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CLINICAL STUDY

Validation of the Friedewald formula for the determination of low-density lipoprotein cholesterol in renal transplant recipients

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ABSTRACT

In large patient populations, it has been established that calculated (c) and measured (m) plasma levels of low-density lipoprotein cholesterol (LDL-C) were comparable, but this issue is not known to be tested in renal transplant recipients (RTRs). Herein we aimed to compare the plasma levels of LDL-C that was calculated by Friedewald formula (FF) and direct measurement in RTRs. Methods: LDL-C was measured by direct method and by FF in 193 fasting venous blood samples obtained from 103 RTRs. Patients had triglyceride (TG) levels <400 mg/dL. Patients were treated with prednisolone, calcineurin inhibitors (CNIs), and/or sirolimus and everolimus. Results: The mean plasma levels of LDL-C for calculated and direct measurement were 100.81 ± 32.79 mg/dL and 107.82 ± 33.23 mg/dL, respectively ($p < 0.01$). The differences between cLDL-C and mLDL-C were similar according to usage of angiotensin receptor blockers (ARB)/angiotensin-converting enzyme inhibitors (ACEI), CNI, or mammalian target of rapamycin inhibitor (mTOR), tacrolimus or cyclosporine, and serum creatinine levels. mLDL-C and cLDL (FF) were highly correlated ($r = 0.977$). The mLDL-C level was calculated by following formula: LDL-C = 8.018 + (0.99 × FF cLDL-C) and the mean difference was 0 for last formula. Conclusion: The LDL-C can be calculated by the following formula: LDL-C = 8.018 + (0.99 × FF LDL-C). The coefficient of determination correlation (r) for this regression was 0.977, which indicates that the calculated LDL-C levels can be used in RTRs with TG lower than 400 mg/dL. mLDL-C was significantly higher than cLDL-C. We observed that difference between cLDL-C and mLDL-C levels were not affected by serum creatinine levels and usage of CNIs, sirolimus, everolimus, ACEI, and ARB in RTRs.

Keywords: mLDL-cholesterol; cLDL-cholesterol; Friedewald formula; renal transplantation; immunosuppression

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INTRODUCTION

A high level of low-density lipoprotein cholesterol is an established risk factor for the development of coronary artery disease.[1] Low-density lipoprotein cholesterol (LDL-C) carries most of the circulating cholesterol.[2] The measurement of total cholesterol concentration provides a useful surrogate indicator of LDL-C concentration. Recently, guidelines detail specific LDL-C cut-points for therapeutic goals. In practice LDL-C is usually derived from the Friedewald formula (FF). LDL-C can be directly measured by beta quantification after ultracentrifugation or by using precipitation chromatographic or electrophoretic methodologies. All these methods are expensive and time consuming and some require ultracentrifuge to prepare a plasma or serum fraction that contains only LDL-C and high-density lipoprotein cholesterol (HDL-C). Total cholesterol and HDL-C are directly measured but LDL-C is calculated by subtracting HDL-C from total cholesterol. LDL-C is usually derived from the FF. Plasma triglyceride (TG) concentration exceeds 400 mg/dL, type IV hyperlipoproteinemia, and the presence of chylomicrons is the main limitation of using FF.[3–5] The most important reason of mortality in renal transplant recipients (RTRs) is cardiovascular disease.[6] Dyslipidemia sets with the development of chronic kidney disease in RTRs and majority of patients have pre-existent cardiovascular disease at the time of undergoing renal transplantation.[7] Dyslipemia also plays a significant role in chronic allograft nephropathy.[8] After renal transplantation, TG, total cholesterol, and LDL-cholesterol increase while HDL-cholesterol remained unchanged. The most common lipid abnormality in RTRs is higher levels of LDL-C. Immunosuppressives such as cyclosporine, steroids, and sirolimus are other remediable causes of dyslipemias in

RTRs.[9] So that modifiable cardiovascular risk factors including LDL-C should be treated. FF's accuracy among RTRs is not studied according to our best knowledge. In this study, we compared the diagnostic value of directly measured LDL-C and calculated LDL-C and evaluated the effect of immunosuppressives and angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) on cLDL-C and mLDL-C.

METHODS AND PATIENTS

LDL-C was estimated by a direct method and also by FF in 193, 12 hours fasting venous blood samples which were obtained from 103 RTRs. The mean age of patients was 37.12 ± 11.44 years and post-transplant duration was 37.28 ± 39.51 months. Only 8 of 103 patients had diabetes mellitus. Mean serum creatinine level was 1.34 ± 0.53 mg/dL (range 0.5–3.29). We excluded samples with TG levels above 400 mg/dL. LDL-C was directly measured with the LDL cholesterol direct enzymatic colorimetric method (CHOD-PAP) without sample pretreatment (Instrument: COBAS Integra 800 Roche Diagnostics Germany). LDL-C was calculated from the FF as follows:

$$\text{FF} = \text{total cholestrol} - \left(\text{HDL-C} + \frac{\text{TG}}{5} \right).$$

Ninety-nine of 103 patients were treated with prednisolone (maintenance dose 4 mg/day). Patients were treated with tacrolimus (84 patients) or cyclosporine (15 patients) in a dose which achieves standard target levels. Sirolimus without calcineusin inhibitor (CNI) were given to four patients and everolimus were given to 14 patients. One hundred and fifty-nine of the 193 serum samples were taken from patients treated with tacrolimus, 26 serum samples from cyclosporine group, 5 serum samples from sirolimus, 35 serum samples from everolimus group, 136 measurements from mycophenolate mofetil group, and 6 measurements from azathioprine group. Also 17 measurements from alpha blocker group, 42 measurements from ACEI/ARB group, 114 measurements from calcium channel blocker group, and 9 measurements from diuretic group.

STATISTICAL METHODS

The data was analyzed with SPSS v16. A *t*-test was performed to compare the differences between FF-calculated LDL and measured LDL among groups and a regression analysis was performed to estimate the validity of FF cLDL. Variables are expressed as mean and standard deviation. Passing–Bablok regression analysis and the Bland–Altman method were also applied. Statistically significant differences were defined as $p < 0.05$.

RESULTS

The characteristics and biochemical results of the patients are summarized in Table 1. The differences

TABLE 1. The characteristics and some biochemical test results of renal transplant recipients.

	Mean ± SD	Range
Age (year)	37.12 ± 11.44	18–64
Gender (M/F)	63/40	
Body weight (kg)	65.65 ± 13.01	44–110
DM/NODM	3/5	
Post-transplant duration (months)	37.28 ± 39.51	1–216
SBP (mmHg)	124.81 ± 18.25	85–180
DBP (mmHg)	78.50 ± 10.16	70–110
Glucose (mg/dL)	90.74 ± 24.37	69–246
Serum creatinine (mmHg)	1.34 ± 0.53	0.5–3.2
mLDL (mg/dL)	107.82 ± 33.23	39–209
cLDL (mg/dL)	100.81 ± 32.79	31–200
mLDL–cLDL (FF)	−7.0 ± 7.09	−8 and −5
mLDL–cLDL (regression model)	0	−26 and +16
Triglyceride (mg/dL)	158.38 ± 70.25	43–388
Total cholesterol (mg/dL)	182.25 ± 43.90	87–315

Notes: Abbreviations: DM: diabetes mellitus, NODM: post transplant new onset diabetes mellitus, SBP: systolic blood pressure, DBP: diastolic blood pressure, mLDL-C: measured low-density lipoprotein cholesterol, cLDL-C: calculated low-density lipoprotein cholesterol.

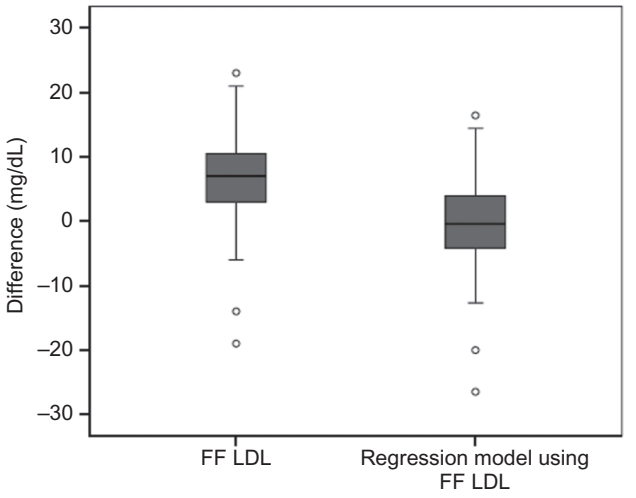


FIGURE 1. The differences between measured and calculated LDL-C (FF and regression model using FF).

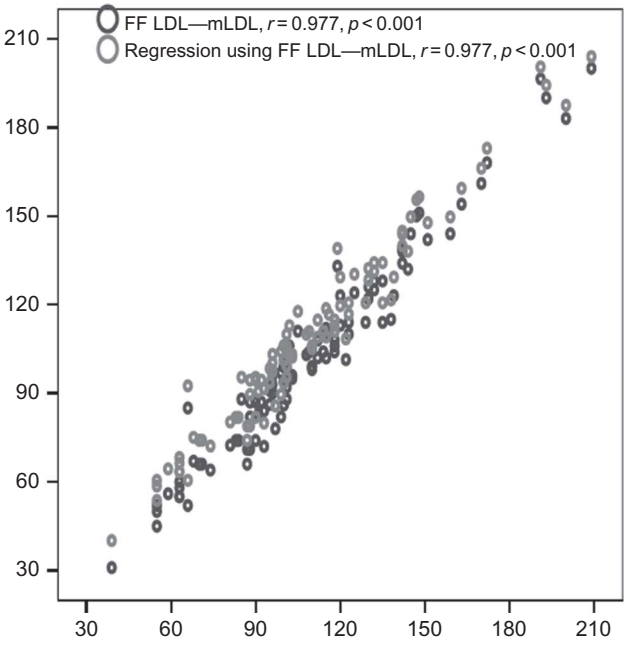


FIGURE 2. The correlations of calculated LDL-C (FF and using regression method) and measured LDL-C.

between mLDL-C and cLDL-C (FF and regression model using FF) are shown on Figure 1. The correlations of cLDL-C (FF) and mLDL-C are shown in Figure 2. mLDL-C was higher than cLDL in 90% of plasma samples. The differences between cLDL-C and mLDL-C were similar according to the usage of CNI or mammalian target of rapamycin inhibitor (mTOR), tacrolimus or cyclosporine. mLDL-C and cLDL (FF) were highly correlated (r = 0.977). In the regression analysis of measured LDL on calculated LDL we observed a R^2 = 0.954, adding alpha blocker

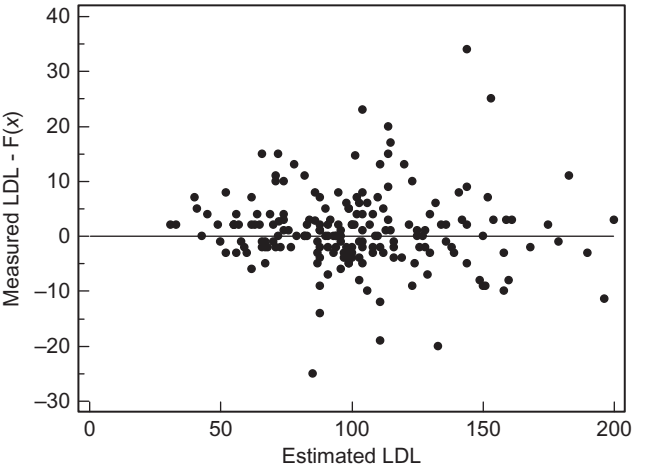


FIGURE 3. The Bland–Altman graph for estimated and measured LDL.

variable to the model did result in a significant p-value (p = 0.037) for alpha blocker but did not cause any increase for R^2 nor an important decrease in standard error of estimate (7.102 vs. 7.091) in our regression analysis. Adding other variables like serum creatinine levels, ACEI/ARB, beta blocker, calcium channel blockers, or use of diuretics to the regression model did not result in significant p-values for any of them. The difference between mLDL-C and FF cLDL-C was −7.00 ± 7.09 (minimum −8 and maximum −5). The mLDL-C level was calculated by the following formula: LDL-C = 8.018 + (0.99 × FF cLDL-C) and difference was 0 for this last formula (minimum −26, maximum +16, range 42) (Figures 2 and 3).

DISCUSSION

Lipid abnormalities are one of the major causes of accelerated atherosclerosis in RTRs.[6] LDL-C is routinely calculated in laboratories by applying FF for logistic reasons. Hypertriglyceridemia is the main limitation in the use of the FF, and the estimation of LDL-C therefore FF is not reliable on these patients.[3–5] An accurate quantitation of LDL-C is needed to initiate lipid lowering therapy. In this study, we compared directly measured LDL-C [LDL cholesterol direct enzymatic colorimetric method (CHOD-PAP) without sample pretreatment] and calculated LDL-C levels in RTRs and evaluated the effect of serum creatinine levels, immunosuppressives [CNIs (cyclosporine A, tacrolimus), mTOR inhibitors (sirolimus, everolimus)] and ACEI, and ARB on cLDL-C and mLDL-C. Because TG levels were lower than 400 mg/dL in our patients, LDL-C levels could be calculated by FF, and mLDL-C and cLDL-C were highly correlated. Also in other

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series, FF and similar formulas determine the LDL-C accurately if TG levels are lower than 400 mg/dL. Although cLDL-C was found to be higher than directly measured LDL levels by ultracentrifugation method in a study,[10] the levels of mLDL-C were higher than cLDL-C in >90% samples in our study as in many other studies published in the literature.[11,12]

The recently updated National Cholesterol Education Programme/Adult Treatment Programme III guidelines maintain the focus of diagnosis and treatment efforts on total cholesterol and LDL-C. Therapy is targeted on lowering LDL-C values below a cut-off value, which depends on the number of other risk factors present.[13] HDL-C, LDL-C, and very low-density lipoprotein cholesterol (VLDL-C) may be determined accurately by ultracentrifugation according to established protocols. But this procedure is both time consuming and expensive. The FF has not been tested in RTRs according to our best knowledge. In our study also, there was a good correlation ($r = 0.977$) for mLDL-C with LDL-C calculated from FF and our new formula in RTRs with TG levels lower than 400 mg/dL. The values of FF cLDL-C were a little bit lower than direct measurements. We found that mLDL-C or cLDL-C levels were not affected by serum creatinine levels or by using CNIs, mTOR inhibitor, ACEI, and ARB. So cLDL-C is safe in RTRs who take many drugs for immunosuppression, hypertension, and so on. Our formula correlated well with the FF as well and had a better correlation when compared with the direct method.

In conclusion, the measured LDL-C can be calculated from the following formula: LDL-C = 8.018 + (0.99 × FF LDL-C). The coefficient of correlation (r) for this regression was 0.977, which indicates that the calculated LDL-C levels can be used instead of measuring them in RTRs with TG levels lower than 400 mg/dL. Measured LDL-C was significantly higher than calculated LDL-C. Also we found that calculated and measured LDL-C levels were not affected by drugs such as CNIs, mTOR inhibitors, ACEI, and ARB in RTRs.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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