Lipoprotein (a): Is it important for Friedewald formula?

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Abstract

Aim: To investigate the effect of serum lipoprotein (a) concentration on the estimated Friedewald formula with the corrected Dahlen formula.
Methods: 269 consecutive patients (122 women and 147 men) were enrolled. Total cholesterol, HDL cholesterol, triglycerides and lipoprotein (a) levels were measured, whereas LDL cholesterol was calculated using both the Friedewald and Dahlen formula.
Results: A significant difference between Friedewald and Dahlen formula was found ($P<0.001$). For lipoprotein (a) values below 50 mg/dl, we did not find any difference between LDL cholesterol levels. However, for lipoprotein (a) values above 50 mg/dl, there was a significant difference in LDL-cholesterol levels ($P<0.05$).
Conclusion: The Friedewald's estimation for LDL cholesterol can be used for screening of patients with cardiac risk. Friedewald's estimation is limited in patients whose lipoprotein (a) levels are above 50 mg/dl. More research work is needed to validate the Dahlen calculation and drug intervention with high lipoprotein (a).

Keywords: Dahlen formula, Friedewald formula, LDL cholesterol, lipoprotein (a).

Introduction

Cardiovascular diseases (CVD) are the main causes of death in most countries. CVD include non-modifiable risk factors such as older age, male sex, heredity and modifiable risk factors such as obesity, smoking, hypertension, diabetes mellitus, total and low density lipoprotein (LDL) cholesterol (1-2). Elevated LDL cholesterol is one of the most important modifiable risk factors for the development of atherosclerosis and cardiovascular disease. The exposure to elevated LDL cholesterol increases the risk of such morbidity and mortality; and lowering LDL cholesterol, recommended by treatment guidelines, is a key strategy to reduce CVD risk (3). LDL cholesterol above 100 mg/dl appears to be atherogenic and the goal is to achieve LDL cholesterol <100 mg/dl, which has been considered as an optimal value recently. Atherogenesis occurs when LDL cholesterol concentrations are between 100–129 mg/dl, and this is revealed as above optimal. At borderline high level (130–159 mg/dl), atherogenesis proceeds at a significant rate, whereas at high levels (160–189 mg/dl) and very high levels (>190 mg/dl) it increases markedly. Therefore, measurement of the LDL cholesterol must be accurately performed. LDL cholesterol calculation by the Friedewald equation is the most commonly used method to calculate LDL cholesterol in routine clinical laboratories throughout the world due to its simplicity, reliability and cost effectiveness (1). The Friedewald equation estimates LDL cholesterol as total cholesterol minus high density lipoprotein (HDL) cholesterol minus triglycerides/5 in milligrams per deciliter (4). Friedewald formula cannot be applied to samples containing triglycerides levels above 400 mg/dL, to non-fasting samples and to samples of patients with dysbetalipoproteinemia (1). Also a greater difference in the Friedewald estimated LDL cholesterol versus directly measured LDL cholesterol occurred and this equation gives an overestimation of LDL cholesterol (5-6).

Lipoprotein (a), is a cholesterol ester rich LDL-like particle in which apolipoprotein (apo) B100 is covalently linked, in a 1:1 molar ratio, to apo(a) (7). Although the mechanisms are not clearly understood, lipoprotein (a) is known to accumulate in plaques and to promote atherosclerosis in the arterial intima. It's also known to impair coagulation and fibrinolysis within blood vessels (8). The Friedewald equation does not use lipoprotein (a) which is associated with LDL cholesterol. Dahlen offered to modify the Friedewald formula by using lipoprotein (a) (9).

In the present study we investigated the effect of serum lipoprotein (a) concentration on the estimated Friedewald formula with the corrected Dahlen formula.

Methods

The study population consisted of 122 women (age 20-85 years) and 147 men (age 20-85 years) from inpatients and outpatients. Results on serum samples from patients were obtained from the laboratory information system. The study was approved by the Ethics Committee of Zonguldak Bülent Ecevit University.

Morning blood samples (2-3 mL) were obtained from all subjects for total cholesterol, HDL cholesterol, triglycerides and lipoprotein (a) measurements. Samples were separated by centrifugation and all samples were studied at the same time. Total cholesterol, HDL cholesterol, triglycerides measurement was performed by using the Siemens commercially assay kit with Advia 2400 (Siemens Diagnostic, Tarrytown, USA) analyzer. Lipoprotein (a) was measured by immunoturbidimetric method (RANDOX Laboratories, Crumlin, UK) using the Advia 2400 analyzer.

The LDL cholesterol, expressed in mg/dl, was calculated using both the Friedewald formula (4) and Dahlen formula (9) excluding samples with triglycerides concentrations $\geq$400 mg/dl.

LDL cholesterol = Total cholesterol -VLDL cholesterol-HDL cholesterol (4).

LDL cholesterol = Total cholesterol -VLDL cholesterol-

HDL cholesterol-(Lipoprotein (a) × 0.3) (9).

Statistical analysis

Statistical analyses were performed using SPSS software (Statistical Package for the Social Sciences, version 15.0, SPSS Inc, Chicago, III, USA). Continuous variables within group data were calculated as mean ± standard deviations (SD) and categorical variables as numbers and percentages. Continuous variables were compared using Student's t-test, and categorical variables were compared using the chi-square test. For comparison of continuous variables that were not homogenously distributed, the nonparametric Mann-Whitney U-test was employed. Pearson's and Spearman's correlation coefficients were used to determine the relationship between continuous variables. Values of $P \leq 0.05$ were considered as statistically significant.

Results

A total of 269 individuals were included in this analysis. The mean age of the subjects was 54.08±16.25 years. The mean values of serum total cholesterol, triglyceride, HDL-cholesterol and lipoprotein (a) concentrations in the overall sample were: 190.77±48.47 mg/dl, 147.39±75.36 mg/dl, 47.30±15.18 mg/dl and 35.13±36.08 mg/dl, respectively. The mean levels of LDL cholesterol of Friedewald formula were 114.19±39.80 mg/dl, while the mean values LDL cholesterol of Dahlen formula were 103.64±39.37 mg/dl.

We found a significant difference in LDL cholesterol levels between Friedewald and Dahlen formula ($P<0.001$).

Table 1 shows the demographic data and laboratory test results in men and women. Distribution statistics of lipoprotein (a) concentrations in this population are presented in Table 2.

Table 1. Demographic data and laboratory test results in men and women

Parameters	Women (n=147)	Men (n=122)	P-value
Age (years)	51.66±15.93	56.09±16.25	0.058
Total Cholesterol (mg/dl)	183.34±52.97	196.94±43.62	0.026
Triglyceride (mg/dl)	150.30±78.04	144.98±73.24	0.565
HDL Cholesterol (mg/dl)	41.08±11.85	52.47±15.73	0.001
Friedewald LDL Cholesterol (mg/dl)	112.46±44.21	115.61±35.82	0.519
Dahlen LDL Cholesterol (mg/dl)	100.72 ±42.96	106.08±36.09	0.266
Lipoprotein a (mg/dl)	39.17±42.59	31.78±29.35	0.095

Table 2. Percentile distribution (2.5th, 10th, 25th, 50th, 75th, 97.5th) of lipoprotein (a) (mg/dl) levels

	2.5th	10th	25th	50th	75th	97.5th
Total	4	9	13	21	41	118
Men	3	9	13	21	44	150
Women	5	9	13	21	39	110
Men						
<40 years	3	5	12	26	35	118
40-60 years	4	9	13	23	54	150
>60 years	3	7	12	19	30	115
Women						
<40 years	4	9	10	18	29	95
40-60 years	5	7	13	21	33	130
>60 years	7	9	14	22	49	115

The subjects were grouped into four categories on the basis of their lipoprotein levels: desirable (<14 mg/dl), borderline risk (14-30 mg/dl), high risk (31-50 mg/dl) and very high risk (>50 mg/dl) (10). When we evaluated the patients according to lipoprotein (a) levels, 26% of the patients had <14 mg/dl, 40% of the patients had 14-30 mg/dl, 12% of the patients had 31-50 mg/dl, and 21% of the patients had >50 mg/dl. For lipoprotein (a) values below 50 mg/dl, we did not find any difference between LDL cholesterol levels. However, for lipoprotein (a) values above 50 mg/dl, there was a significant difference in LDL cholesterol levels (P<0.05) (Table 3).

Table 3. LDL cholesterol values according to Lipoprotein (a) levels

Lipoprotein a (mg/dl)	<14 (n=71)	14-30 (n=108)	31-50 (n=33)	>50 (n=57)
Friedewald LDL cholesterol (mg/dl)	110.03±33.77	109.61±33.81	114.42±36.47	127.91±54.40
Dahlen LDL cholesterol (mg/dl)	107.23±33.74	103.45±33.88	102.87±36.52	100.03±54.86
P value	0.622	0.176	0.203	**0.007**

The percentage of the patients who might be treated with cutoffs recommended by NCEP-ATPIII is shown in Table 4. Within the treatment goal of 129 mg/dl and 159 mg/dl, 4% of the patients who would be treated with Friedewald estimation would not have been treated if Dahlen formula had been used. The ratios are decreased to 2% in Friedewald estimation when 189 mg/dl cutoff being used for treatment.

Table 4. Percentage of the patients according to LDL cholesterol cutoffs for treatment recommended by NCEP-ATP III

LDL cholesterol cutoffs for treatment	Friedewald formula (mmol/L)	Dahlen formula (mmol/L)
< 100 mg/dl	% 39 (n=102)	% 51 (n=136)
100-129 mg/dl	% 31 (n=86)	%27 (n=75)
130-159 mg/dl	% 17 (n=48)	% 13 (n=34)
160-189 mg/dl	%10 (n=26)	% 8 (n=21)
≥ 190 mg/dl	% 3 (n=7)	% 1 (n=3)

Total cholesterol, HDL cholesterol, Friedewald and Dahlen LDL cholesterol, lipoprotein (a) and triglyceride concentrations were positively correlated with each other and a negative correlation was observed between HDL cholesterol and triglyceride (Table 5).

Table 5. Correlations among parameters

Parameters	Correlation coefficient	P-value
Total cholesterol - Friedewald LDL cholesterol	0.932	<.001
Total cholesterol - Dahlen LDL cholesterol	0.905	<.001
Total cholesterol - Triglyceride	0.313	<.001
Total cholesterol - HDL cholesterol	0.357	<.001
Total cholesterol - Lipoprotein (a)	0.135	<.05
Triglyceride - HDL cholesterol	-0.282	<.001
HDL cholesterol - Friedewald LDL cholesterol	0.162	<.01
HDL cholesterol - Dahlen LDL cholesterol	0.188	<.01
Lipoprotein (a) - Friedewald LDL cholesterol	0.176	<.01

Discussion

Lipoprotein (a) is an LDL-like particle which contains apolipoprotein B100 linked by a disulfide bridge to the highly polymorphic glycoprotein apolipoprotein (a). There are 34 different lipoprotein (a) isoforms depending on the size of the apolipoprotein (a). The constituent of lipoprotein (a) is similar to LDL in its composition. The results of the present study showed that lipoprotein (a) concentrations and LDL cholesterol with Friedewald formula are positively correlated. These findings are not surprising, because elevated plasma levels of total cholesterol and LDL cholesterol and lipoprotein (a) levels are all known to be highly correlated with an increased risk for CVD. It is suggested that they share a similar mechanism. In our study, we did not find differences in the mean and median plasma lipoprotein (a) concentrations between genders. However, there was a general trend in women to have higher lipoprotein (a) values than men and this is consistent with other studies (11-12). Associations between elevated lipoprotein (a) and CVD in women are less robust than in men, possibly because of the cardioprotective and vasoprotective effects of endogenous estrogen in premenopausal women. Age is also important as a predictor of CVD. In our study increased age was positively associated with lipoprotein (a) concentrations in men and in women aged sixty and above, lipoprotein (a) levels decline both in men and women but this decrease is higher in men. This result is consistent with previous population studies and suggested the hypothesis that a continuous reshaping in lipid physiology occurs with age (13).

Cantin et al. followed 2222 men free from ischemic heart disease for 5 years for the appearance of myocardial infarction, coronary insufficiency or coronary death. They found that modification of the Friedewald formula accounting for lipoprotein (a) levels does not improve evaluation of ischemic heart disease risk (14) but they assumed the value as 25 mg/dl to define higher ischemic heart disease risk associated with lipoprotein (a). Saeedi et al. evaluated lipid profile and lipoprotein (a) of 223 patients (men and women) and found overestimated LDL cholesterol with Friedewald formula in patients with high lipoprotein (a) levels [percent overestimation of LDL-C 60-90 mg/dl lipoprotein (a) 19%, 90-120 mg/dl lipoprotein (a) 26% and >120 mg/dl lipoprotein (a) 40%], particularly in those with extreme lipoprotein (a) levels (15). In our study, the mean baseline concentrations of Dahlen LDL cholesterol were lower by ~ 3 to 27 mg/dL, respectively, compared with Friedewald LDL-cholesterol. We found significant difference in Dahlen and Friedewald's estimation for LDL-cholesterol, particularly in lipoprotein (a) levels of >50 mg/dl, but at lower levels the difference was not significant.

However, the lower LDL cholesterol concentrations calculated by Dahlen formula may misclassify a substantial proportion of individuals into a lower NCEP risk category especially at high lipoprotein (a)

levels. The Adult Treatment Panel III recommendation to include total cholesterol, HDL cholesterol, triglyceride and LDL cholesterol in screening all adults does not favor estimation of LDL cholesterol with Dahlen formula (1). While small, this systematic difference in mean LDL cholesterol concentrations may be clinically important when assessing the need for drug intervention in this particular individual group based on NCEP risk categories.

In conclusion, the Friedewald's estimation for LDL cholesterol can be used for screening of patients with cardiac risk groups. Friedewald's estimation is limited in patients whose lipoprotein (a) levels are above 50 mg/dl. More research work is needed to validate the Dahlen calculation and drug intervention with high lipoprotein (a).

Conflicts of interest: None declared.

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