Data 2019).

1.4 Renal Transplantation

Renal Transplantation (RTP) is the preferred treatment for ESRD. Renal transplantation significantly reduces mortality and morbidity in ESRD patients (Shi et al., 2015). Furthermore, it has been linked to significant improvements in patient quality of life (QoL), cost savings, a reduction in cardiovascular complications, and sensitization events among dialysis patients (Kyles, 2016; Tonelli et al., 2011). This advancement (RTP) is due to the development of novel and efficient immunosuppressive medications that prevent acute transplanted kidney rejection. Renal transplantation requires lifelong immunosuppressant drugs, which include a steroid and immune modulator (e.g., Mycophenolate Mofetil, and a Calcineurin Inhibitor (CNI) like Cyclosporine A and Tacrolimus (TAC) (Al-Nasser et al., 2016).

Calcineurin inhibitors (Cyclosporine and tacrolimus (TAC)) are the main immunosuppressive agents that prevent acute rejection in renal transplant by inhibiting dephosphorylation reactions essential for T-cell gene transcription and interleukin production. Most studies have shown that a tacrolimus-based regimen has a better renal function, improved GFR, and fewer acute rejection episodes incomparable to cyclosporine-based therapy (Alghamdi et al., 2011).

1.5 Tacrolimus

1.5.1 Structure and Mechanism of Action of Tacrolimus

Tacrolimus (FK506) or fujimycin is an immunosuppressive agent related to the calcineurin inhibitor group (CNI) that is the keystone of most immunosuppressive regimens in solid organ transplantation (Prytuła et al., 2019). It is a 23-membered

macrolide lactone that was isolated in 1984 from a Japanese soil sample containing the bacteria *Streptomyces tsukubaensis* (Weltz et al., 2014).

It is highly effective and significantly reduces the incidence and severity of Acute Cellular Rejection (ACR) in heart transplant recipients (Crespo-Leiro et al., 2002; Skalická et al., 2010), intestine (Santeusanio et al., 2021; Vianna et al., 2020), pancreas (Harriman & Jeffrey, 2020; Jindal et al., 2000), bone marrow, lung (Hachem et al., 2007; Kao et al., 2021), liver (Pauldhillon et al., 2012; Reyes et al., 2000; Wente et al., 2006; Wu, Z. et al., 2013), and kidney (Berloco et al., 2001; Jouve et al., 2017; Liu, Y. et al., 2018; Rath, 2013; Salcedo-Herrera et al., 2019) recipients and for the treatment of autoimmune diseases (Broen et al., 2020; Chen et al., 2017).

Although there are structural differences between cyclosporin and tacrolimus, both have the same cellular mechanism of action. Tacrolimus is 10 to 100 times more potent than cyclosporin at the molecular level (Almawi et al., 2000). After entering the cell, both drugs bind to their respective cytosolic immunophilins: cyclosporine to cyclophilin and tacrolimus to the FK506-binding proteins (FKBP) (Albekairy et al., 2013). The resulting complex then binds to the enzyme calcineurin, preventing the dephosphorylation of the cytoplasmic component of the nuclear factor of activated T-cells (NF-ATc). This inhibits NF-ATc transport into the nucleus, preventing nuclear NF-ATn from binding to the nuclear promoter of the interleukin-2 (IL-2) gene. As a result, T cells fail to produce IL-2, which is required for complete T cell activation (Bennett et al., 2016). It also has an effect on the production of other cytokines, such as interleukin-3 (IL-3), interferon- (INF-), and tumor necrosis factor (TNF-) (Op den Buisch, 2007).

1.5.2 Tacrolimus Dose

The FDA recommends the tacrolimus dose depending on the patient's age, race, transplanted organ, time posttransplant, and concomitant immunosuppressive medication. The current "Clinical Pharmacogenetics Implementation Consortium guidelines" for CYP3A5 genotypes and tacrolimus dose have summarized and emphasized the importance of these genotype variations in tacrolimus pharmacokinetics interindividual variability. Tacrolimus initial doses of 0.075 to 0.1 mg/kg twice daily were reported in 39% of adult renal transplant studies (Campagne et al., 2019).

1.5.3 Tacrolimus Target Blood Concentration

Tacrolimus (FK506) blood concentrations should be monitored for optimal efficacy and minimal toxicity in kidney and liver transplantation, and blood levels should be kept in the 5-15 ng/ml range (Albekairy et al., 2013; Al Nasser et al., 2016). **Table 1.2** shows the target tacrolimus trough concentration level (FK506-C0) implemented in Saudi kidney transplant patients (SKTP), which varies depending on the time since post-transplantation.

Table 1.2 The Target of Tacrolimus Trough Concentration Level: (Al-Nasser et al., 2016)

10-12 ng/ml	1-14 days post renal transplantation
8-10 ng/ml	15-28 days
6-8 ng/ml	29 days to 180 days
5-7 ng /ml	> 180 day

1.5.4 Pharmacokinetics of Tacrolimus

Absorption: Tacrolimus is a poorly absorbed oral drug. Bioavailability in adults ranges from 5% to 93%, with a maximum of 25% (Op den Buisch, 2007; Prytuła et al., 2019). The peak plasma/blood concentrations were reached between 0.5 and 6 hours (Venkataramanan et al., 1995). Oral doses of tacrolimus should typically be three to four times higher than intravenous doses in order to achieve the same effect after oral and intravenous administration.

Tacrolimus has a narrow therapeutic index and significant inter-individual variability in pharmacokinetics. It is critical to achieve the steady-state target blood concentration in order to reduce rejection and adverse drug effects. Lower trough blood concentrations of tacrolimus can cause rejection, whereas higher trough blood concentrations can cause toxicity and infections (Shi et al., 2015).

Distribution: Tacrolimus is tightly bound to erythrocytes, with TAC whole blood concentrations exceeding 15- to 35-fold those detected in plasma. On the other hand, more than 90% of the TAC in plasma is strongly protein-bound, mostly to α-1 acid glycoprotein and albumin. (Prytuła et al., 2019).

Metabolism: Tacrolimus is primarily metabolized by cytochrome P450 3A4 (CYP3A4) and CYP3A5, which are found mainly in the liver and intestinal mucosa (Campagne et al., 2019).

Elimination: The elimination half−life of tacrolimus has been reported to be 12 hours in liver transplant recipients and 19 hours in renal transplant recipients. The biliary route eliminates more than 95% of tacrolimus metabolites (Möller et al., 1999).

1.5.5 Factors that Affect the Pharmacokinetics of Tacrolimus

Food, cytochrome P450 3A4 and cytochrome P450 3A5, P-glycoprotein expression, hepatic dysfunction, post-transplantation time, hematocrit, serum albumin, age, ethnicity, drug interactions, and genetic factors (Arns et al., 2017; Shi et al., 2015; Shuker et al., 2016), all have an impact on tacrolimus pharmacokinetics. Tacrolimus dose is influenced by genetic variables such as CYP3A5*3, CYP3A4*1B, CYP3A4*22, ABCB1, and POR*28 (Andrews et al., 2019; Yu et al., 2018). Also, Tacrolimus pharmacokinetics may be changed in patients with reduced gastric emptying time secondary to long-term diabetes mellitus (Prescott et al., 2004; Staatz & Tett, 2004).

Genetic Factors: Andrews et al. described the population pharmacokinetics of tacrolimus during the first three months of postrenal transplantation. They found that CYP3A5 expressers and CYP3A4*1 homozygotes had a higher tacrolimus clearance to bioavailability ratio (CL/F). They concluded that the tacrolimus initial dose should be increased to 160% in patients carrying the CYP3A5*1 allele, whereas in patients with the CYP3A4*22 allele should be lowered to 80 percent (Andrews et al., 2019).

Campagne et al. discovered that twenty-nine covariates had a significant effect on tacrolimus clearance CL(/F). The most common covariate was the CYP3A5*3 (rs776746) genotype (46 percent of studies, N = 29). This enzyme is responsible for most tacrolimus metabolism in the liver and small intestine, and genetic variations in the CYP3A5 enzyme might account for 40% to 50% of the variability in tacrolimus clearance (Campagne et al., 2019).

Age: Several studies have discovered that pediatric transplant patients require 2-4 fold higher tacrolimus doses than adults to maintain comparable trough concentrations (Jain et al., 1991; Mehta et al., 1999), which may be related to the higher tacrolimus clearance in younger patients (Andrews et al., 2019).

Furthermore, differences in cytochrome P450 3A (CYP3A3,CYP3A4, CYP3A5, and CYP3A7) have been linked to the higher tacrolimus doses required in pediatric patients C). The content of CYP3A4 in fetal liver tissue is extremely low, but it rapidly increases after birth to 120% of adult levels by the age of one year (Wrighton et al., 1990).

Gender: Gender was not a significant covariate in tacrolimus pharmacokinetics.(Campagne et al., 2019; Katsakiori et al., 2010). On the other hand, other studies reported that female renal transplant patients reached higher Cmax levels than male patients (Kuypers et al., 2004). Gender differences might contribute to variations observed between women and men in pharmacokinetics. (Degraeve et al., 2020).

Race: Tacrolimus doses (mg/kg) are higher in African-American transplant patients than in Asians (Chinese or Japanese) or Caucasians (Op den Buisch, 2007). Furthermore, black people require higher dosages than white people to achieve equal concentrations. (Campagne et al., 2019). The bioavailability of tacrolimus is significantly reduced in black patients (Fitzsimmons et al., 1998). The differences between ethnic groups may result from ethnic variations in intestinal CYP3A or P-glycoprotein activity (Lu et al., 2019).

Haematocrit and albumin concentrations: Tacrolimus pharmacokinetics are influenced by hematocrit (Lu et al., 2019), serum albumin, and hemoglobin levels

(Kim et al., 2012). Andrews et al. observed that individuals with a lower hematocrit had higher tacrolimus clearance. Since erythrocytes contain approximately 70-80% of tacrolimus, a lower hematocrit results in lower tacrolimus concentrations in the whole blood. Low albumin concentrations increase tacrolimus unbound fraction (Andrews et al., 2019).

Time after transplantation: Numerous studies have found that the dose of tacrolimus required to maintain similar trough concentrations decreases with increasing time post-solid organ transplant (Felipe et al., 2001; Undre et al., 1998). Tacrolimus dose reduction is usually thought to be caused by a decrease in tacrolimus clearance over time. Possible explanations include lower corticosteroid dosage and higher hematocrit and albumin concentrations (Undre et al., 1998).

Corticosteroid dosage: The concomitant use of corticosteroids influences the elimination of the tacrolimus. Corticosteroids may induce CYP3A iso-enzymes and increase the tacrolimus metabolism (Undre & Schäfer 1998).

Hepatic dysfunction: Several studies have found that poor liver function can reduce tacrolimus clearance (Lu et al., 2019). Hepatitis C-positive transplant patients require a significantly lower mean dose of tacrolimus than hepatitis C-negative patients to achieve the same trough concentrations (Staatz & Tett, 2004). The replication of the hepatitis virus in liver cells alters the cytochrome P450 system, reducing tacrolimus metabolism (Horina et al., 1993).

Administration of food: The fat content of the meal, as well as the time of administration, influence tacrolimus oral absorption. Coadministration of a low-fat meal has little effect on tacrolimus absorption and delays the time to reach Cmax (Sewing, 1994).

1.5.6 Tacrolimus Associated Adverse Effects

Post-Transplant Diabetes Mellitus (PTDM), hypertension, hyperlipidemia, nephrotoxicity, neurotoxicity, gastrointestinal disturbances, infectious complications, malignancies, and other electrolytes imbalance like hypomagnesemia are tacrolimus-associated adverse effects.

Although tacrolimus is an effective immunosuppressive drug to prevent acute kidney rejection, its nephrotoxicity may affect and delay the initiation of graft function (Salcedo-Herrera et al., 2019). Also, post-transplant diabetes mellitus and increased incidence of infectious complications, hypertension, and hyperlipidemia associated with a high incidence of cardiovascular disease (CVD) are severe complications that may adversely affect patient and graft survival.

1.6 Health-Related Quality of Life

Health-Related Quality of Life (HRQoL) refers to patient-reported outcome measures that assess how disease and treatment influence a patient's subjective well-being. Patients with CKD have significantly lower HRQoL than the general population (Webster et al., 2017). The majority of HRQoL data has been collected from ESRD patients receiving dialysis or kidney transplantation. Fewer studies have been conducted in less advanced stages of CKD, despite the fact that a consistent reduction in quality of life has been shown as GFR decreases (Morton et al., 2014; Soni et al., 2010).

Many approaches are used to assess Quality of Life (QoL) in CKD, like Short Form-36 and Beck Depression Inventory. Shortform-36 (SF-36), a self-reported multi-dimensional, and generic instrument, has been widely used to assess the QoL of

dialysis patients (Sesso et al., 2003; Valderrabano et al., 2001) and QoL in renal transplant patients (Kostro et al., 2016; Mokarram Hossain et al., 2015).

The Kidney Disease Quality of Life Survey English Version 1

The Kidney Disease Quality of Life ™ (KDQOL™-36), English Version 1, is a kidney disease-specific measure of health-related quality of life (HRQoL). It is a 36-question survey instrument published in 2000 based on a longer KDQOL instrument first developed in 1994 (Cohen et al., 2019; Hays et al., 1994) and developed by RAND and the University of Arizona ("RAND Corporation. 'Surveys.' Kidney Disease Quality of Life (KDQOL) Instrument.,"). It was validated to measure the quality of life for kidney-ill patients (Ajeebi et al., 2020; Cohen et al., 2019; Ricardo et al., 2013). Moreover, it was translated from English into formal Arabic using forward and backward translation by two independent local professional bilingual experts (Elamin et al., 2019). Many studies have used this tool to compare transplant patients to hemo- and peritoneal dialysis patients, and there were significant improvements following kidney transplantation in the recipient's QoL in all domains (Czyżewski et al., 2014; Yunanto et al., 2022).

1.7 Patient's Treatment Satisfaction

Patient treatment satisfaction is a significant factor in making health decisions about treatment adherence and continuation. The complexity of the prescribed regimen, the severity of the disease, the duration of treatment, and other factors like the cost and side effects of the drug all play a role in treatment satisfaction (Albekairy et al., 2016; Sweileh et al., 2011). Treatment satisfaction has recently been linked to adherence as an indicator of the quality of care provided, as satisfied patients are more

likely to continue taking their medications (Albekairy et al., 2016). As a result, health care providers must be aware of their patients' level of satisfaction with the drugs they are taking (Sweileh et al., 2011).

Many tools are used to measure treatment satisfaction, like the Renal Treatment Satisfaction Questionnaire (RTSQ) (Gibbons et al., 2021) and the Treatment Satisfaction Questionnaire for Medication TSQM 1.4 (Van Boekel et al., 2013; Zyoud et al., 2013). Quintiles Strategic Research Services, USA, provides a free Arabic-validated version of the Treatment Satisfaction Questionnaire for Medication (TSQM 1.4) for academic research (Albekairy et al., 2016; Alkatheri et al., 2016; Bharmal et al., 2009).

The Treatment Satisfaction Questionnaire for Medication

Despite the fact that disease-specific evaluation for patient satisfaction with medication was considered much earlier in the literature (Chatterton et al., 1999; Colman et al., 2001; Lewis et al., 2001; Payne et al., 1998), only a few studies focused on developing a scale that would allow comparisons across medication types and patients' conditions. IQVIA, formerly Quintiles and IMS Health, Incorporation, an American multinational company servicing the combined sectors of health information technology and clinical research, created the Treatment Satisfaction Questionnaire for Medication (TSQM 1.4) to address this gap. Furthermore, the TSQM 1.4 has been validated and found to be reliable in several studies that assessed treatment satisfaction in patients with various disease states (mild, moderate and severe) and different medications (Atkinson et al., 2004; Sweileh et al., 2011; Zyoud et al., 2013). The TSQM is designed for adults 18 and up. It was intended to be given in paper form 2-3 weeks after the medication was taken. TSQM Version 1.4 has 14 questions and four

domains: Effectiveness, Convenience, Side Effects, and Global Satisfaction. The domain scores range from 0 to 100, with higher scores indicating greater satisfaction in the respective domain (Alkatheri et al., 2016).

1.8 Problem Statement

The number of renal transplanted patients in Saudi Arabia is markedly increased. It is worth noting that between 1979 and 2019, a total of 13,641 kidneys were transplanted within the Kingdom of Saudi Arabia; of these transplantation operations, 9,471 (69%) were from live-related donors, 3,394 (25%) were from deceased donors, and 776 (6%) were from living unrelated kidney donors. Moreover, it is reported that 981 kidneys were transplanted from live donors and 140 from deceased donors, for a total of 1,121 transplants within the Kingdom of Saudi Arabia in 2019 (Saudi Center for Organ Transplantation Annual Data 2019), and around 9810 patients undergoing follow-up after kidney transplantation (Mousa et al., 2021).

Tacrolimus is a well-known immunosuppressive drug. It is generally used in transplantation (solid organ and hematopoietic stem cell transplants) to prevent allograft rejection. However, the significant improvement in short-term allograft and patient clinical outcomes does not mean a similar improvement in longer-term allograft survival. By 10 years post-transplant, only about 50% of deceased donor and 70% of living donor kidney grafts remain functional (Langewisch, E., & Mannon, R. B. 2021). Due to tacrolimus- unwanted adverse effects (Ali et al., 2018), narrow therapeutic index, drug-drug interactions, and significant inter-individual variability in pharmacokinetics, it requires constant therapeutic drug monitoring (Seibert et al., 2018). The adverse effects of tacrolimus may affect transplant patients' HRQoL and treatment satisfaction. Therefore, it is crucial to increase treatment satisfaction by

making drug therapy more convenient and educating patients on the efficacy and potential side effects of their prescribed drugs (Alkatheri et al., 2016).

1.9 The Rationale of the Study

The population of Saudi Arabia is known to have a high prevalence of DM, hypertension, and hyperlipidemia. These conditions are expected to increase the prevalence of renal failure in the future life of the patients. As a result, the number of renal transplant recipients in Saudi Arabia has significantly increased (AlGhonaim et al., 2020).

Renal transplanted patients in Security Force Hospital (SFH) in Riyadh received maintenance immunosuppressants after kidney transplantation containing tacrolimus, prednisone, and mycophenolate mofetil based on the hospital protocol. (British Columbia Transplant Society, 2021; "Medication Guidelines for Solid Organ Transplants," 2021). In the previous literature, tacrolimus was preferred over cyclosporin. It prevents acute rejection, death-censored grafts, and the incidence of hypertension, dyslipidemia, facial side effects, hirsutism, gingivitis, and gum hyperplasia when compared to cyclosporine.(Akbarzadeh Pasha et al., 2017; Heisel et al., 2004; Webster et al., 2005). However, tacrolimus has a 70% higher incidence of new-onset DM than other immunosuppressive agents (Sen, A. et al., 2019). Lower tacrolimus trough concentrations can cause kidney rejection, whereas higher trough blood concentrations can cause toxicity and infections. As a result, continuous therapeutic drug monitoring is essential. Furthermore, one recent study found that immunosuppressive patients treated with a combination of tacrolimus and azathioprine, cyclosporine and azathioprine, or cyclosporine and mycophenolic acid

metabolites had significantly improved patient survival than those treated with tacrolimus and mycophenolic acid. The group treated with azathioprine in any combination also had significantly improved patient survival than mycophenolic acid-treated individuals (Foroncewicz et al., 2019).

Surprisingly, there has been a lack of detailed research on tacrolimus-associated adverse effects and other factors associated with the occurrence of these side effects among tacrolimus-treated patients in Saudi Arabia for many years after RTP. In addition, there is a scarcity of data on the outcomes of renal transplants in Saudi Arabia (Tawhari et al., 2022).

HRQoL and treatment satisfaction studies are also lacking and require further investigation in Saudi Arabia for several years post-renal transplantation (Alkatheri et al., 2016). To the best of our knowledge, no study on this topic has been conducted in Saudi Arabia for many years, and the entire field is still open for further studies, debates, investigation, and experimentation (Alqahtani et al., 2021).

Since the estimated half-lives for deceased and alive kidney donor transplants are now expected to be greater than 11 and 19 years, respectively (Poggio et al., 2021), 14 years of follow-up of patients were selected to reach the maximum enrolment of patients treated with tacrolimus in the Security Force Hospital and to collect a tremendous patients medical information to determine the tacrolimus-associated adverse effects and the factors associated with the occurrence of these adverse effects post-renal transplantation. Patients who had received kidney transplants for more than 14 years were on cyclosporine medication in SFH. This long duration allows the author to observe the fluctuations in laboratory analysis tests and follow up with patients over

time with continuous monitoring of risk factors. Furthermore, the factors associated with acute cellular rejection, graft loss, and patient loss (death) could be detected.

1.10 Study Objectives

1.10.1 General Objectives

To determine tacrolimus-associated adverse effects and to evaluate the HRQoL and treatment satisfaction among tacrolimus treated patients for long years post-renal transplantation.

1.10.2 Specific Objectives

1. To determine the tacrolimus-associated adverse effects for long years post-renal transplantation in the Saudi population. (PTDM, hypertension, dyslipidemia, nephrotoxicity, neurotoxicity, and hypomagnesemia).
2. To determine the factors associated with tacrolimus adverse effects post renal transplantation (factors associated with PTDM, HTN, dyslipidemia, nephrotoxicity, neurotoxicity, and hypomagnesemia) in Saudi Population.
3. To determine the factors associated with acute cellular rejection, graft loss, and patient loss among tacrolimus treated patients post-RTP
4. To evaluate the relationship between tacrolimus trough concentration (FK506-C0) with its post-renal transplantation adverse effects, acute cellular rejection, and graft loss.
5. To determine the effect of other demographic, clinical, and social factors on QoL and treatment satisfaction among tacrolimus treated patients post-RTP.

1.11 Significance of the Study

The current study will provide beneficial information and valuable results to healthcare providers, especially physicians and clinical pharmacists. The results may help improve the effectiveness of tacrolimus and minimize its side effects, in addition to achieving optimal patient care by preventing long-term risks. This research recommends that long-term monitoring of tacrolimus blood trough levels is required, especially when any medication with possible interactions is prescribed. Monitoring of the tacrolimus blood trough levels will prevent the development of other comorbid conditions and graft failure. Furthermore, the study findings may assist patients in achieving cost-effectiveness, adhering to the treatment, and improving their quality of life by identifying the factors that affect those patients' quality of life and developing new interventions to improve it. The current study's findings may help to develop medical guidelines or protocols for the use of tacrolimus, as well as methods of patient follow-up and the precautions to be taken before and after surgery to ensure the patient's and graft's survival. Finally, the research may provide enough data to plan future interventional trials to mitigate risk.

CHAPTER 2

REVIEW OF LITERATURE

As previously stated, renal transplantation is the ideal treatment of choice for ESRD, but long-term immune suppressant medications are required. This chapter discussed tacrolimus-associated adverse effects in kidney transplant patients, risk factors for acute rejection and graft loss, HRQoL, and treatment satisfaction after renal transplantation.

2.1 Tacrolimus-Associated Adverse Effects among Kidney Transplant Patients

Tacrolimus was accompanied by an increased incidence of development of new-onset diabetes mellitus after transplantation (NODAT), electrolyte abnormalities (hypomagnesemia), neurotoxicity (headache/tremor), nephrotoxicity, gastrointestinal disturbances, infections, and malignancies (European FK506 Multicentre Liver Study Group, 1994). In addition, recent studies mentioned the hepatotoxic effect of tacrolimus (Lv, B. et al., 2023; Terzi, F., & Ciftci, M. K. 2022). According to Busuttil et al., the side effects of tacrolimus tend to appear primarily in the first few months after transplantation and gradually decrease with time, possibly in line with decreases in FK-506 concentration (Busuttil et al., 1996).

A retrospective study by Ali et al. included 100 patients after renal transplantation who were treated with tacrolimus and followed up for 2 years. They reported nephrotoxicity (46%), hypertension (27%), new-onset diabetes mellitus (18%), infections (22%), hyperlipidemia (28%), and hypomagnesemia in (85%) of patients. Ali and his colleagues mentioned a decrease in the incidence of hypertension, dyslipidemia, facial side effects, hirsutism, gingivitis, and gum hyperplasia in

comparison to cyclosporine. (Ali et al., 2018). Nevertheless, Staatz et al. mentioned that tacrolimus could cause alopecia and pruritus in some patients (Staatz & Tett, 2004). Al-Nasser et al. also mentioned that tacrolimus is susceptible to a number of drug interactions, particularly with agents that affect the cytochrome P-450 system, such as food and herbal supplements. These interactions may result in severe toxicity, rejection of the transplanted organ, or cardiovascular risk. Also, they found that after 180 days post-RTP a significant relationship between tacrolimus trough concentration and incidence of kidney rejection (Al-Nasser et al., 2016).

2.1.1 Tacrolimus- Associated Diabetes Mellitus among Kidney Transplant Patients

According to the literature, post-transplant diabetes mellitus is a serious complication that can have a negative impact on both patient and graft survival (Cosio et al., 2001; First, 2004) and raises the risk of infectious complications (Liu et al., 2016). The incidence of PTDM is significantly higher in transplant recipients treated with tacrolimus than in those treated with cyclosporin. A recent study by Abdulrahman et al. reported that 4%–25% of renal transplant recipients develop new-onset diabetes after transplant (Abdulrahman et al., 2018). Another large meta-analysis study by Montori et al. reported that the incidence of NODAT ranged from 2 to 50 % one-year post solid organ transplantation (Montori et al., 2002). Starzl et al. reported that cyclosporine and FK506 influence carbohydrate metabolism by inhibiting insulin secretion and enhancing peripheral insulin resistance (Starzl et al., 1990). In a separate study, Werzowa et al. concluded that β-cell dysfunction is a more influential factor on the development of PTDM than insulin resistance (Werzowa et al., 2015). B-cell growth and function need calcineurin. Calcineurin inhibition causes B-cell toxicity

and, as a result, impaired insulin production that is dose-dependent and potentially reversible (Ammari et al., 2018). According to Op den Buisch, many risk factors associated with PTDM development include race, high tacrolimus trough concentrations, and a high corticosteroid dosage (Op den Buisch, 2007). Furthermore, other studies have linked obesity, increasing age, and hepatitis B and C infection to an increased risk of NODAT (Johnston et al., 2008; Kasiske et al., 2003; Kumar et al., 2018). Ambachew et al. mentioned that HCV infections appear to affect glucose metabolism through alteration of the host innate immune response, and some hypotheses have proposed that alteration in carbohydrate and hepatic lipid metabolism, the expression of the HCV core protein, and the activity of hepatic tumor necrosis factor-α induce insulin resistance through the alteration of the insulin receptor substrate signaling pathway (Ambachew et al., 2019). Moreover, Kumar et al. mentioned that some risk factors are distinctive to transplant patients. These include the type of immunosuppressant, human leukocyte antigen mismatch, donor gender, underlying renal disease, impaired glucose tolerance before transplant, and hyperglycemia in the immediate perioperative period may recognize patients at higher risk for the development of NODAT (Kumar et al., 2018). In addition, the literature mentioned that the novel risk factors, such as hypomagnesemia, pre-transplant dyslipidemia, insulin resistance, insulin sensitivity, and beta-cell function, may help predict the development of NODAT in non-diabetic patients following renal transplantation (Garnier et al., 2018; Kumar et al., 2018). The stress of surgery, treatment for acute cellular rejection, and polycystic kidney disease were revealed to be significantly related to the risk of NODAT. Alagbe et al. explored that other clinical and biochemical characteristics such as type of donor (deceased or alive), blood pressure, serum cholesterol, and urine protein/creatinine ratios were similar in the

NODAT and control groups (Alagbe et al., 2017). Numerous common genetic variants have recently been linked to an increased risk of type-2 diabetes mellitus. Kurzawski et al. investigated the impact of single nucleotide polymorphisms previously linked to type-2 diabetes mellitus on the risk of NODAT in tacrolimus-treated kidney transplant recipients. They found no significant association between the risk of NODAT and any of the analyzed single nucleotide polymorphisms. The IGF2BP2 rs4402960 T allele, on the other hand, was significantly more common in patients diagnosed with NODAT more than two weeks after transplantation. (Kurzawski et al., 2012).

2.1.2 Tacrolimus- Associated Hypertension among Kidney Transplant Patients

Hypertension is one of the factors that may contribute to the high incidence of cardiovascular disease morbidity and mortality after transplantation. Long-term graft survival may also be affected by hypertension. According to Ong et al., tacrolimus is less likely to cause hypertension than cyclosporin (Ong et al., 2021). Hypertension was also reported as an adverse effect in 49.8% of tacrolimus-treated patients and 52.2% of cyclosporine-treated patients by Pirsch et al. (Pirsch et al., 1997). According to Hoorn et al., calcineurin inhibitor-induced hypertension is associated with vasoconstriction, sympathetic excitation, and renal sodium retention. The activation of the renal sodium chloride cotransporter causes tacrolimus-induced hypertension (Hoorn et al., 2012).

2.1.3 Tacrolimus- Associated Hyperlipidemia among Kidney Transplant Patients

Post-transplant hyperlipidemia has been associated with cardiovascular disease with its high morbidity and mortality rate. All previous studies found that tacrolimus