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Original article

Discordance between non-HDL cholesterol and LDL cholesterol levels in patients with diabetes without previous cardiovascular events

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Abstract

Objectives. – Despite achieving desirable LDL cholesterol levels, the residual cardiovascular (CV) risk remains high among patients with diabetes. This is partly due to the increased number of atherogenic LDL particles and apoB levels, despite optimal LDL levels. As correlation studies have shown that non-HDL cholesterol is an acceptable surrogate marker for apoB, this study aimed to determine the concordance between non-HDL and LDL cholesterol in diabetic patients with different triglyceride and HbA_{1c} levels and metabolic syndrome (MS) status.

Methods and results. – Data from 11,005 diabetes patients from a large UK primary-care electronic database, with no previous CV events and not taking lipid-lowering therapy, were analyzed. Of the patients with LDL cholesterol < 1.8 mmol/L, only 58.6% had correspondingly low levels of non-HDL cholesterol (< 2.6 mmol/L). Concordance between very low LDL and very low non-HDL values was significantly less among patients with high triglycerides (25.5%) compared with those with low triglycerides (76.2%) (Pearson's χ^2 test = 177.6; $P < 0.001$). However, greater concordance between very low LDL and very low non-HDL cholesterol levels was seen in patients without (77.9%), compared with those with (50.3%), the MS (Pearson's χ^2 test = 59.7; $P < 0.001$). This persisted even after adjusting for hypertriglyceridaemia. Concordance was similar at different levels of glycaemia.

Conclusion. – There was a significant discordance between LDL and non-HDL cholesterol levels in diabetes patients with high triglycerides or the MS. This might explain patients' high residual CV risk despite having achieved their desirable LDL cholesterol levels. Thus, treating both non-HDL and LDL cholesterol to achieve target values should be considered to reduce residual CV risk in patients with diabetes.

Keywords: Diabetes; Discordance; Non-HDL cholesterol; Residual risk; Cardiovascular disease

Résumé

Discordance entre les concentrations de cholestérol non HDL et de cholestérol LDL chez des patients diabétiques indemnes d'antécédents cardiovasculaires.

Objectifs. – En dépit de l'obtention de concentrations plasmatiques de cholestérol LDL (LDLc) satisfaisantes, le risque cardiovasculaire résiduel reste élevé chez les patients diabétiques. Cela peut être expliqué en partie par l'augmentation du nombre de particules athérogènes LDL et des concentrations plasmatiques d'apoB, malgré un LDLc optimal. Des études de corrélation ont montré que le cholestérol non-HDL (non-HDLc) était un marqueur acceptable de substitution pour l'apoB, nous avons étudié la corrélation entre non-HDLc et LDLc chez des patients diabétiques pour différents niveaux de triglycérides, statut de syndrome métabolique (MS) et taux d'HbA_{1c}.

Méthodes et résultats. – L'analyse a été réalisée à partir d'un échantillon de 11,005 patients diabétiques sans antécédents cardiovasculaires et sans traitement hypolipémiant à partir du registre électronique des médecins généralistes du Royaume-Uni. Parmi les patients avec LDLc < 1,8 mmol/L, seuls 58,6 % avaient un non-HDLc correspondant bas (< 2,6 mmol/L). La corrélation entre les valeurs très basses de LDLc et de non-HDLc était moins étroite chez les patients avec triglycérides élevés (25,5 %) que chez les patients avec triglycérides bas (76,2 %) (χ^2 Pearson = 177,6, $P < 0,001$). Une corrélation plus étroite entre des concentrations de LDLc et de non-HDLc basses a été observée chez les patients sans MS (77,9 %) par rapport aux patients avec MS (50,3 %) (χ^2 Pearson = 59,7, $P < 0,001$), corrélation qui persistait après ajustement sur l'hypertriglycéridémie. La corrélation était similaire quelque soit le niveau de glycémie.

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Conclusion. – Une discordance significative existe entre les concentrations de LDLc et de non-HDLc chez les patients diabétiques avec des triglycérides élevés ou un SM. Cela pourrait expliquer le risque cardiovasculaire résiduel élevé persistant chez ces patients en dépit d'un LDLc satisfaisant. Le traitement du cholestérol non-HDL et celui du LDLc devraient être envisagés conjointement pour réduire le risque cardiovasculaire résiduel des patients diabétiques.

Mots clés : Cholestérol non HDL ; Cholestérol LDL ; Diabète de type 2 ; Syndrome métabolique

1. Introduction

There is significant evidence to suggest that the risk of atherosclerotic vascular disease is directly related to plasma low-density lipoprotein (LDL) cholesterol levels [1]. However, despite having achieved their desirable LDL cholesterol levels, cardiovascular events remain high in patients with diabetes [2]. This residual risk may reflect the large quantity of circulating atherogenic LDL particles that come into contact with and enter the arterial wall rather than the measured concentrations of these lipoprotein cholesterol fractions. One study has shown a significant discordance between LDL cholesterol levels and LDL particles (measured using nuclear magnetic resonance techniques) in patients with diabetes [3]. As each of the atherogenic lipoprotein particles contains a single molecule of apolipoprotein B (apoB) [4], the latter provides a direct measure of the number of circulating atherogenic LDL particles, and is a better marker of LDL particle levels than the calculated LDL cholesterol values.

Although apolipoproteins can be precisely measured using World Health Organization standardized methods and reference intervals [5], these methods are not as readily available as are those for cholesterol, triglycerides (Tg) and calculated LDL in many clinical laboratories. It is, therefore, important to recognize that epidemiological evidence has shown that both apoB and non-HDL cholesterol are better predictors of cardiovascular events than is LDL cholesterol [6–8]. In a post-hoc analysis of the Treating to New Targets (TNT) and the Incremental Decrease in End Points Through Aggressive Lipid-Lowering (IDEAL) studies [9], levels of both non-HDL cholesterol and apoB were shown to be more closely associated with cardiovascular outcomes than were levels of LDL cholesterol. Furthermore, on the basis of correlation studies [10], the Adult Treatment Panel III (ATP III) concluded that non-HDL cholesterol was an acceptable surrogate marker for apoB and, thus, was included as a therapeutic target for hypertriglyceridaemic patients in the most recent National Cholesterol Education Program (NCEP) recommendations [11] on the basis that the non-HDL cholesterol fraction would also represent cholesterol from triglyceride-rich lipoproteins.

The present study aimed to examine further the relationships between LDL and non-HDL cholesterol levels in a large number of diabetic patients with no previous cardiovascular events (primary cardiovascular prevention) and not taking any lipid-lowering therapy, using data from a large UK primary-care electronic database. The study also aimed to examine the relationship between the two cholesterol indices based on different Tg levels, glycaemic control and metabolic syndrome (MS) status.

2. Methods

2.1. Patients

This cross-sectional cohort study used The Health Improvement Network (THIN) database, which contains anonymous patients' data from 304 general practitioner (GP) practices throughout England and Wales. The information obtained from the database was validated against UK patients' characteristics by comparing the demographics, morbidity, mortality, prevalence and geographical rates with various national data sources [12,13].

A total of 60,258 patients with diabetes were identified, and their biochemical and demographic profiles as of 31 December 2005 were taken. Patients had to have been registered by their clinics for the whole of the preceding 12 months in order to be included in the analysis. The result was that 11,005 patients with diabetes – aged 30 to 74 years, and not prescribed any lipid-lowering drug therapy and with no arterial disease (no history of ischaemic heart disease, cerebrovascular disease or peripheral vascular disease) – were suitable for analysis. This large patient cohort reflects the clinical and biochemical parameters of patients prior to the full implementation of the new Joint British Societies (JBS 2), National Institute for Clinical Excellence (NICE) and General Medical Services Contract guidelines. Also, the present study was approved by the appropriate UK multicentre research ethics committee.

To explore the question of concordance/discordance, the cohort was divided into corresponding ranges in the two cholesterol indices in question: very low (< 1.8 mmol/L), low (1.8–2.6 mmol/L) and high (> 2.6 mmol/L) for LDL cholesterol; and < 2.6 mmol/L, 2.6–3.37 mmol/L and > 3.37 mmol/L, respectively, for non-HDL cholesterol measures. These corresponding ranges of LDL and non-HDL cholesterol were based on equivalent values of apoB levels among patients in the Collaborative Atorvastatin Diabetes Study (CARDS) [14]. Concordance was defined as when the two indices placed a subject within the same corresponding ranges. On the other hand, if the LDL and non-HDL cholesterol levels for a subject did not fall within corresponding ranges, the values were deemed discordant. Concordance/discordance between LDL and non-HDL cholesterol was also determined separately as a function of: (i) fasting Tg levels (low < 2.2 mmol/L, high 2.2–4.0 mmol/L); (ii) glycaemic control (good HbA_{1c} levels < 7%, poor 7–9% and very poor > 9%); and (iii) MS status based on NCEP–ATP III criteria.

Not included in the present analyses were patients with fasting Tg > 4.0 mmol/L. All samples were taken from patients seen in routine clinical practice. Non-HDL cholesterol was calculated