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Dyslipidemia in renal transplant patients at King Chulalongkorn Memorial Hospital

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- Background** : *Dyslipidemia is a major risk factor of cardiovascular disease and atherosclerosis. To know the incidence and characteristics of post-transplantation dyslipidemia is therefore beneficial for the management of this problem in Thai renal transplant patients.*
- Objective** : *To estimate the prevalence and determine the characteristics of dyslipidemia in patients at Renal Transplantation Clinic of King Chulalongkorn Memorial Hospital.*
- Setting** : *King Chulalongkorn Memorial Hospital*
- Research design** : *Cross-sectional descriptive study*
- Methods** : *We gathered medical information of the patients who visited the Renal Transplantation Clinic from January 1st, 2001 to December 31st, 2002. Eligible patients were those who followed up at the clinic for at least 3 months and their serum lipid levels were available. Their clinical data and lipid profiles during the 6 months period before renal transplantation were collected retrospectively. After the operation, their lipid profiles were obtained retrospectively and prospectively at 1, 3, 6, 9, 12 months post-transplantation and hence every 6 months after. The prevalence of hyperlipidemia was then calculated. The means of serum lipid levels before and after transplantation were analyzed by one-way repeated ANOVA and multiple comparisons with Bonferroni. The correlation of serum lipid levels and various factors were determined by stepwise multiple regression analysis.*

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Results : *One hundred and thirty-three renal transplant patients were recruited. The mean follow-up period was 3.46 ± 2.22 years. The highest prevalence of dyslipidemia (83 %) was seen at the end of the first month after transplantation. The prevalence of dyslipidemia remained higher than baseline for at least 5 years. Hypercholesterolemia was more frequently found than hypertriglyceridemia. The mean of total cholesterol levels was significantly elevated during the first month after transplantation and declined 6 months later. The mean of high-density lipoprotein cholesterol significantly increased after surgery and remained above the baseline level for 9 months. Serum triglyceride and low density lipoprotein cholesterol levels were not significantly changed.*

We use data at 3 months post-transplantation to determine the correlation between serum lipid levels and other related factors. Prednisolone dose was significantly correlated with serum cholesterol level. Of patients who received cyclosporine, prednisolone dose and trough concentration of cyclosporine were associated with total cholesterol level. The prednisolone dose was also associated with low-density lipoprotein level. β -blocker use was associated with the increase of triglyceride level while the increasing age and the female gender were associated with increased level of high-density lipoprotein cholesterol after transplantation.

Conclusion : *The prevalence of dyslipidemia and the mean of serum lipid levels were highest during the first 6 months after transplantation. Prednisolone dose, trough concentration of cyclosporine, increasing age, female gender and β -blocker use are risk factors of post-transplantation dyslipidemia.*

Keywords : *Dyslipidemia, Hypercholesterolemia, Hypertriglyceridemia, Renal transplantation.*

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- เหตุผลของการทำการวิจัย** : ภาวะไขมันในเลือดสูงเป็นสาเหตุส่วนหนึ่งของการเกิดโรคหลอดเลือดหัวใจ ซึ่งโรคหลอดเลือดหัวใจเป็นสาเหตุที่สำคัญของการเสียชีวิตในผู้ป่วยปลูกถ่ายไต ข้อมูลในเรื่องความชุกและลักษณะการเกิดภาวะไขมันในเลือดสูงจะเป็นประโยชน์ในการควบคุมภาวะแทรกซ้อนดังกล่าวในผู้ป่วยปลูกถ่ายไตชาวไทย
- วัตถุประสงค์** : เพื่อหาความชุกและลักษณะของการเกิดภาวะไขมันในเลือดสูงในผู้ป่วยที่ได้รับการรักษาที่คลินิกหลังปลูกถ่ายไต ณ โรงพยาบาลจุฬาลงกรณ์
- สถานที่ทำการวิจัย** : โรงพยาบาลจุฬาลงกรณ์
- รูปแบบการวิจัย** : การวิจัยเชิงพรรณนา ณ จุดเวลาใดเวลาหนึ่ง
- วิธีการ** : รวบรวมข้อมูลต่าง ๆ และวิเคราะห์ระดับไขมันในเลือดของผู้ป่วยที่ได้รับการตรวจติดตามหลังการผ่าตัดปลูกถ่ายไต ณ โรงพยาบาลจุฬาลงกรณ์ ตั้งแต่วันที่ 1 มกราคม 2544 ถึงวันที่ 31 ธันวาคม 2545 ผู้ป่วยเหล่านี้เป็นผู้ป่วยนอกที่ได้รับการตรวจวัดระดับไขมันในเลือดร่วมกับตรวจติดตามผลการรักษาเป็นเวลาอย่างน้อย 3 เดือน โดยผู้วิจัยติดตามประวัติการรักษาและระดับไขมันในเลือดก่อนปลูกถ่ายไต 6 เดือนและหลังการปลูกถ่ายไตเป็นระยะที่ 1, 3, 6, 9, 12 เดือนและต่อไปทุก 6 เดือน ก่อนนำข้อมูลมาคำนวณหาความชุกของภาวะไขมันในเลือดสูง เปรียบเทียบค่าเฉลี่ยของระดับไขมันในเลือดแต่ละชนิดที่เวลา 1 ปีหลังปลูกถ่ายไตกับค่าเฉลี่ยของระดับไขมันในเลือดชนิดนั้น ๆ ก่อนปลูกถ่ายไตด้วย one way repeated measure ANOVA และเปรียบเทียบค่าเฉลี่ยของระดับไขมันในเลือดแต่ละชนิดที่ระยะเวลาต่าง ๆ แบบ multiple comparison ด้วย Bonferoni นอกจากนี้ผู้วิจัยได้วิเคราะห์หาความสัมพันธ์ของระดับไขมันในเลือดแต่ละชนิดกับปัจจัยต่าง ๆ ด้วย stepwise multiple regression

ผลการศึกษา : จากผู้ป่วยที่เข้าร่วมวิจัย 133 ราย และมีระยะเวลาติดตามเฉลี่ยเท่ากับ 3.46 ± 2.22 ปี นับจากวันที่ทำการปลูกถ่ายไต พบว่า ความชุกของภาวะไขมันในเลือดสูงในระยะเวลา 5 ปีแรกหลังการปลูกถ่ายไตสูงกว่าความชุกของภาวะไขมันในเลือดสูงก่อนปลูกถ่ายไต โดยมีความชุกของภาวะไขมันในเลือดสูงสูงสุด (ร้อยละ 83) ที่ 1 เดือนหลังการปลูกถ่ายไต และพบภาวะ total cholesterol ในเลือดสูงมากกว่าภาวะ triglyceride ในเลือดสูง ค่าเฉลี่ยของระดับ total cholesterol จะสูงสุดในเดือนที่ 1 และลดลงในเดือนที่ 6 หลังการปลูกถ่ายไต นอกจากนี้พบว่าค่าเฉลี่ยของ high-density lipoprotein cholesterol จะสูงขึ้นตลอด 9 เดือนหลังการปลูกถ่ายไต ในขณะที่ค่าเฉลี่ยของ low-density lipoprotein cholesterol และ triglyceride ไม่เปลี่ยนแปลง

จากการวิเคราะห์ความสัมพันธ์ระหว่างระดับไขมันในเลือดที่ 3 เดือน หลังการผ่าตัดปลูกถ่ายไตกับลักษณะต่าง ๆ ของผู้ป่วย พบว่าขนาด prednisolone มีความสัมพันธ์กับระดับ total cholesterol และเมื่อแยกวิเคราะห์เฉพาะกลุ่มผู้ป่วยที่ได้รับ cyclosporine พบว่าขนาด prednisolone และระดับความเข้มข้นของยา cyclosporine ในเลือดที่ต่ำสุด (C_0) มีความสัมพันธ์กับระดับ total cholesterol และ C_0 ยังสัมพันธ์กับระดับของ low-density lipoprotein cholesterol อีกด้วย นอกจากนี้ยังพบว่าการได้รับ β -blocker drug ทำให้ระดับ triglyceride เพิ่มขึ้นได้ ในขณะที่ระดับของ high-density lipoprotein cholesterol ในผู้หญิงจะสูงกว่าในผู้ชายและระดับ high-density lipoprotein cholesterol มีความสัมพันธ์กับอายุของผู้ป่วยที่มากขึ้น

สรุป : ความชุกของภาวะไขมันในเลือดสูงและค่าเฉลี่ยของระดับไขมันในเลือดผู้ป่วยหลังปลูกถ่ายไต จะพบมากที่สุดในระยะ 6 เดือน หลังการปลูกถ่ายไต ขนาด prednisolone, C_0 , เพศและอายุของผู้ป่วย ตลอดจนการได้รับ β -blocker drug เป็นปัจจัยเสี่ยงของภาวะไขมันในเลือดสูงในผู้ป่วยปลูกถ่ายไต

คำสำคัญ : ภาวะไขมันในเลือดสูง, ภาวะ cholesterol ในเลือดสูง, ภาวะ triglyceride ในเลือดสูง, การปลูกถ่ายไต

It has been accepted that the majority of the patients in their end stage of renal disease (ESRD) have higher quality of life after renal transplantation than those who are on peritoneal dialysis or hemodialysis.⁽¹⁻²⁾ However, a number of renal transplant recipients suffer from graft loss and death after the transplantation from various causes. Among these causes of death, coronary disease is common. It is found that 36 % of death of the patients with functioning graft is contributed by coronary artery disease.⁽³⁾

Dyslipidemia is generally manifested by the rise of total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) both are main risk factors of coronary heart disease in general population. In renal transplant recipients, dyslipidemia is not only associated with coronary heart diseases of renal transplant patients, but is also related to graft survival,⁽³⁾ patient survival, and chronic allograft rejection.⁽⁴⁻⁵⁾

The main causes of dyslipidemia in renal transplant patients is immunosuppressive agents, namely, steroids, cyclosporine, and tacrolimus, which are reported to be associated with dyslipidemia. Other risk factors of dyslipidemia are, diuretic drugs, non-selective β -blocker, proteinuria, diabetes and allograft dysfunction.

There are conflicting reports on the prevalence of dyslipidemia in renal transplant patients. The diversity of the findings might cause by different definition of dyslipidemia and the follow-up time in each study. The National Kidney Foundation Task Force on Cardiovascular Disease reported that diagnosis of dyslipidemia in renal transplant patients can be establish by TC level more than 240 mg/dl ,

LDL-C more than 130 mg/dl, triglyceride (TG) more than 200 mg/dl and high-density lipoprotein cholesterol (HDL-C) less than 35 mg/dl which by the difenition the prevalence are 60 %, 60 %, 35 %, and 25 % respectively.⁽⁶⁾ Mostly, dyslipidemia is detected in 6 month – 1 year after transplant.⁽⁷⁻⁸⁾ Race of the population also plays an important role on the prevalence of dyslipidemia: Asians and Mexicans have lower prevalence that Caucasian.⁽⁹⁻¹⁰⁾

The rational of the study is based on the fact that, currently, there are few long term studies on characteristics and prevalence of dyslipidemia on renal transplant patients in Thailand.

Methodology and data analysis

The recruited subjects in this study were renal transplant patients at King Chulalongkorn Memorial Hospital. All of them were followed up at the Renal Transplantation Clinic from January 1st, 2001 to December 31st, 2002. They were required to visit the clinic at least every 3 months and their blood lipid concentration was checked for at less 3 months after transplantation. Nephrotic syndrom as cause of patients' ESRD and de novo nephrotic syndrome after the transplantation were excluded from the study. Lena Ong-Ajyooth *et al.* reported 80 % prevalence of dyslipidemia in renal transplant patients from sample size of 43 cases with the degree of confidence set at 95% and p value = 0.15.⁽¹¹⁾

Dyslipidemia is the condition which a person, after at least 12 hours of fasting, has one of the following condition, namely, TC more than 200 mg/dl or LDL-C more than 130 mg/dl or TG more than 200 mg/dl with anti-lipemic drug or the person is registered in medical record of having dyslipidemia.

A person is identified as diabetic when he has the following condition: having blood sugar more than 126 mg/dl after fasting more than 8 hours for no less than twice consecutively, or the person is depending on oral hypoglycemic drug and/or insulin or registered in medical record as diabetic.

Post-transplant diabetes mellitus is the person who develops diabetes after renal transplant which is not detected in the first 6 months post-transplant.

Accordingly, we were obliged to follow the level of blood lipid and anti-lipid drugs for at less 6 months after transplant, hence at month 1, 3, 6, 9 and then every 6 months post-transplant until in February 28th, 2003 when all the data were collected. Also, the use of drugs, such as immunosuppressive agents, is closely monitored.

This study has been reviewed and approved by the Research Ethics Committee of the Faculty of Medicine, Chulalongkorn University. The followings are definitions employed in the study:

Statistical Methods

The prevalence of dyslipidemia in renal transplant patients was analyzed in terms of percentage in comparison to the average level of blood lipid before transplantation throughout the first year post-transplant with one way repeated measure ANOVA. The mean level of blood lipid is compared to the time frame using Bonferroni multiple comparison, including the calculation for the association of the blood lipid concentration of different types of the patients which are expected to cause post-transplant hyperlipidemia by multiple regression analysis. All of the characters were analyzed with the level of

significance at p value less than 0.05 with stepwise analysis.

Results

Of the total of 133 subjects, 54 % were male, and 46 % were female. Among them, 124 (93 %) cases were patients who received renal transplantation during the period of seven years between 1995 - 2002. The most common cause of chronic renal failure were diabetes (15 %). All transplanted patients were first-time recipients of the organ. Most of them (68 %) received their kidney from cadavers; 80 % of these patients had been on dialysis before their transplant. Averagely, when the patients received their renal transplant they were between 16 - 67 years old (average age 41 ± 10.52 years). Table 1 illustrates general demographic characters of the patients.

In average, we followed up with the patients for 3.46 ± 2.22 years (3 months -10.5 years). The number of the patients at different periods of time is shown in Fig 1. It is found that in the fifth year post-transplant, the number of the patients is less than the calculated size (43 cases).

Every patient who participated in the study received prednisolone as their maintenance therapy. The majority of the patients, 90 % (119 cases) and 91 % (108 cases) received cyclosporin at the end of the first month and at the end of the first year after transplantation, respectively.

Prevalence of dyslipidemia

The prevalence of dyslipidemia is higher after transplantation, 53 % pre-transplant and 83 % at the first month after transplant. The lipid concentration continuously rose throughout the study with the lowest

Table 1. Demographical characteristics of the patients.

Demographical data	Number of cases	Percentage
Gender		
Male	72	54
Female	61	46
Age (Mean \pm SD)	41.83 \pm 10.52 yrs.	
Cause of Chronic Renal Failure		
Diabetic nephropathy	20	15
Chronic glomerulonephritis	11	8
IgA nephropathy	10	8
ADPKD*	9	7
Others	83	62
Pre-transplant treatments		
Hemodialysis	107	80
Peritoneal dialysis	6	5
No treatment	20	15
Follow-up time (years)		
Mean \pm SD	3.46 \pm 2.22	
MMax	0.25 - 10.50	
Year of kidney transplant		
1990 - 1994	9	7
1995 - 1999	64	48
2000 - 2002	60	45
Number of kidney transplant		
First time	131	98
Second time	2	2
Graphic illustration		
Kidney taken from cadavers	90	68
Kidney taken from living donors		
Blood relation	39	29
(living - related donors)		
No blood relation	4	3
(living - unrelated donors)		

*ADPKD = autosomal dominant polycystic kidney disease

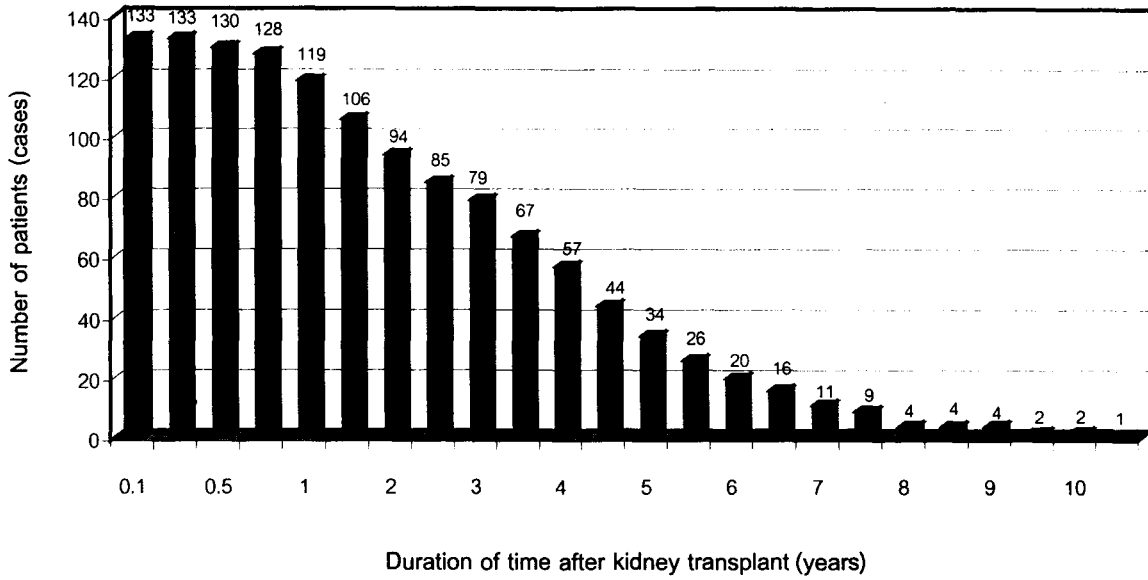


Figure 1. Number of patients who followed up at the post-transplant clinic at different time after their kidney transplant.

prevalence at 50 %, as shown in Fig 2. The timing of the highest prevalence of dyslipidemia was the first three months after transplantation. The prevalence of high total cholesterol and high level of HDL-C

in the blood persisted five years after transplant. At 6 months after transplant, the prevalence of hypertriglyceridemia and high blood LDL-C decreased than the pre-transplantation prevalence (Fig 3).

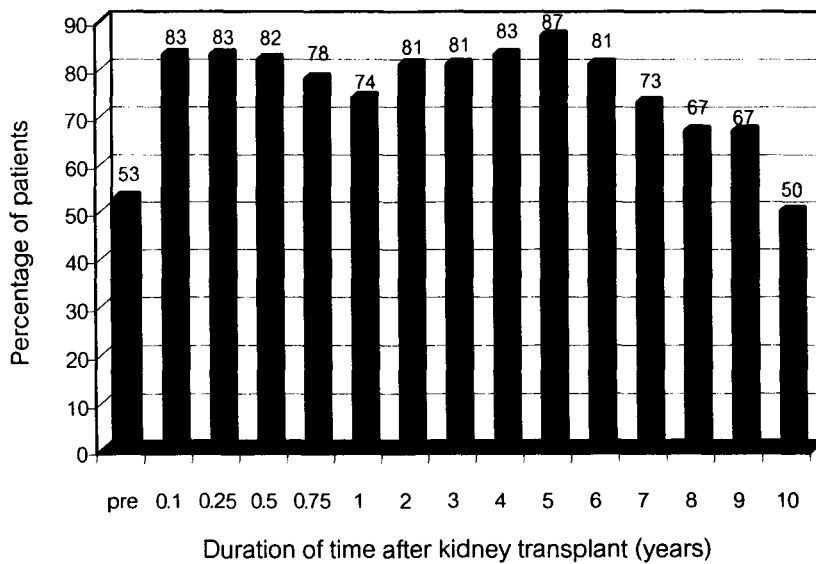


Figure 2. Percentage of patients with hypercholesterolemia at different times, before and after kidney transplant.

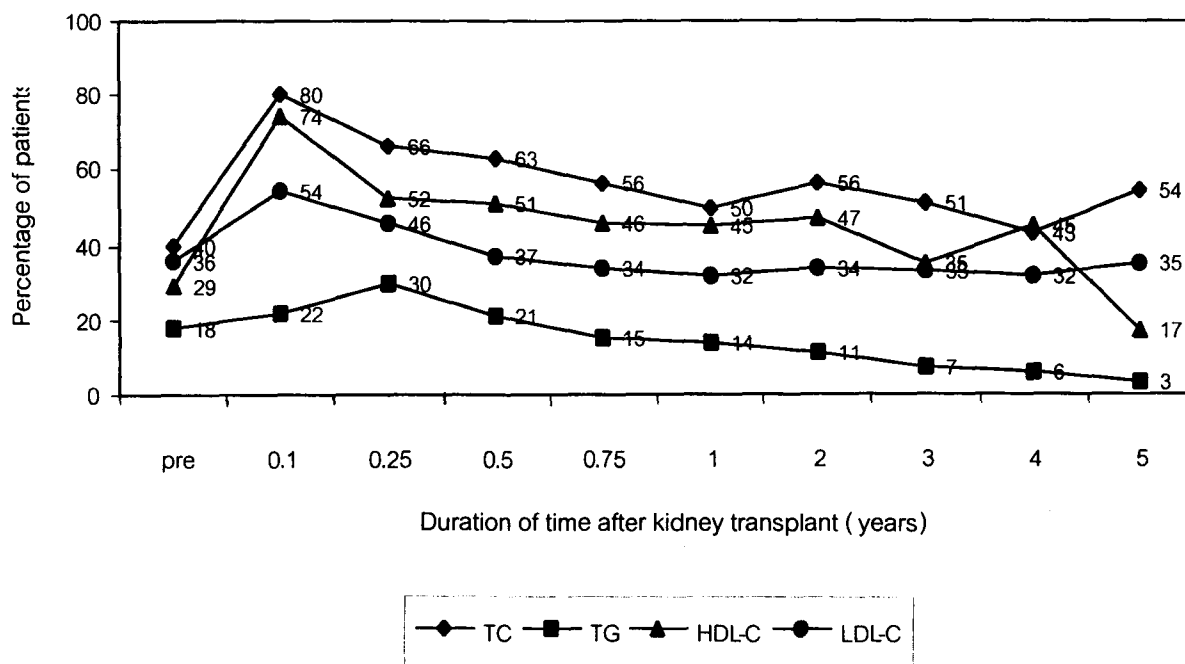


Figure 3. Prevalence of hypercholesterolemia of different type at different times after kidney transplant.

Onset of dyslipidemia

The means blood level of TC, TG, HDL-C, and LDL-C at different periods of time namely, pre-transplantation, and 1, 3, 6, 9 and 12 month post-transplantation were compared (Table 2 and Fig 4) There were no significant differences of the mean levels of TG and LDL-C, pre and post-transplant, whereas there is a significant increase of the means of TC and HDL-C post-transplant.

The mean level of TC pre-transplant was significantly different from that post-transplantation ($p < 0.005$). At 1 month post-transplant, the mean level of pre-transplant TC was higher than pre-transplantation (243.27 ± 46.16 mg/dl VS 194.50 ± 51.30 mg/dl, $p < 0.001$). At 6, 9 and 12 month post-transplant, the mean level of TC was 211.05 ± 38.24 mg/dl, 206.20 ± 33.71 mg/dl, and 201.15 ± 35.98 mg/dl respectively.

Table 2. Statistical analysis of the difference of means of pre/post-transplant blood cholesterol levels using one-way repeated measure ANOVA.

Types of blood cholesterol	Mauchly's Test of Sphericity	Sphericity Assumed	Huynh-Feldt
TC (N = 40)	0.000	-	0.000
TG (N = 39)	0.002	-	0.108
HDL-C (N = 22)	0.443	0.000	-
LDL-C (N = 21)	0.110	0.062	-

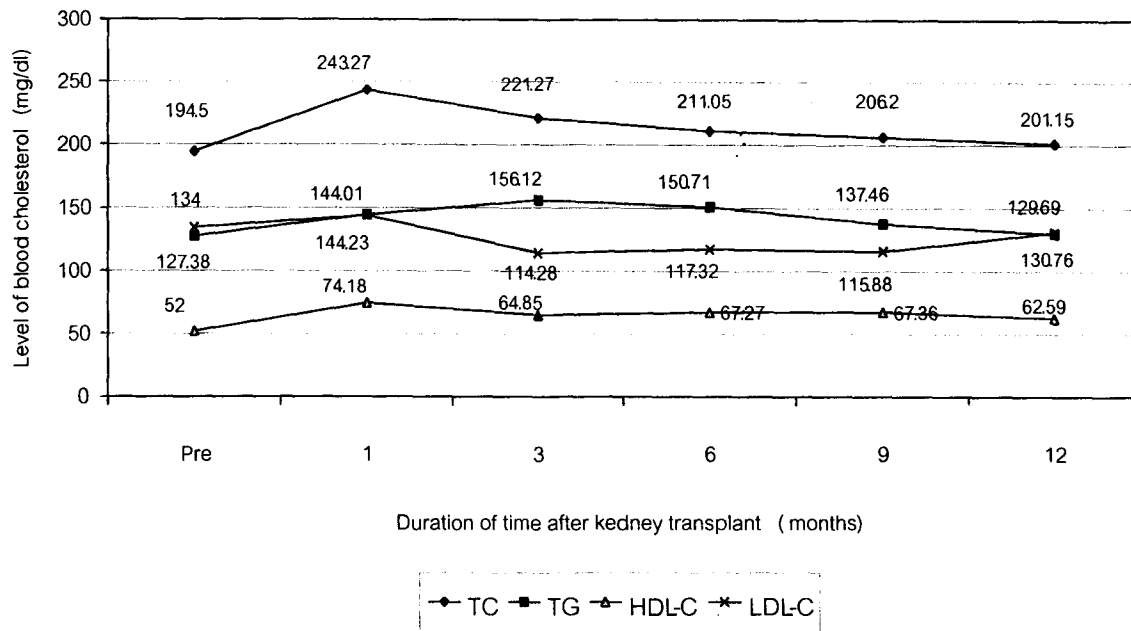


Figure 4. Mean levels of different types of blood cholesterol in patients at different times before their transplant and during their first year after transplant.

There was also a significant difference between the mean level of HDL-C pre and post-transplant ($p < 0.001$). The HDL-C concentration at different periods of time post-transplantation was significantly increased (52.00 ± 18.19 mg/dl to 74.18 ± 18.84 mg/dl, 64.85 ± 18.97 mg/dl, 67.27 ± 13.78 mg/dl, and 67.36 ± 15.94 mg/dl at 1, 3, 6 and 9, month post-transplantation respectively. The mean HDL-C concentration significantly at 12 month post-transplantation compared to 1 month post-transplantation (74.18 ± 18.84 mg/dl VS 62.59 ± 17.48 mg/dl, $p < 0.005$).

Relations between various characters of patients and blood lipid levels

Since post-transplant hyperlipidemia was common in the first 6 months after transplant, 85 blood samples in the third month post-transplantation

were collected to analyze for the correlation between different types of blood lipid and various specific variables with multiple regressive method.

The data showed that the dose of prednisolone correlated with the level of TC and whether the patients received β -blocker correlated with the level of TG. Also, the analysis showed that HDL-C was associated with female gender and age. However, there was no correlation between cyclosporine and methyl prednisolone, as the treatment of acute allograft rejection, with dyslipidemia (Table 3).

The analysis of 59 cases who received cyclosporine to analyze the relation between dyslipidemia at 3 months post-transplant with other factors, including the dose of cyclosporine and cyclosporine trough concentration (C_0) with multiple regressive equations by putting all the variables into

Table 3. Statistical analysis of the multiple regression coefficients between characteristics of the patients and their blood cholesterol levels.

	r	R ²	B	Std. Error	T	P value
Total cholesterol	0.223	0.050				
Prednisolone dose			2.367	1.135	2.085	0.040
Triglyceride	0.253	0.064				
β - blockers			52.387	21.97	2.384	0.019
HDL - C	0.395	0.094				
Female			12.154	4.031	3.015	0.003
Age			0.448	0.183	2.452	0.016

r = Regression Coefficient, R² = Multiple Coefficient of Determination, B = Unstandardized Coefficient

Table 4. Statistical analysis of the multiple regression coefficients between characteristics of the patients and their blood cholesterol levels in those who mainly received CSA as their primary drug and their lowest levels of blood CSA (C₀).

	r	R ²	B	Std. Error	T	P value
Total cholesterol	0.389	0.151				
C ₀			0.168	0.68	2.467	0.017
Prednisolone dose			2.426	1.171	2.072	0.043
LDL - C	0.276	0.076				
C ₀			0.129	0.060	2.167	0.034
HDL - C	0.407	0.166				
Female			11.24	4.983	2.255	0.028
Age			0.494	0.229	2.155	0.035

r = Regression Coefficient, R² = Multiple Coefficient of Determination, B = Unstandardized Coefficient

equations by stepwise method. The data showed that the dose of prednisolone and C₀ correlated with the level of TC and LDL-C concentration (Table 4).

Discussion

In this study, the prevalence of hypercholesterolemia and high level of LDL-C in renal transplantation were 45 percent 30 percent,

respectively. Considering the target limits of blood lipid level based on the advice of the National Kidney Foundation (NKF)/DOQI published in 2003 (B.E. 2546)⁽¹²⁾, renal transplant patients are considered as high risk as diabetics and coronary heart diseases patients. The study has found that throughout the five years of data collection over 60 % of the patients have blood LDL-C higher than 100 mg/dl (Fig 5). A

cross sectional study of Leena Ongachyuth *et al.*⁽¹¹⁾ reported the prevalence of high total blood cholesterol (TC \geq 200 mg/dl) in Thai renal transplant patients was 82.5 %, and the prevalence dropped to 51 % at three years post-transplantation. A report from Australia by Ong CS *et al.*⁽¹³⁾ illustrated that the prevalence of high total cholesterol (TC \geq 240 mg/dl) in the first month and fifth year after transplant were 61 % and 59 %, respectively. In general, the prevalence of pre and post-transplant dyslipidemia among Asian populations is lower than that of the European and Americans. This phenomenon is probably contributed by a number of factors for example eating habits and life styles.

We have found that the prevalence of hypertriglyceridemia increases in the first six months after transplantation before it starts to decline. The main cause of the anomaly is the defect in lipoprotein

lipase enzyme which is active in extraction of TG from the molecule of triglyceride enriched lipoprotein. The defect is caused by the insufficiency of lipoprotein lipase enzyme stimulator, apoC-II, insulin resistance and the rise of lipoprotein lipase enzyme inhibitor which cause by the accumulation of uremic toxin and hyperparathyroid.⁽¹⁴⁾

Our data also shows that the prevalence of high HDL-C after renal transplant correspond to that of earlier reports (Fig 6). Kisielnicka *et al.*⁽¹⁵⁾ reported that the level of HDL-C significantly increases in the first month after renal transplant when compared to those patients who were on dialysis. Kasiske and Umen⁽¹⁶⁾ reported that HDL-C after renal transplant significantly rises from 51.7 ± 1.7 mg/dl in the first year to 64.2 ± 1.5 mg/dl in the fifth year after transplant.

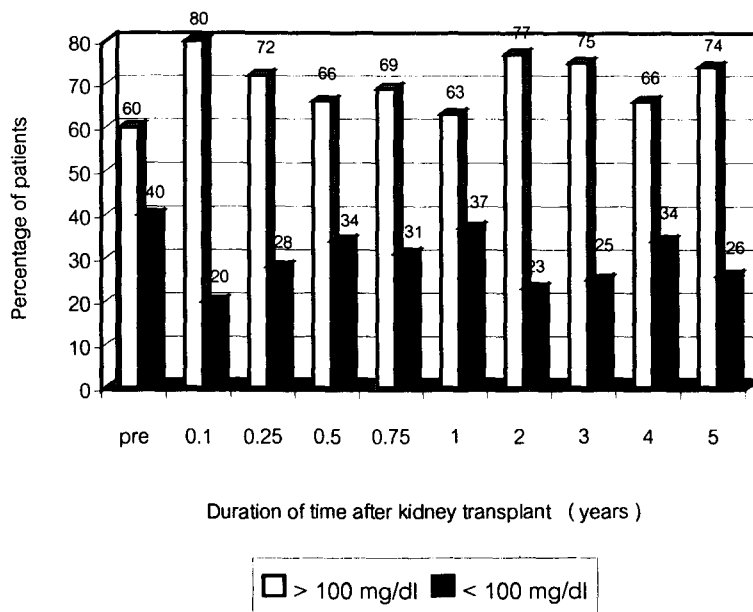


Figure 5. Number of patients classified according to their level of LDL - C at different times, before and after kidney transplant.

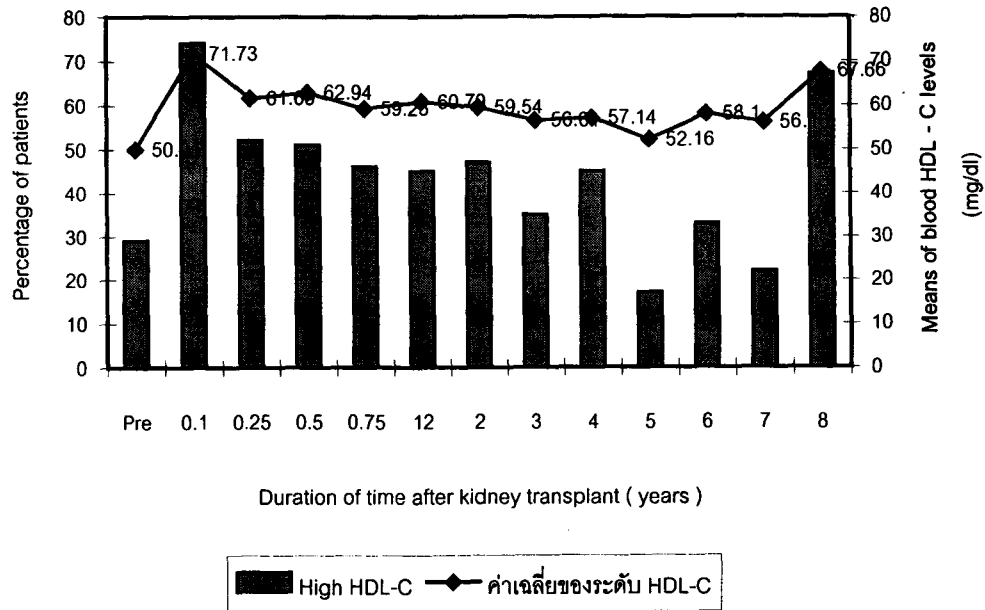


Figure 6. Number of patients with HDL - C \geq 60 mg/dl and the means of HDL - C at different times before and after kidney transplant.

The multiple regression analysis of the blood lipid level 3 months after renal transplant found that the dose of prednisolone affect the rise of the level cholesterol. We also found that the dose of prednisolone and C_0 correlated with the level of TC. The finding coincides with earlier reports that the dose of prednisolone is related to the level of TC. ⁽¹⁸⁻²¹⁾ Although the study could not find the relation between the dose of cyclosporine and the blood lipid level, we found that C_0 is related to the level of TC and LDL-C which concur with the study of Kuster GM *et al.* ⁽²²⁾

Conclusion

Dyslipidemia is common in the first six months of kidney transplantation. The cause of the dyslipidemia is contributed by several factors, for example, the high dose of immuno-suppressive drugs and antihypertensive drug. It is therefore necessary to monitor and control the lipid level, especially LDL-

C to prevent vascular diseases in renal transplanted patients.

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