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ANALYSIS OF LDL-C MEASUREMENT USING DIRECT AND FRIEDEWALD FORMULA IN TYPE 2 DIABETES MELLITUS PATIENTS

Liong Boy Kurniawan¹, Windarwati², Budi Mulyono²

¹Department of Clinical Pathology, Faculty of Medicine, Hasanuddin University/Hasanuddin University Hospital, Makassar, Indonesia. E-mail: liongboykurniawan@yahoo.com ²Department of Clinical Pathology, Faculty of Medicine, Gadjah Mada University, Yogyakarta, Indonesia

ABSTRACT

LDL-C is important to evaluate the risk of cardiovascular disease. LDL-C can be measured directly or by using the Friedewald equation. Type 2 Diabetes Mellitus (DM) patients have tighter LDL-C target compared with normal population. This research is aimed to analyze the difference of LDL-C level measured by direct test and Friedewald equation in DM and non-DM. This research was a cross-sectional study using LDL-C data of 208 patients who were tested in Laboratory of Clinical Pathology, Hasanuddin University Hospital from a period of August 2015 to January 2016. LDL-C and other lipid were measured using ABX Pentra 400 meanwhile Friedewald LDL-C was calculated with equation LDL-C = Total Cholesterol-HDL-C-(1/5 Triglycerides). Type 2 DM patients were diagnosed by ADA 2015 criteria or who had previous DM history. Friedewald LDL-C estimates lower than direct method (139.07±50.60 mg/dL vs 155.33±51.74 mg/dL, p=0.000). Delta of direct LDL-C and Friedewald equation measurement is higher in DM than non-DM patients (11.97±11.52% vs 8.49±11.27%, p=0.030) Fridewald LDL-C estimates LDL-C lower than direct method and the difference is wider in DM than non-DM. It is suggested to measure LDL-C directly in DM type 2 to reach the actual LDL-C target.

Key words: Direct LDL-C, Friedewald, diabetes mellitus

INTRODUCTION

Hypercholesterolemia is a common condition related to atherosclerosis. Low-density lipoprotein cholesterol (LDL-C) can be used as a marker of the major risk factor of cardiovascular events in the future of hyperlipidemia patients and as therapy goal in those patients. Accuracy and precision of LDL-C measurement are very important for coronary heart disease patients.¹

Reference method of LDL-C measurement in serum is b-Quantitation procedure which needs an ultracentrifugation technique. This procedure is time consuming, expensive, and needs more volume of serum, therefore it is not suitable for routine testing. LDL-C quantification is often measured by two methods, direct measurement and quantification by using Friedewald Formula (FF) which is commonly accepted.²

Friedewald et al. in 1972 described a formula for estimating LDL-C value by using total cholesterol, High-Density Lipoprotein Cholesterol (HDL-C) and triglycerides measurements. The limitation of this formula is that the patients must be in a fasting condition and the level of triglycerides may not exceed 400 mg/dL.³

Type 2 Diabetes Mellitus (DM) is characterized by dyslipidemia. Dyslipidemia in diabetes shows low level of HDL-C, abnormal Very Low-Density Lipoprotein (VLDL), high triglycerides with normal or slightly increased of LDL-C, and total cholesterol. This condition is related to coronary heart disease.⁴ Type 2 DM patients often have dyslipidemia, so routine LDL-C measurement is performed to stratify the risk factor of cardiovascular events in the future.⁵ Low density lipoprotein cholesterol analysis is usually performed by using direct test or by calculating it using Friedewald Formula, therefore the accuracy of this formula in estimating exact LDL-C level in diabetes patients is needed to stratify cardiovascular risk and as therapy target.

In this study, measurement and comparison of LDL-C in type 2 diabetes mellitus patients using direct test and Friedewald Formula was conducted. The aim of this study was to evaluate the accuracy of this formula compared with the direct method.

METHODS

A cross-sectional study performed by taking data of diabetic and non-diabetic patients who were for tested LDL-C in the Hasanuddin University Hospital, Makassar from the period of August 2015 to January 2016. A direct test of LDL-C, total cholesterol, HDL-C, and triglycerides were performed by using ABX Pentra 400. Quantification with Friedewald Formula was performed by using an equation: LDL-C = Total cholesterol – HDL-C – triglycerides/5. Type 2 diabetes mellitus patients were diagnosed by the American Diabetic Association (ADA) 2015 criteria or those who had a previous diabetic history. Non-diabetic subjects as a control were also recruited.
for the comparison. LDL-C test was performed after at least 8 hours period of fasting. Samples with triglycerides exceeding 400 mg/dL were excluded. Normality of data were analyzed with the Kolmogorov-Smirnov test. Normally distributed data were percentage of rLDL while age, total cholesterol, HDL-C, LDL-C triglycerides, and LDL-C calculated with the Friedewald Formula (LDL-FF) were not normally distributed. rLDL was described as direct LDL minus LDL-FF. LDL-C level than LDL-FF, 37 (17.79%) had a higher LDL-FF than direct LDL-C meanwhile 1 (0.48%) sample had the same value of direct LDL-C and LDL-FF.

In the DM group (Table 2), direct LDL-C was higher than LDL-FF (156.63±58.58 vs. 138.07±60.94 mg/dL) with a mean difference of 18.56±19.69 mg/dL or 11.97±11.52% meanwhile the Mann-Whitney test was used for abnormal distributed data.

### RESULTS AND DISCUSSION

Total samples of this study were 208 subjects (Table 1) consisting of 90 type 2 diabetes mellitus patients and 118 non-diabetic patients. Male subjects were 85 patients (40.9%) while female were 123 patients (59.1%). Briefly, in both groups, the mean difference of direct LDL-C and LDL-FF (rLDL) was 16.26 ± 18.62 mg/dL and the mean percentage of difference was 9.99±11.48%. From all samples, 170 (81.73%) samples had a higher direct LDL-C level than LDL-FF, 37 (17.79%) had a higher LDL-FF than direct LDL-C meanwhile 1 (0.48%) sample had the same value of direct LDL-C and LDL-FF.

In the DM group (Table 2), direct LDL-C was higher than LDL-FF (156.63±58.58 vs. 138.07±60.94 mg/dL) with a mean difference of 18.56±19.69 mg/dL or 11.97±11.52% meanwhile the Mann-Whitney test was used for abnormal distributed data.

### Controlled LDL-C

Controlled LDL-C is one of the therapeutic targets in DM patients. LDL-C target in DM patients was tight, and considered as the same as patients with coronary heart disease. Measurements of LDL-C are commonly performed by direct method or by calculated Friedewald formula using total cholesterol, HDL-C and triglycerides for estimating LDL-C level. Friedewald formula uses triglycerides/5 equation (in mg/dL) for estimating VLDL.

In type 2 DM patients, dyslipidemia commonly occurs, marked by low HDL-C, abnormal VLDL-C and high triglycerides. The high level of triglycerides reported has a correlation with false low calculated LDL using Friedewald formula. Even though direct LDL and LDL-FF has a strong correlation but the difference of both is wider as the triglycerides level increases, and the correlation is weakened as the triglycerides level exceeds 400 mg/dL.

### Table 1. Characteristics of samples

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57.06±9.36</td>
</tr>
<tr>
<td>Cholesterol total (mg/dL)</td>
<td>214.04±54.69</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>50.07±14.28</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>124.50±64.37</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>155.33±51.74</td>
</tr>
<tr>
<td>LDL-FF (mg/dL)</td>
<td>139.07±50.60</td>
</tr>
<tr>
<td>(rLDL) (mg/dL)</td>
<td>16.26±18.62</td>
</tr>
<tr>
<td>(%rLDL) (%)</td>
<td>9.99±11.48</td>
</tr>
</tbody>
</table>

In this study, a significant difference between direct method and Friedewald Formula was found. There were 81.73% samples which had lower LDL-FF than direct LDL-C. This finding was consistent with Garoufi et al. who reported that 75.6% of children with normal cholesterol and 77.3% of children with dyslipidemia had LDL-FF lower than direct LDL-C.

### Table 2. The difference of age, lipid profile, LDL-C, LDL-FF, and \(rLDL\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-DM Mean±SD</th>
<th>DM Mean±SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.94±10.12</td>
<td>57.21±8.31</td>
<td>0.825a</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dL)</td>
<td>212.93±43.15</td>
<td>215.48±67.02</td>
<td>0.543a</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>49.86±14.18</td>
<td>50.36±13.90</td>
<td>0.754a</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>116.24±59.33</td>
<td>135.32±69.29</td>
<td>0.078a</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>154.34±46.08</td>
<td>156.63±58.58</td>
<td>0.75a</td>
</tr>
<tr>
<td>LDL-FF (mg/dL)</td>
<td>139.83±41.28</td>
<td>138.07±60.94</td>
<td>0.204a</td>
</tr>
<tr>
<td>(rLDL) (mg/dL)</td>
<td>14.51±17.63</td>
<td>18.56±19.69</td>
<td>0.106a</td>
</tr>
<tr>
<td>(%rLDL) (%)</td>
<td>8.49±11.27</td>
<td>11.97±11.52</td>
<td>0.030a</td>
</tr>
</tbody>
</table>

* Mann-Whitney test

The difference of direct and calculated Friedewald LDL-C mean was increased as the increase of triglycerides and fasting glucose level in type 2 DM patients. Viera et al. reported that the difference of LDL-C was higher in patients with HbA1c >8% than those with HbA1c <8%. Contrary, Kopfholz et al. reported that there was no significant difference of direct and calculated Friedewald LDL-C in metabolic syndrome patients at triglycerides levels <150 mg/dL and >150 mg/dL.
One of the long-term diabetes mellitus complications is coronary heart disease. Risk of coronary heart disease can be measured with LDL-C so the accuracy of LDL-C measurement is important for evaluating cardiovascular risk and therapy. In this study, it was found that calculated LDL-C using Friedewald Formula mostly gave false lower LDL-C value, therefore, this formula was not recommended to be used for evaluation of cardiovascular risk in type 2 DM patients. The researchers suggested a direct method for LDL-C measurement.

Evaluation of several formulas for estimating LDL-C is suggested and compare them with a direct method as an alternative of Friedewald Formula which seems not ideal to be used in type 2 DM population.\textsuperscript{14-17}

CONCLUSION AND SUGGESTION

The majority of calculated LDL-C levels using Friedewald Formula showed false low LDL value than the direct method and the mean difference was higher in type 2 DM patients than in non-diabetic ones. The researcher suggest the use of direct method to measure LDL-C for evaluation of cardiovascular risk in type 2 DM patients.

REFERENCES