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# Evaluation of Immunosuppressive Regimens in Kidney Transplanted Patients in Iraq

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*Abbreviations : CNI= Calcineurin inhibitor, CsA= Cyclosporine A, MMF= Mycophenolate mofetil, Aza= Azathioprine, Tac= Tacrolimus.*

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*Strictly as per the compliance and regulations of:*

# 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$\mu$mol/L for urea and creatinine respectively) than in patients receiving standard-dose cyclosporine (6.28 mmol/L, 133.57$\mu$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-dose cyclosporine) nor group II (low-dose cyclosporine) and group III (low-dose tacrolimus) were significantly effects on patients fasting blood glucose and patients serum electrolyte (Na& K). The most prominent adverse-effects associated with the all regimens were hypertension, whereas the use of cyclosporine based regimen is associated with a higher incidence of cosmetic adverse-effects (hirsutism & gum hyperplasia). Tremor and gastrointestinal adverse-effects are more frequent in tacrolimus-treated recipients than in cyclosporine-treated recipients. In conclusion, reduced the cyclosporine doses provided improvement in renal function, and immunosuppressive regimen of low-dose tacrolimus with mycophenolate mofetil in combinations with steroids provided significantly higher efficacy, advantageous for renal function, and associated with a more favourable lipid profile and liver function, as compared with regimens containing either standard-dose cyclosporine with mycophenolate mofetil or low-dose cyclosporine with azathioprine in combinations with prednisolone.

*Abbreviations : CNI= Calcineurin inhibitor, CsA= Cyclosporine A, MMF= Mycophenolate mofetil, Aza= Azathioprine, Tac= Tacrolimus.*

## I. Introduction

Kidney transplant is the treatment of choice in end-stage 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), anti-proliferative 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).

## II. Subject and Methods

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.

*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.

*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.

*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).

*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.

*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.

*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.

## III. Results

*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.

Table 3-1 :

| Parameter | at first month | at 2nd month | at 3rd month | Healthy control |
|---|---|---|---|---|
| **Urea** *(mmol/L)* | 6.24 ± 0.39* | 6.37 ± 0.36* | 6.24 ± 0.34* | 3.96 ± 0.18 |
| **Creatinine** *(µmol/L)* | 130.50 ± 7.48* | 134.67 ± 7.99* | 135.54 ± 7.60* | 109.52 ± 3.40 |
| **Ccl** *(ml/min)* | 74. 53 ± 4.47* | 73.58 ± 3.03* | 71.69 ± 2.63* | 91.53 ± 5.76 |

**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.

Table 3-2 :

| Parameter | at first month | at 2nd month | at 3rdmonth | Healthy control |
|---|---|---|---|---|
| **Urea** *(mmol/L)* | 6.34 ± 0.36* | 6.38 ± 0.35* | 6.56 ± 0.39* | 3.96 ± 0.18 |
| **Creatinine** *(µmol/L)* | 119.62 ± 7.06 | 123.65 ± 9.97 | 125.32 ± 9.72 | 109.52 ± 3.40 |
| **Ccl** *(ml/min)* | 83.81 ± 3.54 | 83.04 ± 3.96 | 81.64 ± 3.30 | 91.53 ± 5.76 |

** 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.

| Parameter | at first month | at 2nd month | at 3rd month | Healthy control |
|---|---|---|---|---|
| **Urea** *(mmol/L)* | 4.30 ± 0.35 | 4.28 ± 0.19 | 4.22 ± 0.19 | 3.96 ± 0.18 |
| **Creatinine** *(µmol/L)* | 111.08 ± 2.92 | 112.43 ± 2.94 | 112.52 ± 2.99 | 109.52 ± 3.40 |
| **Ccl** *(ml/min)* | 88.92 ± 4.97 | 88.37 ± 4.24 | 88.23 ± 4.29 | 91.53 ± 5.76 |

Table 3-4 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 follow-up. The estimated serum urea and serum creatinine were significantly lower in the group III (low-dose 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 3-4 :*

| Serum urea | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **at first month** | | **P value** | **at 2nd month** | | **P value** | **at 3rd month** | | **P value** |
| 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 |

*S: significant NS: no significant (P<0.05 for the comparisons between groups)*

*b) Safety Results*

i. *Effect of treatment groups on lipid profile*

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.

*Table 3-5 :*

| Serum lipid | at first month | at 2nd month | at 3rd month | Healthy control |
|---|---|---|---|---|
| **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 |

**P < 0.05 significant difference from the control*

Table 3-6 shows the effect of group II treatment regimen (low – dose CsA/ Aza/ Pred.) on lipid profile in kidney transplanted patients measured for three consecutive months. Both cholesterol and triglyceride showed significant elevations compare to healthy control. However there were no significant changes in both serums HDL-c and LDL-c value in patients compared to the control.

*Table 3-6 :*

| Serum lipid | at first month | at 2nd month | at 3rd 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 |

** 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.

*Table 3-7 :*

| Serum lipid | at first month | at 2nd month | at 3rd 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 |
| **LDL-c** *(mmol/L)* | 2.71 ± 0.23 | 2.97 ± 0.21 | 2.97 ± 0.21 | 2.87 ± 0.16 |

Table 3-8 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 (standard-dose 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.

*Table 3-8 :*

| Total Cholesterol | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| at first month | | P value | at 2nd month | | P value | at 3rd month | | P value |
| Group I | Group II | 0.533 NS | Group I | Group II | 0.483 NS | Group I | Group II | 0.822 NS |
| | Group III | 0.005 S | | Group III | 0.004 S | | Group III | 0.005 S |
| Group II | Group III | 0.046 S | Group II | Group III | 0.02 S | Group II | Group III | 0.03 S |
| **Triglyceride** | | | | | | | | |
| Group I | Group II | 0.556 NS | Group I | Group II | 0.552 NS | Group I | Group II | 0.550 NS |
| | Group III | 0.030 S | | Group III | 0.047 S | | Group III | 0.034 S |
| Group II | Group III | 0.014 S | Group II | Group III | 0.022 S | Group II | Group III | 0.016 S |
| **HDL-c** | | | | | | | | |
| Group I | Group II | 0.796 NS | Group I | Group II | 0.668 NS | Group I | Group II | 0.642 NS |
| | Group III | 0.111 NS | | Group III | 0.142 NS | | Group III | 0.122 NS |
| Group II | Group III | 0.218 NS | Group II | Group III | 0.284 NS | Group II | Group III | 0.240 NS |
| **LDL-c** | | | | | | | | |
| Group I | Group II | 0.817 NS | Group I | Group II | 0.782 NS | Group I | Group II | 0.689 NS |
| | Group III | 0.295 NS | | Group III | 0.215 NS | | Group III | 0.245 NS |
| Group II | Group III | 0.445 NS | Group II | Group III | 0.435 NS | Group II | Group III | 0.489 NS |

*S: significant NS: no significant (P<0.05 for the comparisons between groups)*

ii. *Effect Of Treatment Groups On Liver Function*

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 and 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.

*Table 3-9 :*

| Parameter | at first month | at 2nd month | at 3rd month | Healthy control |
|---|---|---|---|---|
| **ALP** *(U/L)* | 240.03 ± 11.96 | 239.23 ± 11.30 | 240.19 ± 12.42 | 206.52 ± 12.97 |
| **ALT** *(U/L)* | 24.83 ± 2.64 | 23.71 ± 1.83 | 24.71 ± 1.83 | 19.90 ± 1.52 |
| **AST** *(U/L)* | 20.85 ± 1.25 | 20.76 ± 1.51 | 21.41 ± 1.51 | 19.76 ± 0.69 |
| **T. Bilirubin** *(umol/L)* | 16.39 ± 1.25* | 16.31 ± 1.15* | 16.06 ± 1.11* | 12.57 ± 1.10 |
| **Bilirubin(direct)** *(umol/L)* | 10.29 ± 0.87 | 10.08 ± 0.70 | 9.91 ± 0.69 | 8.50 ± 0.72 |
| **Bilirubin(indirect)** *(umol/L)* | 6.10 ± 0.82* | 6.23 ± 0.62* | 6.15 ± 0.58* | 4.07 ± 0.53 |

**P < 0.05 significant difference from the control*

Table 3.10 shows the effect of group II treatment regimen (low – dose CsA/ Aza/ Pred.) on serum liver function parameter in kidney transplanted patients measured for three consecutive months. No significant differences were observed in the values of serum ALP, ALT and AST of the patients at all intervals compare 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 significantly compare to the healthy control. However the direct bilirubin values were not significantly changed.

*Table 3-10 :*

| Parameter | at first month | at 2nd month | at 3rd month | Healthy control |
|---|---|---|---|---|
| **ALP** *(U/L)* | 221.53 ± 15.49 | 218.86 ± 15.09 | 229.91 ± 15.60 | 206.52 ± 12.97 |
| **ALT** *(U/L)* | 21.66 ± 1.10 | 20.53 ± 1.15 | 21.40 ± 1.19 | 19.90 ± 1.52 |
| **AST** *(U/L)* | 20.45 ± 1.23 | 21.10 ± 1.33 | 20.65 ± 1.46 | 19.76 ± 0.69 |
| **T. Bilirubin** *(µmol/L)* | 16.40 ± 1.76* | 16.94 ± 1.81* | 16.77 ± 1.79* | 12.57 ± 1.10 |
| **Bilirubin (direct)** *(µmol/L)* | 8.98 ± 0.71 | 9.15 ± 0.71 | 9.15 ± 0.69 | 8.50 ± 0.72 |
| **Bilirubin(indirect)** *(µmol/L)* | 7.42 ± 0.54* | 7.79 ± 0.49* | 7.62 ± 0.58* | 4.07 ± 0.53 |

** P < 0.05 significant difference from the control*

Table3.11 shows the effect of group III treatment regimen (low – dose Tac/ MMF/ Pred.) on serum ALP, serum ALT, serum AST and total bilirubin (direct & indirect) in kidney transplanted patients measured for three consecutive months. No significant differences were observed in the values of serum ALP, 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.

*Table 3-11:*

| Parameter | at first month | at 2nd month | at 3rd month | Healthy control |
|---|---|---|---|---|
| **ALP** *(U/L)* | 224.62 ± 13.76 | 226.87 ± 14.03 | 228.81 ± 14.03 | 206.52 ± 12.97 |
| **ALT** *(U/L)* | 20.09 ± 3.56 | 23.50 ± 2.32 | 22.50 ± 3.12 | 19.90 ± 1.52 |
| **AST** *(U/L)* | 19.79 ± 2.24 | 20.23 ± 4.15 | 20.75 ± 4.15 | 19.76 ± 0.69 |
| **T. Bilirubin** *(µmol/L)* | 15.44 ± 1.94 | 15.95 ± 2.31 | 15.66 ± 1.99 | 12.57 ± 1.10 |
| **Bilirubin (direct)** *(µmol/L)* | 9.58 ± 1.81 | 10.72 ± 1.63 | 10.40 ± 1.53 | 8.50 ± 0.72 |
| **Bilirubin(indirect)** *(µmol/L)* | 5.86 ± 0.78 | 5.23 ± 1.46 | 5.26 ± 0.84 | 4.07 ± 0.53 |

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.

*Table 3-12 :*

| Serum alkaline phosphatase | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **at first month** | | **P value** | **at 2nd month** | | **P value** | **at 3rd month** | | **P value** |
| Group I | Group II | 0.264 NS | Group I | Group II | 0.283 NS | Group I | Group II | 0.222 NS |
| | Group III | 0.405 NS | | Group III | 0.414 NS | | Group III | 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 | 0.203 NS | Group I | Group II | 0.252 NS | Group I | Group II | 0.250 NS |
| | Group III | 0.708 NS | | Group III | 0.747 NS | | Group III | 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 | 0.829 NS | Group I | Group II | 0.848 NS | Group I | Group II | 0.842 NS |
| | Group III | 0.969 NS | | Group III | 0.942 NS | | Group III | 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 | 0.804 NS | Group I | Group II | 0.812 NS | Group I | Group II | 0.789 NS |
| | Group III | 0.783 NS | | Group III | 0.715 NS | | Group III | 0.745 NS |
| Group II | Group III | 0.604 NS | Group II | Group III | 0.635 NS | Group II | Group III | 0.689 NS |

*S: significant NS: no significant (P<0.05 for the comparison between groups)*

iii. *Effect Of Treatment Groups On Fasting Blood Glucose*

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).

*Table 3-13 :*

| Glucose | at first month | at 2nd month | at 3rd month | Healthy control |
|---|---|---|---|---|
| **Group I n = 30** | 5.32 ± 0.23 | 5.31 ± 0.27 | 5.30 ± 0.27 | 4.80 ± 0.19 |
| **Group II n = 15** | 5.66 ± 0.49 | 5.77 ± 0.70 | 5.92 ± 0.68 | |
| **Group III n = 7** | 4.86 ± 0.27 | 5.02 ± 0.51 | 5.10 ± 0.50 | |

*Table 3-14 :*

| Serum fasting glucose | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| at first month | | P value | at 2nd month | | P value | at 3rd month | | P value |
| Group I | Group II | 0.400 NS | Group I | Group II | 0.388 NS | Group I | Group II | 0.398 NS |
| | Group III | 0.567 NS | | Group III | 0.514 NS | | Group III | 0.522 NS |
| Group II | Group III | 0.182 NS | Group II | Group III | 0.122 NS | Group II | Group III | 0.131 NS |

*S: significant NS: no significant (P<0.05 for the comparisons between groups)*

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

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) .

*Table 3-15 :*

| Na *(mmol/L)* | at first month | at 2nd month | at 3rd month | Healthy control |
|---|---|---|---|---|
| Group I n = 30 | 139.84 ± 0.52 | 139.74 ± 0.59 | 139.85 ± 0.61 | 139.36 ± 0.43 |
| Group II n = 15 | 140.83 ± 0.60 | 141.05 ± 0.58 | 140.90 ± 0.61 | |
| Group III n = 7 | 139.75 ± 1.65 | 139.60 ± 1.55 | 139.70 ± 1.65 | |
| K *(mmol/L)* | | | | |
| Group I n = 30 | 4.37 ± 0.10 | 4.36 ± 0.07 | 4.40 ± 0.07 | 4.32 ± 0.11 |
| Group II n = 15 | 4.37 ± 0.12 | 4.48 ± 0.09 | 4.44 ± 0.09 | |
| Group III n = 7 | 4.33 ± 0.23 | 4.36 ± 0.17 | 4.36 ± 0.22 | |

*Table 3-16 :*

| Serum Na | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| at first month | | P value | at 2nd month | | P value | at 3rd month | | P value |
| Group I | Group II | 0.139 NS | Group I | Group II | 0.183 NS | Group I | Group II | 0.122 NS |
| | Group III | 0.997 NS | | Group III | 0.914 NS | | Group III | 0.925 NS |
| Group II | Group III | 0.389 NS | Group II | Group III | 0.322 NS | Group II | Group III | 0.331 NS |
| **Serum K** | | | | | | | | |
| Group I | Group II | 0.410 NS | Group I | Group II | 0.452 NS | Group I | Group II | 0.450 NS |
| | Group III | 0.968 NS | | Group III | 0.947 NS | | Group III | 0.934 NS |
| Group II | Group III | 0.600 NS | Group II | Group III | 0.622 NS | Group II | Group III | 0.616 NS |

*S: significant NS: no significant (P<0.05 for the comparisons between groups)*

v. *Adverse Effects Of Treatment Groups Observed In Kidney Transplanted Patients*

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.

*Table 3-17 :* Adverse effects associated with different group's treatment in kidney transplanted patients.

| Adverse Effects | Group I (n =30) | | Group II(n =5) | | Group III (n =7) | |
|---|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | No. | (%) |
| Hypertension | 25 | 83% | 12 | 80% | 5 | 71% |
| Tremor | 8 | 26% | 3 | 20% | 3 | 42% |
| GI upset | 7 | 23% | 2 | 13% | 2 | 28 % |
| Hirsutism | 13 | 43% | 5 | 33% | 0 | --- |
| Gum hyperplasia | 5 | 16 % | 2 | 13% | 0 | --- |

## IV. Discussion

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 Van Buren et al., 1994 (26); Lassila, 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 Wissmann et al., 1996 (22); Moroni, et al, 2006 (31); Bobadilla 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 urea concentration may increase out of proportion 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 3.3 showed the effects of group III treatment regimen (low dose Tac/ MMF/ Pred.) on renal function in seven kidney transplanted patients. No significant increases in serum urea & serum creatinine, and no significant decreased in creatinine clearance level were observed when compared to healthy control for three consecutive months. These results are in agreement with the results of other studies conducted by Artz et al., 2003 (34); Kramer et al., 2005 (4); Naesens et al., 2009 (35) who found less calcineurin-

inhibitor nephrotoxicity with the use tacrolimus in kidney 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 point among the three groups treatment regimen. The mean calculated serum urea and serum creatinine during study were significantly lower in patients receiving low-dose tacrolimus (4.26mmol/L, 112.01$\mu$mol/L for urea and creatinine respectively) than in patients receiving standard-dose cyclosporine (6.28 mmol/L, 133.57$\mu$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). 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 Jurewicz, 2003 (37); Ekberg et al., 2007 (30); Bobadilla and Gamba, 2007 (32) who found improvement in renal function with reducing cyclosporine dosage, and the uses of low-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 Ilgenli et al., 1999 (42); Vaziri et al., 2000 (43); Ichimaru et al., 2001 (39); Abramowicz et al.,2005 (28); Hami 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 down-regulation of enzyme cholesterol 7α-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 patients in this study has only a minimal effect on 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 Vaziri 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 (49); McCune et al., 1998 (50); Ligtenberg et al., 2001 (51); Artz et al., 2003 (34); Morales and Domınguez-Gil, 2006 (36) who revealed no significant effects of tacrolimus on lipid metabolism in renal transplanted recipient.

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 3-8). 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 Scott et al., 2003 (48); Kramer, 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, numerous current findings suggest that oxidative stress mechanism playing an important role in its pathology.

CsA therapy induces overproduction of reactive oxygen species (ROS) in hepatocytes and lowers their antioxidant capacity) 55).

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 results of other studies conducted by Schade et al., 1983 (56); Kahan, 1987 (21); Cadranel, et al, 1992 (57); Hecking, 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 Lorber et al, 1987 (62); Gulbis, et al, 1988 (63); Taniai 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 Taniai, 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 3-12). 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 (low-dose 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 dose-dependent 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 β-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 3-14). This results is not in parallel with other studies results conducted by Filler et al., 2000 (71); Vincenti et al., 2007 (72); Johnston et al., 2008 (73); Hornum 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 Ligtenberg et al., 2001 (51); Hooda 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 3-16). This could indicate no significant effects of the three group's treatment regimen on serum Na and serum K.

In this study, Table 3-17 showed the most common adverse effects for all groups treatment regimen (I & II & III) experienced in patients, and ranged from hypertension (83%) to gum hyperplasia (13%). Hypertension is usually reversible after discontinuation of short-term CsA therapy (77). The effect seems to be more dependent on vasoconstriction than salt retention as demonstrated by hypertension present in an anuric transplant on cyclosporine therapy (78).

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 Lassila, 2000 (27); Castillo-Lugo and Vergne-Marini, 2005 (79); Catarsi 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 Schnuelle et al., 2002 (81); Jose, 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 Kasiske et al, 2000 (16); Ciavarella et al., 2007 (82); Webster 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 Jose, 2007 (52); Chan 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 Morales 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. Conclusion

- Immunosuppressive regimen of low-dose tacrolimus with mycophenolate mofetil in combination with steroids and regimen of low-dose cyclosporine with azathioprine in combinations with steroids provided significantly higher efficacy by improvement in renal function, as compared with regimen containing standard-dose cyclosporine with mycophenolate mofetil in combinations with steroids.
- Immunosuppressive regimen of low-dose tacrolimus with mycophenolate mofetil in combination with steroids associated with a more favourable lipid profile and liver function, as compared with regimens containing either standard-dose cyclosporine with mycophenolate mofetil or low-dose cyclosporine with azathioprine in combinations with steroids.
- Neither low-dose tacrolimus/ mycophenolate mofetil/ steroid, standard-dose cyclosporine/ mycophenolate mofetil/ steroid nor low-dose cyclosporine/ azathioprine/ steroid immunosuppressive regimens are associated with post transplant diabetes mellitus and disturbance in serum electrolyte (Na& K).
- 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.

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