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Friedewald's formula and direct LDL assay: a comparative study

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Contextualisation

LDL-Cholesterol (LDL-C) levels are used to define cardiovascular risk. The determination of LDL-C concentration must therefore be the most exact to assess the cardiovascular risk as accurately as possible and to adapt the treatment.

Objectives

In this study, we aimed to compare LDL-C calculated (LDLc) results according to Friedewald's formula (FF) with those directly measured (LDLm).

Patients and Methods

Population distribution

Total: 307 patients

LDLm based distribution	
LDLm<1,4mmol/L	5 Patients
LDLm=[1,4-1,8[mmol/L	27 Patients
LDLm=[1,8-2,6[mmol/L	90 Patients
LDLm=[2,6-3[mmol/L	51 Patients
LDLm=[3-4,9[mmol/L	122 Patients
LDLm≥ 4.9 mmol/L	12 Patients

Triglycerids (TG) based distribution	
TG<1,13 mmol/L	141 patients
TG=[1,13 – 2.26[mmol/L	132 patients
TG=[2,26 – 3.39[mmol/L	28 patients
TG≥3,39mmol/L	6 patients

Diabetes based distribution		
Diabetes	Total	225 patients
	Lipids lowering therapy	152 patients
	No lipid lowering therapy	72 Patients
No diabetes		82 patients

Analytical method

- **Biological matrix**: Heparin plasma.
- **Friedwald's formula:**

C-LDL (mmol/L) = C. Total - HDL - (TG/2,2)

- **LDL direct assay summarized:** Preliminary hydrolysis of most serum lipoproteins followed by the double action of a cholesterol oxydase/esterase couple.

- **Chemistry analyzer:** Beckman Coulter® DXC 700 AU

Statistical method

- Used software: SPSS
- Significance threshold: <0,05

Statistical tests

-Passing bablock linear regression
- Spearman's correlation coefficient
- Bland altman plot
- Concordance coefficient Kappa (K)
-ANOVA analysis

Results and discussion

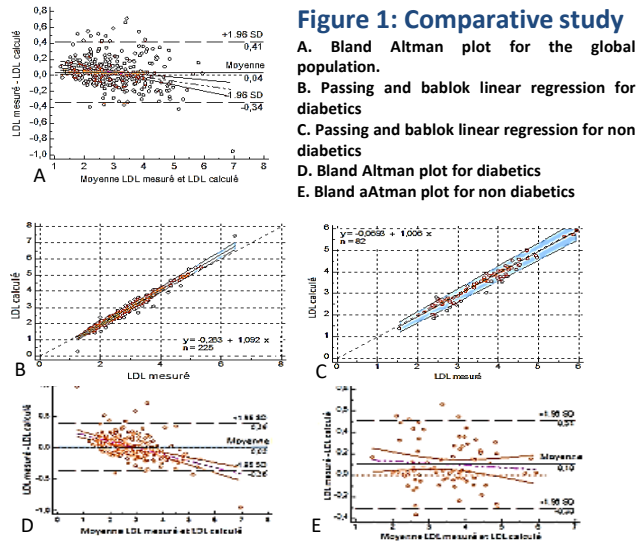

Figure 1: Comparative study

A. Bland Altman plot for the global population.
B. Passing and bablok linear regression for diabetics
C. Passing and bablok linear regression for non diabetics
D. Bland Altman plot for diabetics
E. Bland aAtman plot for non diabetics

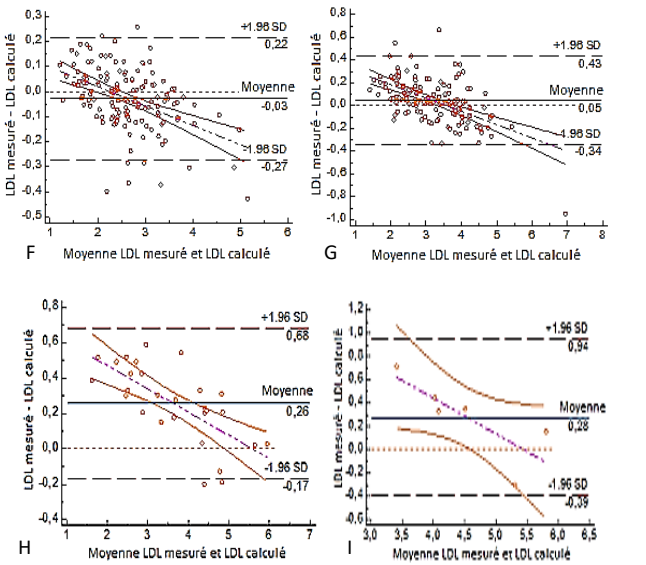

Figure 2: Comparative study according to Triglycerid values

F. Bland Altman plot for TG < 1,13mmol/L (group I)
G. Bland Altman plot for TG [1,13 – 2.26[mmol/L (group II)
H. Bland Altman plot for TG [2,26– 3.39[mmol/L (group III)
I. Bland Altman plot for TG≥3,39mmol/L (group IV)

The linear correlation between LDLm and LDLc was satisfying, but better within the diabetic population (**Spearman coefficient=0,98**) than within the non diabetics (**Spearman coefficient=0,96**). The diabetic patients present however a systematic and proportional bias which is absent in the non diabetics (**Figures 1: B and C**). The Bland Altman plots denote a statistically significant mean difference of **0,1 mmol/L** between LDLm and LDLc within the non diabetic population, the difference is however non significative for the diabetics (**p=0,203**) (**Figure 1: D and E**). Choi SY et al. also report a good correlation between LDLm and LDLc but they mention an underestimation of C-LDL using the FF [1].
The mean difference between LDLm and LDLc in the global population was **0,04 mmol/L, p=0,0011** (**Figure 1A**). There is however no global agreement on this topic in the litterature as Ghasemi et al. determined an overestimation of C-LDL by the FF while Nanda et al. concluded to a perfect correlation between LDLm and LDLc [2,3].

The linear regression revealed an underestimation of C-LDL by direct assay increasing with TG concentration.
The different Bland Altman plots show a statistically significant mean difference between LDLc of **0,03; 0,04 and 0,26 mmol/L** respectively for group I,II and III. It was however non statistically significant for group IV (**0,28 mmol/L**), which can be caused by the low number of patients in this group (**Figure 2: F,G,H and I**). The correlation between LDLm and LDLc is thereafter satisfying when **TG<2,26 mmol/L**, these resultats are identical to those described by Nanda et al. [3].

The concordance between LDLm and LDLc and cardiovascular risk was evaluated using the **Kappa coefficient**. Globally, **12,4%** of the results were underclassified using the FF. The concordance was better within the diabetic population (**κ=0,754**) than with non diabetics (**κ=0,624**). The diabetic patients not undergoing lipid-lowering therapy also showed a better concordance (**κ=0,822**) than the diabetic patients with lipid lowering medication (**κ=0,725**). These results are similar to those reported by Choi SY et al. [1].

Conclusion and perspectives

According to our results, diabetes associated with other factors such as triglycerides greater than 2.26 mmol/L or the presence of lipid-lowering treatment, affects FF and leads to errors in classifying patients regarding the cardiovascular risk. However, the absence of a clear consensus in the litterature prevents us from giving a clear critical point of view of the utility of the FF in the estimation of C-LDL. Nonetheless, the direct assay, although more costly, appears more efficient in the long run in determining C-LDL and precisely assessing cardiovascular risk.

References

[1] Choi SY, Park HE, Kim MK, Shin CS, Cho SH, Oh BH. Difference between calculated and direct-measured low-density lipoprotein cholesterol in subjects with diabetes mellitus or taking lipid-lowering medications J Clin Lipidol 2012
[2]Ghasemi A, Asgari S, Hadaegh F, Kheirandish M, Azimzadeh I, Azizi F, et al. New modified Friedewald formulae for estimating low-density lipoprotein cholesterol according to triglyceride levels: extraction and validation. Endocr. J 2018
[3] Nanda SK, Bharathy M, Dinakaran A, Ray L, Ravichandran K. Correlation of Friedewald's calculated low-density lipoprotein cholesterol levels with direct lowdensity lipoprotein cholesterol levels in a tertiary care hospital. Int J Appl Basic Med Res 2017;