Evaluation of Immunosuppressive Regimens in Kidney Transplanted Patients in Iraq

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Abstract

Immunosuppressive regimens with the fewest possible toxic effects are desirable for transplant recipients. This study evaluated the efficacy and relative toxic effects of three immunosuppressive regimens used after kidney transplantation in Kirkuk city. 52 kidney transplanted patients were enrolled in this study and categorized into three treatment groups. The group I patients received standard-dose of CsA, MMF in combinations with prednisolone, and the group II patients received low-dose CsA, Aza in combinations with prednisolone, while the group III patients received low-dose Tac, MMF in combinations with prednisolone. The primary efficacy end point was the renal function; secondary end points were incidence of serious adverse effects and the complication of immunosuppression therapy in transplanted recipient. The mean calculated serum urea and serum creatinine during study were significantly lower in patients receiving low-dose tacrolimus (4.26mmol/L, 112.01?mol/L for urea and creatinine respectively) than in patients receiving standard-dose cyclosporine (6.28 mmol/L, 133.57?mol/L for urea and creatinine respectively). The mean calculated creatinine clearance was significantly higher in patients receiving low-dose tacrolimus (88.50 ml/min) than in patients receiving standard-dose cyclosporine (73.26 ml/min). Whereas there were no significant differences in serum creatinine and creatinine clearance in patients receiving group III (low-dose tacrolimus) and those receiving group II (low-dose cyclosporine). The serum total cholesterol and serum triglyceride concentrations were significantly lower in the group III (low-dose tacrolimus) than in the other two groups. The serum total bilirubin and bilirubin indirect concentrations were significantly elevated in both group I II receiving patients, while in the group III (low-dose tacrolimus) receiving patients there were no significant changes in serum bilirubin and hepatocellular enzyme. Neither group I (standard-dos

Index terms— CNI= Calcineurin inhibitor, CsA= Cyclosporine A, MMF= Mycophenolate mofetil, Aza= Azathioprine, Tac= Tacrolimus.

1 INTRODUCTION

idney transplant is the treatment of choice in endstage renal disease (ESRD) patients, as it reduces morbidity and mortality rates and improves the quality of life (1). In the absence of the ideal immunosuppressive drug, maintenance immunosuppression is achieved with combinations of immunosuppressive agents at lower doses when the recipient requires less immunosuppression to prevent rejection (2). Standard protocols in use typically involve three immunosuppression drug groups each directed to a site in the T-cell activation or proliferation cascade which are the central to the rejection process: Calcineurin inhibitors (cyclosporine, tacrolimus), antiproliferative agents (azathioprine, mycophenolate mofetil) and steroids (prednisolone) (3). Calcineurin

inhibitors (CNIs) are considered the mainstay of immunosuppression in renal transplantation. Cyclosporine A (CsA) and tacrolimus (Tac) are currently the most widely used baseline immunosuppressant for prevention of acute rejection following kidney transplantation (4). Known adverse effects are similar for both calcineurin inhibitors, which are related to the concentration of the drug, the most prominent of which is nephrotoxicity (5,6); much of this nephrotoxicity is mediated by impairment of renal hemodynamics (7). Tacrolimus has been associated with more diabetes and neurotoxic reactions, but with less hypertension, dyslipidaemia, hirsutism and gingival hyperplasia than cyclosporine (8,9). Recent data suggest that calcineurin inhibitors may shorten graft half-life by their nephrotoxic effects (10). MMF is devoid of any diabetogenic, hyperlipidemic, or hypertensive effects (11). Leucopenia, anemia, and gastrointestinal side effects are common with MMF (12). Dose-limiting adverse effects of azathioprine are often hematologic. Leukopenia, anemia, and thrombocytopenia can occur within the first few weeks of therapy and can be managed by dose reduction or discontinuation of azathioprine (13). Corticosteroids have been an integral component of immunosuppressive regimens in renal transplantation for ? 50 yr. (14). Corticosteroids are associated with myriad complications. These include the development of obesity, hypertension, glucose intolerance, hyperlipidemia, osteoporosis, glaucoma, cataracts, myopathy, Cushingoid habitus, and neuropsychiatric complications after transplantation (15). These distinct adverse effect profiles may impact on individual patient compliance and quality of life differently (16). Therefore when using immunosuppressant agents in renal transplantation, achieving low rejection rates while minimizing long term toxicities (eg, nephrotoxicity and cardiovascular disease) associated with these agents is the primary goal (17).

This retrospective study was carried out in Kirkuk governorate between the first of November 2010 to the end of May 2011. Patients were taken from the artificial Kidney Unit in Kirkuk General Hospital in Kirkuk. The study included 52 kidney transplanted patients (41 male and 11 female) with an age range from (17 to 60) year old 38.68 ± 1.6 (mean ± SE) were divided into three groups according to immunosuppression medication they received. a) Group I (Standard-Dose Cyclosporine) This group included thirty patients (26 male and 4 female) with an age range from 17 to 45 years (37.04 ± 2.1) who underwent kidney transplantation range from 2 months to 24 months (median 8 months) and were received: standard-dose of cyclosporine (microemulsion formulation), oral dose of 3 to 5 mg/kg, mean dose (214.42 ± 7.8) mg twice daily, mycophenolate mofetil at fixed doses (2g) per day and prednisolone in a mean dose (9.03 ± 0.66) mg per day in a single morning dose.

2 b) Group II (Low-Dose Cyclosporine)

This group included fifteen patients (10 male and 5 female) with an age range from 24 to 60 years (43.46 ± 3.2) who underwent kidney transplantation range from 2 years to 5 years (median 3 years) and were received: low-dose of cyclosporine (microemulsion formulation), oral dose of 1 to 2 mg /kg, mean dose (88.46 ± 6.08) mg twice daily, azathioprine at fixed doses (50mg) per day and prednisolone in a mean dose (5.7 ± 0.52) mg per day in a single morning dose.

3 c) Group III (Low-Dose Tacrolimus)

This group included seven patients (5 male and 2 female) with an age range from 28 to 46 years (32.6 ± 2.1) who underwent kidney transplantation range from 12 months to 24 months (median 14 months) and were received: low-dose of tacrolimus, oral dose of 0.1 mg /kg, mean dose (6.25 ± 0.69) mg twice daily, mycophenolate mofetil at fixed doses (2g) per day and prednisolone at fixed doses (10 mg) per day in a single morning dose.

4 d) Control Group

The control groups consist of 30 subjects. They were collected from medical staff and relatives who were free from signs and symptoms of renal disease, lipid disorders, diabetes mellitus and hypertension. 22 were males and 8 were females, and their ages ranged from 16 to 60 years (34.5 ± 2.1).

5 e) Exclusive Criteria

The exclusion criteria included patients with: ? Nephrotic syndrome. ? Primary hyperlipidemia. ? Liver dysfunction resulting from hepatitis, biliary obstruction or cirrhosis. ? Severe hypertension ? Diabetic patients ? Gastrointestinal disorder ? Overdose of cyclosporine dosages.

6 f) Collection Of Samples

Five milliliters of venous blood were drawn from each fasting patient (8-12 hours fasting). Slow aspiration of the venous blood sample via the needle of syringe to prevent hemolysis with tourniquet applies 15cm above the cubital fossa. The samples were dropped into clean disposable tubes, left at room temperature for 30 minutes for clot formation and then centrifuged for 3 minutes at 3000 run per minute. The serum was separated and used for estimating renal function (urea, creatinine), lipid profile (total cholesterol, triglyceride, HDL-c, LDL-c), liver function (ALP, ALT, AST, total bilirubin and bilirubin direct), fasting blood glucose and electrolyte (Na and K) by Auto analyzer (Flexor-E). Similarly the blood samples were taken from the control group.

7 g) Statistical Analysis

All data are expressed as mean ± standard error means (M ± SEM) and statistical analysis was carried out using statistically available software (SPSS Version 18). Statistical analyses were carried out using independent sample t-test to compare between mean values of parameters. Analysis of variance (ANOVA) was used for comparing the mean of different parameters used for evaluation of treatments between the treated groups. P value < 0.05 was considered statistically significant.

8 III.

9 RESULTS

10 a) Efficacy Measurements i. Kidney function parameters

Significant elevations in the serum urea and serum creatinine were observed, whereas creatinine clearance (Ccl) had decreased significantly compared to the healthy controls in kidney transplanted patients treated with group I treatment regimen (standard-dose CsA/ MMF/ Pred.) measured for three consecutive months as shown in table 3-1. *P < 0.05 significant difference from the control Table 3.2 shows the effect of group II treatment regimen (low -dose CsA/ Aza/ Pred.) on renal function parameters in kidney transplanted patients measured for three consecutive months. Significant elevation was observed only in the serum urea value. Serum creatinine and creatinine clearance level showed no significant differences compared to the healthy controls. * P < 0.05 significant difference from the control Table 3.3 shows the effect of group III treatment regimen (low -dose Tac/ MMF/ Pred.) on renal function parameters in kidney transplanted patients measured for three consecutive months. No significant changes were observed in the parameters measured. shows comparison between the effects of the three group's treatment regimen on renal function. There were significant differences between group I (standard-dose CsA) received patients and those on group III (low-dose Tac) at three months followup. The estimated serum urea and serum creatinine were significantly lower in the group III (lowdose Tac) than in group I (standard-dose CsA) and the estimated creatinine clearance was significantly higher in the group III (low-dose Tac) than in group I (standard-dose CsA). Whereas the changes where only significant in serum urea and not significant in serum creatinine and creatinine clearance between group II (low-dose CsA) received patients and those on group III (low-dose Tac). Table 3.5 shows the effect of group I treatment regimen (standard-dose CsA/ MMF/ Pred.) on lipid profile in kidney transplanted patients measured for three consecutive months. Both total cholesterol and triglyceride showed significant elevations compare to healthy control. However there were no significant changes in both serums HDL-c and LDL-c values in patients compared to the healthy control. i. Effect of treatment groups on lipid profile * P < 0.05 significant difference from the control Table 3.7 shows the effect of group III treatment regimen (low -dose Tac/ MMF/ Pred.) on lipid profile in kidney transplanted patients measured for three consecutive months. No significant differences were observed in all values of total cholesterol, triglyceride, HDL-c, and LDL-c of the patients at all intervals compared to healthy controls. shows comparison between the effects of the three group's treatment regimen on lipid profile. There were significant differences in serum total cholesterol and triglyceride between groups I (standarddose CsA) and group II (low-dose CsA) received patients and those on group III (low-dose Tac) at three months follow-up. The estimated serum total cholesterol and serum triglyceride were significantly lower in the group III (low-dose Tac) than in other two groups. Whereas no significant changes in serum total cholesterol and triglyceride were observed between group I (standard-dose CsA) received patients and those on group II (low-dose CsA). Also no significant changes were observed in serum HDL-c and serum LDL-c among all groups treatment regimen. S: significant NS: no significant (P<0.05 for the comparisons between groups) Table 3.9 shows serum liver function parameters in kidney transplanted patients treated with group I treatment regimen (standard -dose CsA/ MMF/ Pred.) for three consecutive months. No significant differences were observed in the serum values of ALP, ALT an d AST of the patients at all intervals compared to the healthy controls. Total bilirubin values were significantly increased compare to the healthy control, this increases in the total bilirubin value properly came from the indirect bilirubin values which were also increases compare to the healthy control. However the direct bilirubin values were not significantly changed. serum ALT and serum AST of the patients at all intervals compare to the healthy controls. And no significant differences were observed in the values of total bilirubin, bilirubin direct and bilirubin indirect of the patients at all intervals compare to the healthy controls.

11 Table 3-11:

Table 3-12 shows comparison between the effects of the three group's treatment regimen on liver function. There were no significant differences in serum ALP, ALT, AST and total bilirubin among all groups treatment regimen at the three months follow-up.

12 Bilirubin(indirect)

(µmol/L) S: significant NS: no significant (P<0.05 for the comparison between groups) Table 3.13 shows fasting blood glucose in kidney transplanted patients treated with different groups treatment regimen measured for three consecutive months. No significant differences were observed in the serum fasting glucose of the patients at all

intervals compared to the healthy control. And when comparing among the three treatment groups there were no significant differences in serum fasting glucose among the groups treatment at three months follow-up (Table 3-14). iii. Effect Of Treatment Groups On Fasting Blood Glucose Table 3.15 shows serum electrolyte (Na, K) in kidney transplanted patients treated with different groups treatment regimen measured for three consecutive months. No significant differences were observed in the serum electrolyte (Na, K), of the patients at all intervals compared to the healthy controls in all groups. Also when comparing among the three treatment groups there were no significant differences in serum electrolyte (Na, K) among the groups treatment at three months follow-up (Table 3-16) . The primary efficacy end point in this study was renal function. Therefore standard analysis such as serum urea, serum creatinine and creatinine clearance measurement are used to monitor the renal function that changes only after significant kidney injury (18). The glomerular filtration rate (GFR), the underlying indicator of renal function, is inversely proportional to the concentration of creatinine in plasma (19). Creatinine clearance gives an acceptable estimate of the glomerular filtration rate. The most widely used equations for calculation creatinine clearance are the Cockcroft-Gault equations (20).

On the basis of our results and literature review it was shown that nephrotoxicity (functional changes) induced by calcineurin inhibitor drug (CsA) is characterized by dose-dependent functional changes of the kidney function, which are reversible with a decrease in the dose or drug withdrawal (21,22,23,24,25).

In this study, table 3.1 showed the effects of group I treatment regimen (standard-dose CsA/ MMF/ Pred.) on renal function in thirty kidney transplanted patients. There were significant increases in serum urea, serum creatinine and significant decreased in creatinine clearance level when compared to the healthy control for three month consecutively. These results are in agreement with results of other studies conducted by **??**an Buren et al., 1994 (26); **??**assila, 2000 (27); puigmule et al., 2009 (18) who found that there were a significant increases in serum urea and serum creatinine, and a significant decreases in creatinine clearance after standard doses of cyclosporine administered in kidney transplanted patients. Since MMF has favorable safety profile and not adversely affect kidney function (28,29). Therefore we suggested that the standard doses of cyclosporine causes significant changes in renal function (30). Table 3.2 showed the effects of group II treatment regimen (low-dose CsA/ Aza/ Pred.) on renal function in fifteen kidney transplanted patients. Serum urea was only significantly increased, and serum creatinine and creatinine clearance level were slightly increased and decreased respectively compared to the healthy control for three consecutive months (not significant). These results are in agreement with the results of other studies conducted by **??**issmann et al., 1996 (22); **??**oroni, et al, 2006 (31); **??**obadilla and Gamba, 2007 (32) who found that the cyclosporine nephrotoxicity is dose -dependent and the low doses of cyclosporine did not significantly changes renal function. Therefore we suggest that to find a significant association between CsA and changes in renal function may depend on the dosage used in the regimen. The explanation for the only significant increase in serum urea in this group is probably that, serum concentration increase of with a change in serum creatinine (33), and the rate of urea production is not constant, urea can be grossly modified by a high protein intake, critical illness (i.e. sepsis, burns, and trauma), or drug therapy such as use of corticosteroids or tetracycline, and the rate of renal clearance of urea is also not constant, an estimated 40-50% of filtered urea is passively reabsorbed by proximal renal tubular cells (33).

Table 3.

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It is obvious from the below table that the group I treatment regimen (standard-dose CsA/ MMF/ Pred.) had the greatest incidence adverse effects including: (83%) of patients had hypertension, (26%) had tremors, (23%) had gastrointestinal upset, (43%) had hirsutism, and (16 %) had gum hyperplasia. While the group II treatment regimen (low -dose CsA/ Aza/ Pred.) had a similar percent of adverse effect regarding hypertension and tremor (80% and 20%) respectively and lower percent of adverse effects regarding hirsutism (33%), GI upset(13%) and gum hyperplasia (13%). However group III treatment regimen (low -dose Tac/ MMF/ Pred.) had the lowest adverse effects with hypertension (71%), tremor (42%) and GI upset (28%) with no other adverse effects. 01µmol/L for urea and creatinine respectively) than in patients receiving standard-dose cyclosporine (6.28 mmol/L, 133.57µmol/L for urea and creatinine respectively). The mean calculated creatinine clearance was significantly higher in patients receiving low-dose tacrolimus (88.50 ml/min) than in patients receiving standard-dose cyclosporine (73.26 ml/min). Whereas there were no significant differences in serum creatinine and creatinine clearance in patients receiving group III (low-dose tacrolimus) and those receiving group II (lowdose cyclosporine). Therefore the reduced doses of cyclosporine improve renal function, and low-dose tacrolimus based regimen provided better renal function when compared with standard-dose cyclosporine based regimens as shown in (Table 3- 4). The results of this study is in agreement with other studies **??**urewicz, 2003 (37); **??**kberg et al., 2007 (30); **??**obadilla and Gamba, 2007 (32) who found improvement in renal function with reducing dosage, and the uses of dose tacrolimus based regimens in kidney transplanted patients had advantageous for renal function than standard-dose of cyclosporine based regimen.

The causes of post transplant dyslipidemia include increased nutrient intake after transplantation (38), and adverse effects of steroids or cyclosporine used for immunosuppression (39,40,41).

In this study, Table 3.5 and Table 3-6, there were mild significant elevations of plasma total cholesterol and triglyceride concentrations compared to healthy control. This results is in agreement with other studies conducted by **??**lgenli et al., 1999 (42); **??**aziri et al., 2000 (43); **??**chimaru et al., 2001 (39); **??**bramowicz et al.,2005 (28);

??ami et al., 2010 (44) who revealed that long-term administrations of CsA and steroid were significantly raise plasma total cholesterol and triglyceride concentrations in renal transplanted patients. This reported changes in serum lipids has been found to be related with the mechanism of CsA adverse effects, since neither azathioprine (45) nor mycophenolate mofetil ??28 , 46) and corticosteroids (in daily dose of 12.5 mg or less) (42) are known to be associated with changes of serum lipid profile. Although the mechanism of calcineurin inhibitor induced hyperlipidemia is not well understood. Calcineurin inhibitors may decrease the activity of lipoprotein lipase (47). Hypercholesterolemia may be due to downregulation of enzyme cholesterol 7?-hydroxylase. This enzyme is the rate-limiting step in cholesterol conversion to bile acid, which is the principal pathway of cholesterol catabolism (43). Hypertriglyceridemia may be due to lipoprotein lipase and triglyceride hydrolase deficiency (39). Corticosteroids causes decrease in lipoprotein lipase activity, as well as excessive triglyceride production. But a daily dose of 12.5 mg or less of corticosteroid as in cholesterol (42). Also both serum (HDL-c) and (LDL-c) in both groups I & II treatment regimens were slightly increases but not significantly compared to control healthy individual. This finding has been reported only in study of ??aziri et al., 2000 (43) who revealed that the hepatic LDL receptor (play an important role in LDL metabolism) and HDL receptor (which facilitates transport of cholesterol esters from HDL to hepatocytes) expressions were not altered by CsA therapy.

Table 3.7 showed the effects of group III treatment regimen on lipid profile. No significant changes were observed on lipid profile when compared to healthy control, since the tacrolimus have less potential to induce hyperlipidemia than cyclosporine (48). These results are in agreement with other studies conducted by Pirsch et al, 1997 (??9 When comparing serum lipid profile among the three group treatment regimens, there were statistically significant differences among groups treatment at three months follow-up (table [3][4][5][6][7][8]. The serum total cholesterol and serum triglyceride concentrations were significantly lower in the group III (low-dose tacrolimus) than in the other two groups. Therefore the use of low dose tacrolimus based immunosuppressive regimen is associated with a more favourable lipid profile than the use of different cyclosporine dosage based immunosuppressive regimens. The results of this study are in agreement with other studies conducted by ??cott et al., 2003 (48); ??ramer, et al., 2005 (4); Becker-Cohen et al., 2006 (38) who found better lipid profile with the use of tacrolimus based regimen than cyclosporine based regimen. Whereas there were no significant differences between group I (standard-dose cyclosporine) and group II (low-dose cyclosporine), thus the reduced doses of cyclosporine did not improve the changes in lipid profile. Therefore replacement of cyclosporine with tacrolimus reduced the high level of total cholesterol and triglyceride in patients taking cyclosporine (50,52).

Calcineurin inhibitor (CsA & Tac) hepatotoxicity has been reported in few case reports after organ transplantation (53,54). The exact mechanism of CsA induced hepatotoxicity is not completely understood,

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patients in this study has only a minimal effect on point among the three groups treatment regimen. The mean calculated serum urea and serum creatinine transplanted patients. This may reflect a lower nephrotoxicity of tacrolimus-based immunosuppressive regimens and also may reflect a lower immunologic damage of the graft (36).

When comparing renal function as efficacy end inhibitor nephrotoxicity with the use tacrolimus in kidney numerous current findings suggest that oxidative stress mechanism playing an important role in its pathology.

results of other studies conducted by ??chade et al., 1983 (56); ??ahan, 1987 (21); ??adranel, et al, 1992 (57); ??ecking, et al, 2008 (58) who revealed that there is a significant elevations in total bilirubin after cyclosporine treatment. This elevation of total bilirubin seen after cyclosporine treatment is most probably related to a cholestasis (59). This could be due to the toxic metabolite of cyclosporine (AM19 and AM1A) (60), and since the bilirubin and cyclosporine metabolites are eliminated by the same transport system through the biliary membrane, therefore the elevated total bilirubin level suggested impaired cyclosporine elimination (61). Hepatocellular enzymes ALP, ALT and AST in this study in both group I and group II showed no significant differences compared to control healthy individual for three consecutive months. The explanation for that could be attributed to the doses of CsA used. Also many other articles and case reports conducted by ??orber et al, 1987 (62); ??ulbis, et al, 1988 (63); ??aniai et al, 2008 (54); Oto et al, 2010 (53) revealed that the reduction of the cyclosporine doses was sufficient to resolve the presumed hepatotoxicity (elevated level of hepatocellular enzymes).

Table 3.11 showed the effects of group III on liver function, no significant changes in hepatocellular enzymes ALP, ALT and AST and in total bilirubin and (bilirubin direct & bilirubin indirect) were observed in any of the patients in the group compared to control healthy individual. Such results were also reported in case reports conducted by ??aniai, et al, 2008 (54); Oto, et al, 2010 (53) who found that the tacrolimus hepatotoxicity is seemed to be dose-dependent and low doses of tacrolimus did not significantly changes liver function as this study shows.

When comparing liver function among the three group treatment regimens, there were no statistically significant differences among groups treatment at three months follow-up (table [3][4][5][6][7][8][9][10][11][12]. Also patients receiving group II (low-dose cyclosporine) had a mean serum total bilirubin and bilirubin indirect close to those of patients receiving group I (standard-dose cyclosporine). Therefore we suggest the reduced doses of cyclosporine did not resolved the mild elevated values of total bilirubin and bilirubin indirect, and group III (lowdose tacrolimus) regimen has favorable liver function.

New-onset diabetes after renal transplantation (NODAT) represents a serious metabolic complication with a negative impact on graft and patient survival, as well as on cardiovascular morbidity and mortality (64).

Among immunosuppressant, there are no alterations in glucose metabolism due to the use of MMF (65). The use of steroids causes in dosedependent an increase in peripheral insulin resistance and increasing hepatic glucose production (66,67). However, daily prednisone doses (5 mg/day) may not influence insulin sensitivity at all (68). Calcineurin inhibitors contribute to the development of (NODAT) by directly inhibiting insulin secretion from the pancreatic ?islet cell. This effect is dose-dependent, reversible and more pronounced for patients who are treated with tacrolimus than cyclosporine (69,52). Consistent with this, a meta-analysis of randomized controlled trials of cyclosporine versus tacrolimus after renal transplantation found a higher incidence of diabetes among those treated with tacrolimus suggesting that the use of cyclosporine rather than tacrolimus may be an effective strategy to prevent NODAT (70). However, tacrolimus has been reported to be diabetogenic, this risk is predominantly present in the initial period after transplantation and in patients who already had an impaired glucose tolerance before treatment (34).

In this study, table 3.13 showed the effects of all groups' treatment regimen (I & II & III) on fasting blood glucose in kidney transplanted patients. No significant changes in blood glucose level in either group were observed compared to control healthy individual, and also there were no statistically significant differences among groups treatment at three months follow-up (table [3][4][5][6][7][8][9][10][11][12][13][14]. This results is not in parallel with other studies results conducted by **??**iller et al., 2000 (71); **??**incenti et al., 2007 (72); **??**ohnston et al., 2008 (73); **??**ornum et al., 2010 (74) who revealed a highest incidence of new-onset post transplantation diabetes mellitus in patients treated with CsA in combination with MMF or Aza and steroid, and in patients treated with tacrolimus in combination with MMF/steroid. The probable explanation is that cyclosporine and tacrolimus influences glucose metabolism by reducing pancreatic insulin secretion in a dose-dependent manner **??**65, 75, and 69) and patients in this study predominantly received low doses of these drugs. Also other studies conducted by **??**igtenberg et al., 2001 (51); **??**ooda et al., 2007 (76) suggested that low dose tacrolimus significantly reduces incidence of new-onset post transplantation diabetes mellitus and do not impair glycemic control.

In this study, table 3.15 showed the effects of all groups' treatment regimen (I & II & III) on serum electrolyte (Na & K) in kidney transplanted patients. No significant changes in either group compared to control healthy individual were observed, and also there were no statistically significant differences among groups treatment at three months follow-up (table [3][4][5][6][7][8][9][10][11][12][13][14] **??**15][16]. This could indicate no significant effects of the three group's treatment regimen on serum Na and serum K.

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In this study, Table 3.9 and Table 3-10, significant mild elevations were observed only in total bilirubin and bilirubin indirect levels compared to control healthy individual. These results (elevations of total bilirubin and bilirubin indirect) are in agreement with CsA therapy induces overproduction of reactive oxygen species (ROS) in hepatocytes and lowers their antioxidant capacity) 55).

In this study, among patients receiving calcineurin inhibitor, those receiving cyclosporine A based regimen were more prone to develop hypertension (83%) & (80%) in group I & II respectively than those receiving tacrolimus based regimen (71%) in group III. This adverse hypertension effects was also reported by others studies conducted by **??**assila, 2000 (27); Castillo-Lugo and Vergne-Marini, 2005 (79); **??**atarsi et al., 2005 (80). Therefore the use of tacrolimus may lead to less risk for hypertension when compared with treatment with CsA and conversion from treatment with CsA to treatment with tacrolimus may leads to a slight decline in blood pressure (51). Although there were no significant difference in blood pressure between groups treatment regimen (4) .

In this study the blood pressure remained unchanged in the CsA receiving groups; although the low doses of CsA in group II treatment regimens had been received during the study period. Similar results also reported by **??**chnuelle et al., 2002 (81); **??**ose, 2007 (52) who found continued treatment with CsA even at reduced doses frequently results in sustained hypertension.

The other adverse-effects (tremor, GI upset, hirsutism & gum hyperplasia) have been also recorded in other studies **??**asiske et al, 2000 (16); **??**iavarella et al., 2007 (82); **??**ebster et al., 2009 (3). In this study apart from hypertension, these adverse-effects are considered mild. The incidences of these cosmetic conditions (hirsutism and gingival hyperplasia) were predominant in patients taking cyclosporine, hirsutism (43% in group I & 33% in group II) and gum hyperplasia (16% in group I & 13% in group II), than in patients taking tacrolimus (no case reported). Similar results are also reported in other studies **??**ose, 2007 (52); **??**han et al., 2008 (9). CsA induced gingival hyperplasia is connected with increased collagen levels due to the CsA mediated inhibition of collagen phagocytosis (83). Neurological effects (tremor) and gastrointestinal effects (diarrhea, vomiting and dyspepsia) were more frequent in tacrolimus-treated recipients, tremor (42% in group III than 26% & 20% in group I & II respectively) and gastrointestinal effects (28% in group III than 23% & 13% in group I & II respectively). Similar results are also reported in other study **??**orales et al., 2001 (24). These reported gastrointestinal effects were being due to concurrent mycophenolate mofetil use more than to the calcineurin inhibitor associated gastrointestinal effects (84).

V. ? Cyclosporine nephrotoxicity is dose-dependent and reduce the dose of cyclosporine lead to less

nephrotoxicity and improvement in renal function. ? The use of cyclosporine based immunosuppressive regimen is associated with elevations in serums total cholesterol, triglyceride and total bilirubin in dose-independent manner, compared with the use of tacrolimus based immunosuppressive regimen which show no changes in post renal transplant. ? The most prominent adverse-effects associated with the all immunosuppressive regimens were hypertension. Whereas the use of cyclosporine is associated with a higher incidence of cosmetic adverse-effects (hirsutism & gum hyperplasia), and neurological (tremor) adverse-effects are more common in tacrolimus-treated recipients than in cyclosporine-treated recipients.

17 CONCLUSION

Figure 1:

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Figure 2: Table 3 - 1 :

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Figure 3: Table 3 - 2 :

[1] [2] [3]

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Figure 4: Table 3 -

Group I	Group II	0.842 NS	Group I	Group 2	0.483 NS	Group I	Group II	0.822 NS
	Group III	0.040 S		Group III	0.004 S		Group III	0.005 S
Group II	Group III	0.037 S	Group II	Group III	0.002 S	Group II	Group III	0.003 S
			Serum creatinine					
Group I	Group II	0.255 NS	Group I	Group II	0.252 NS	Group I	Group II	0.260 NS
	Group III	0.037 S		Group III	0.046 S		Group III	0.046 S
Group II	Group III	0.413 NS	Group II	Group III	0.586 NS	Group II	Group III	0.599 NS
			Creatinine clearance					
Group I	Group II	0.147 NS	Group I	Group II	0.108 NS	Group I	Group II	0.142 NS
	Group III	0.027 S		Group III	0.015 S		Group III	0.019 S
Group II	Group III	0.525 NS	Group II	Group III	0.499 NS	Group II	Group III	0.502 NS

Figure 5: February Serum urea at first month P value at 2 nd month P value at 3 rd month P value

T. Cholesterol (mmol/L)	5.15 ± 0.25*	5.47 ± 0.27*	5.52 ± 0.28*	4.34 ± 0.13
Triglyceride (mmol/L)	2.17 ± 0.21*	2.29 ± 0.24*	2.31 ± 0.23*	1.33 ± 0.13
HDL-c (mmol/L)	1.13 ± 0.08	1.12 ± 0.07	1.14 ± 0.08	0.97 ± 0.03
LDL-c (mmol/L)	3.46 ± 0.25	3.22 ± 0.27	3.46 ± 0.26	2.87 ± 0.16

Figure 6: Healthy control at 3 rd month at 2 nd month at first month Serum lipid

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Figure 7: Table 3 -

Serum lipid	at first month	at 2 nd month	at 3 rd month	Healthy control
T. Cholesterol (mmol/L)	5.31 ± 0.32*	5.20 ± 0.31*	5.17 ± 0.26*	4.34 ± 0.13
Triglyceride (mmol/L)	2.55 ± 0.36*	2.50 ± 0.35*	2.57 ± 0.35*	1.33 ± 0.13
HDL-c (mmol/L)	1.16 ± 0.11	1.10 ± 0.08	1.10 ± 0.08	0.97 ± 0.03
LDL-c (mmol/L)	3.08 ± 0.24	3.37 ± 0.39	3.37 ± 0.39	2.87 ± 0.16

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Serum lipid	at first month	at 2 nd month	at 3 rd month	Healthy control
T. Cholesterol (mmol/L)	4.48 ± 0.31	4.51 ± 0.27	4.46 ± 0.27	4.34 ± 0.13
Triglyceride (mmol/L)	1.51 ± 0.22	1.58 ± 0.27	1.53 ± 0.28	1.33 ± 0.13
HDL-c (mmol/L)	0.84 ± 0.13	0.90 ± 0.11	0.90 ± 0.11	0.97 ± 0.03
	2.71 ± 0.23	2.97 ± 0.21	2.97 ± 0.21	2.87 ± 0.16

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[Note: LDL-c (mmol/L)]

Figure 8:

3637

Figure 9: Table 3 - 6 :Table 3 - 7 :

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*[Note: *P < 0.05 significant difference from the control © 2012 Global Journals Inc. (US)]*

Figure 10: Table 3 - 9 :

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Figure 11: Table 3 -

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Figure 12: Table 3 .

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Figure 13: Table 3 - 13 :

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			Serum alkaline phosphatase					
at first month		P value	at 2 nd month		P value	at 3 rd month		P value
Group I	Group II Group III	0.264 NS 0.405 NS	Group I	Group II Group III	0.283 NS 0.414 NS	Group I	Group II Group III	0.222 NS 0.425 NS
Group II	Group III	0.929 NS	Group II	Group III	0.922 NS	Group II	Group III	0.931 NS
		Serum alanine aminotransferase						
Group I	Group II Group III	0.203 NS 0.708 NS	Group I	Group II Group III	0.252 NS 0.747 NS	Group I	Group II Group III	0.250 NS 0.734 NS
Group II	Group III	0.652 NS	Group II	Group III	0.622 NS	Group II	Group III	0.616 NS
		Serum aspartate aminotransferase						
Group I	Group II Group III	0.829 NS 0.969 NS	Group I	Group II Group III	0.848 NS 0.942 NS	Group I	Group II Group III	0.842 NS 0.922 NS
Group II	Group III	0.920 NS	Group II	Group III	0.984 NS	Group II	Group III	0.940 NS
			Serum total bilirubin					
Group I	Group II Group III	0.804 NS 0.783 NS	Group I	Group II Group III	0.812 NS 0.715 NS	Group I	Group II Group III	0.789 NS 0.745 NS
Group II	Group III	0.604 NS	Group II	Group III	0.635 NS	Group II	Group III	0.689 NS
	Glucose	at first month		at 2 nd month	at 3 rd month		Healthy control	
	Group I n = 30	5.32 ± 0.23		5.31 ± 0.27	5.30 ± 0.27			
	Group II n = 15	5.66 ± 0.49		5.77 ± 0.70	5.92 ± 0.68		4.80 ± 0.19	
	Group III n = 7	4.86 ± 0.27		5.02 ± 0.51	5.10 ± 0.50			

Figure 14: Table 3 -

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Figure 15: Table 3 -

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[Note: S: significant NS: no significant (P<0.05 for the comparisons between groups)© 2012 Global Journals Inc. (US)February]

Figure 16: Table 3 -

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				Serum fasting glucose		
at first month		P value		at 2 nd month		
Group I	Group II	0.400		Group I	Group II	
	Group III	NS				
		0.567			Group III	
		NS				
Group II	Group III	0.182		Group II	Group III	
		NS				

iv. Effect Of Treatment Groups On Serum Electrolyte (Na, K)

Na (mmol/L)	at first month	at 2 nd month
Group I n = 30	139.84 ± 0.52	139.74 ± 0.59
Group II n = 15	140.83 ± 0.60	141.05 ± 0.58
Group III n = 7	139.75 ± 1.65	139.60 ± 1.55
K (mmol/L)		
Group I n = 30	4.37 ± 0.10	4.36 ± 0.07
Group II n = 15	4.37 ± 0.12	4.48 ± 0.09
Group III n = 7	4.33 ± 0.23	4.36 ± 0.17

				Serum Na		
at first month		P value		at 2 nd month		
Group I Group II	Group II Group III	0.997	0.139 NS NS	Group III	0.389 NS	Group I Group II Group I

				Serum K		
Group I Group II	Group II	0.410		Group I Group II Group I		
	Group III	NS				
	Group III	0.968				
		NS				
		0.600				
		NS				

Figure 17: Table 3 -

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Figure 18: Table 3 -

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